ESOT

Volume 39 | Issue 05
May 2026

Transplant International

From Transplant to Summit: Lung recipient conquers Aconcagua

Transplant International

frontiers | Publishing Partnerships

Transplant International

EDITOR-IN-CHIEF
Thierry Berney

DEPUTY EDITORS-IN-CHIEF
Oriol Bestard
Nina Pilat
Stefan Schneeberger
Maria Irene Bellini
(and Social Media Editor)
Núria Montserrat
(Honorary)

EXECUTIVE EDITORS
Frederike Ambagtsheer, Rotterdam
Federica Casiraghi, Bergamo
John Forsythe, London
Nazia Selzner, Toronto
Olivier Thaunat, Lyon

ASSOCIATE EDITORS
Emin Baris Akin, Istanbul
Chiara Becchetti, Niguarda
Irene Bello, Barcelona
Louise Benning, Heidelberg
Marina Berenguer, Valencia
Ekaterine Berishvili, Tbilisi
Saskia Bos, Leuven
Olivia Boyer, Paris
Jadranka Buturovic-Ponikvar, Ljubljana
Ligia Camera Pierrotti, Brazil
Lionel Couzi, Bordeaux
Fabian Eibensteiner, Vienna
Laure Elkrief, Tours
Juliet Emamaullee, Rochester
Stuart M. Flechner, Cleveland
Maddalena Giannella, Bologna
Nicholas Gilbo, Belgium
Ilkka Helanterä, Helsinki
Sarah Hosgood, Cambridge
Nichon Jansen, Leiden
Marta Jimenez-Blanco, Madrid
Nassim Kamar, Toulouse
Katja Kotsch, Berlin
Cécile Legallais, Compiegne
Wai H. Lim, Perth
Pål-Dag Line, Oslo
Mehdi Maanaoui, Lille
Oriol Manuel, Lausanne
Beat Moeckli, Geneva
Letizia Morlacchi, Milan
Johan Nilsson, Lund
Gabriel Oniscu, Stockholm
Fernanda Ortiz, Helsinki
David Paredes-Zapata, Barcelona
Yael Peled-Potashnik, Ramat Gan
Lorenzo Piemonti, Mialan
Karen C Redmond, Dublin
Elvana Rista, Tirana
Hanne Scholz, Oslo
Norihisa Shigemura, Philadelphia
Piotr Socha, Warsaw
Donzília Sousa Silva, Porto
Christian Toso, Geneva
Ifeoma Ulasi, Enugu
Pablo Daniel Uva, Beunos Aires
Pedro Ventura-Aguiar, Barcelona
Christy Walklin, London
Dafna Yahav, Ramat Gan

EDITOR-IN-CHIEF EMERITUS
Ferdinand Mühlbacher, Vienna

STATISTICAL EDITOR
Silvia Pineda, Madrid
Thomas Neyens, Leuven

EDITORIAL FELLOWS
Antonio Citro, San Raffaele Hospital, Milan
Delphine Kervella, Vall d'Hebron University Hospital, Barcelona
Emilien Seizilles De Mazancourt, Hôpital Saint-Louis, Paris
Arianna Trizzino, Azienda Ospedaliero Universitaria Pisana, Pisa
Andrea Zajacova, University Hospitals Leuven, Leuven

SOCIAL MEDIA EDITORS
Christophe Masset, Nantes
Marco Pascale, Rome

ESOT Project Manager
Ketevan Rukhadze

Editorial Office
Nathan Masters
Richard Hales
ti@frontierspartnerships.org

ESOT

Transplant International

From Transplant to Summit: Lung recipient conquers Aconcagua

Transplant International
Book Copyright Statement

The copyright in the text of individual articles in this eBook is the property of their respective authors or their respective institutions or funders. The copyright in graphics and images within each article may be subject to copyright of other parties. In both cases this is subject to a license granted to Frontiers.
The compilation of articles constituting this eBook is the property of Frontiers.
Each article within this eBook, and the eBook itself, are published under the most recent version of the Creative Commons CC-BY licence. The version current at the date of publication of this eBook is CC-BY 4.0. If the CC-BY licence is updated, the licence granted by Frontiers is automatically updated to the new version.
When exercising any right under the CC-BY licence, Frontiers must be attributed as the original publisher of the article or eBook, as applicable.
Authors have the responsibility of ensuring that any graphics or other materials which are the property of others may be included in the CC-BY licence, but this should be checked before relying on the CC-BY licence to reproduce those materials. Any copyright notices relating to those materials must be complied with.
Copyright and source acknowledgement notices may not be removed and must be displayed in any copy, derivative work or partial copy which includes the elements in question.
All copyright, and all rights therein, are protected by national and international copyright laws. The above represents a summary only. For further information please read Frontiers' Conditions for Website Use and Copyright Statement, and the applicable CC-BY licence.

ISSN 1432-2277
ISBN 978-2-8325-8273-2
DOI 10.3389/978-2-8325-8273-2

Generative AI statement
Any alternative text (Alt text) provided alongside figures in the articles in this ebook has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Transplant International

Table of contents

Letter to the Editor

ESOT®
Leading the way
in transplantation

Are You a Member?

Join us to help shape and nurture the future of ESOT!

Learn more about membership benefits, access, discounts, including reduced publishing fees in Transplant International

ESOT Membership

ESOT®
Leading the way
in transplantation

2026 CALENDAR OF EVENTS

Join us for a dynamic lineup of educational **hands-on workshops** and **in-person events**, dedicated to advancing transplantation through shared knowledge and collaboration.

For the full scope of events, visit:

www.esot.org/events

ESOT®
Leading the way
in transplantation

Transplanting Health:

OVERCOMING METABOLIC BARRIERS

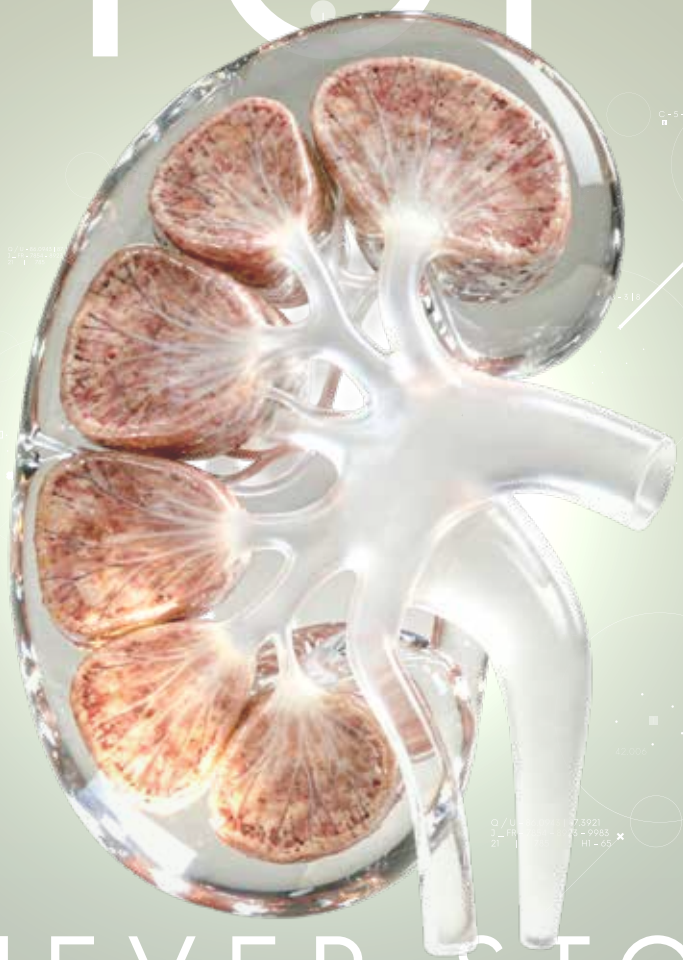
in Modern Medicine

1-3 December, 2026 • Barcelona, Spain

Deadline to submit abstracts: **29 June 2026**
Early registration fees end: **7 September 2026**

Submit and register today!

THOSE AT THE TOP



NEVER STOP

ESOTTRANSPLANTLIVE.ORG

ESOTTRANSPLANTLIVE.ORG

In transplantation, there is no time to waste.
And yet your expertise has to stay current.
The redesigned Transplant Live supports the way you work, with simplified login, clearer navigation, optimised search tools, open access to accredited courses, multidisciplinary case discussions and expert-led webinars.

Transplant Live
The online education platform of the European Society for Organ Transplantation

ESOT TRANSPLANT LIVE ONLINE EDUCATION

WHERE EXPERTISE EVOLVES

ESOT | Transplant International

EDITORIAL
published: 12 May 2026
doi: 10.3389/ti.2026.16595

Living Life to the Fullest After Organ Transplantation

Andrea Zajacova[1,2], *Coby Annema*[3], *Nina Pilat*[4,5] *and Thierry Berney*[6,7]*

[1]Editorial Fellow, Transplant International, [2]BREATHE, KU Leuven, Leuven, Belgium, [3]Department of Health Sciences, Section of Nursing Science, University Medical Center Groningen, Groningen, Netherlands, [4]Deputy Editor-in-Chief, Transplant International, [5]Department of Cardiac and Thoracic Aortic Surgery, Medical University of Vienna, Vienna, Austria, [6]Editor-in-Chief, Transplant International, [7]Division of Transplantation, Immunology and Nephrology, Hospices Civils de Lyon, Lyon, France

Ensuring a good quality of life after organ transplantation is a priority that all transplant physicians, surgeons and healthcare professionals should strive to achieve for their patients. Indeed, organ transplantation is not simply about surviving and the ability to participate in meaningful activities of life is of critical importance [1]. This should be a self-evident fact, but the journey to overcome complications, co-morbidities, medication side-effects, and treatment burden, in order to achieve the desired physical, mental, and social outcomes, can be a bumpy ride, and has been the topic of a recent special issue of *Transplant International* titled "Living well after transplantation" [1, 2].

Living well after transplantation (arguably, the ability to participate in normal life activities) is by definition a subjective concept and assessing it can only be done from the patient perspective, and has been understudied. The development and implementation of patient-reported outcome measures into clinical practice and clinical trials is the first step ensuring the patient voice is heard systematically [3].

To have a meaningful life after a solid organ transplant, patients can use their improved health status to once again enjoy time with family and friends, to travel and to return to work [4]. To achieve this, healthcare providers should look beyond medical support in enhancing long-term wellbeing, and most importantly, organ recipients should see themselves as creators of their own wellbeing [5].

The ability to practice sport and physical activity is a significant part not only of a return to social life but also of health-related quality of life [6]. Indeed, the effect of the quantity of sport activity was significant on the General Health and Role Emotional components of the SF-36 questionnaire, with more sport activity associated with higher HRQoL [7].

Sport and physical activity are increasingly recognized as important components of recovery and long-term quality of life after lung transplantation. Evidence from reviews and interventional studies suggests that exercise training before and after transplantation can improve or preserve exercise capacity, muscle strength, functional status and health-related quality of life in lung transplant recipients [8, 9]. Structured rehabilitation programs and targeted interventions, including high-intensity interval training, have been shown to be feasible and safe while contributing to improvements in aerobic capacity and muscular strength [10, 11]. In addition, studies examining symptom responses during exercise have provided insight into ongoing limitations such as dyspnea, effort perception, and muscle discomfort that may be experienced by lung transplant recipients [12]. Importantly, evidence from cohorts of transplanted athletes indicates that some are able to participate in recreational or competitive sport, demonstrating substantial physical recovery and highlighting the potential for lung transplant recipients to regain high levels of physical functioning and social participation [13, 14].

The letter published in this issue of *Transplant International* is an impressive report of how far organ transplant recipients are able to challenge themselves from the physical standpoint and even achieve feats that most individuals from the general population would be unable to achieve [15]. The

Editorial

OPEN ACCESS

***Correspondence**
Thierry Berney,
eic.ti@frontierspartnerships.org

Received: *16 March 2026*
Accepted: *19 March 2026*
Published: *12 May 2026*

Citation:
Zajacova A, Annema C, Pilat N and Berney T (2026) Living Life to the Fullest After Organ Transplantation. Transpl. Int. 39:16595. doi: 10.3389/ti.2026.16595

transplantation team from the Medical University of Vienna enrolled 9 lung transplant recipients in a high-altitude mountaineering expedition, in which one patient was able to summit Mount Aconcagua, the highest peak in the Andes, without supplemental oxygen. The letter also demonstrates the responsibility and the cautiousness of the medical team, who took great care to acclimatize and monitor their patients, and thus avoid the potential detrimental outcomes of extreme physical activity after organ transplantation [6].

Beside this exceptional achievement from the medical, physical and emotional standpoints, there is a clear symbolic value in the image of a lung transplant recipient climbing to extreme altitudes without supplemental oxygen support. If anything, this experience is an staggering and thrilling demonstration that organ transplant recipients can not only "live well" but also live their lives to the fullest.

REFERENCES

1. Annema C, Fowler K, Jaure A, Dobbels F, De Geest S. Editorial: Living Well After Organ Transplantation. *Transpl. Int* (2025) 38:15345. doi:10.3389/ti.2025.15345
2. Available online at: https://www.frontierspartnerships.org/research-topics/45/living-well-after-organ-transplantation (Accessed February 12, 2026).
3. Fowler KJ. Life After Kidney Transplantation: The Time for a New Narrative. *Transpl Int* (2025) 38:14074. doi:10.3389/ti.2025.14074
4. Mols RE, Løgstrup BB, Bakos I, Horváth-Puhó E, Gustafsson F, Eiskjær H. Employment Status Following Heart Transplantation: Data from the Danish Nationwide Social Service Payment Register During 20 Years. *Transpl Int* (2024) 37:12230. doi:10.3389/ti.2024.12230
5. Sipma WS, de Jong MFC, Ahaus KCTB. "It's My Life and It's now or Never"—Transplant Recipients Empowered From a Service-Dominant Logic Perspective. *Transpl Int* (2023) 36:12011. doi:10.3389/ti.2023.12011
6. Stylemans D, Vandecruys M, Leunis S, Engelborghs S, Gargioli D, Monbaliu D, et al. Physical Exercise After Solid Organ Transplantation: A Cautionary Tale. *Transpl Int* (2024) 37:12448. doi:10.3389/ti.2024.12448
7. Cicognani E, Mazzoni D, Totti V, Roi GS, Mosconi G, Nanni Costa A. Health-Related Quality of Life After Solid Organ Transplantation: The Role of Sport Activity. *Psychol Health Med* (2015) 20(8):997–1004. doi:10.1080/13548506.2014.993404
8. Mathur S, Hornblower E, Levy RD. Exercise Training Before and After Lung Transplantation. *Phys Sportsmed* (2009) 37(3):78–87. doi:10.3810/psm.2009.10.1732
9. Hume E, Ward L, Wilkinson M, Manifield J, Clark S, Vogiatzis I. Exercise Training for Lung Transplant Candidates and Recipients: A Systematic Review. *Eur Respir Rev* (2020) 29(158):200053. doi:10.1183/16000617.0053-2020
10. Ulvestad M, Durheim MT, Kongerud JS, Lund MB, Edvardsen E. Effect of High-Intensity Training on Peak Oxygen Uptake and Muscular Strength After Lung Transplantation: A Randomized Controlled Trial. *J Heart Lung Transpl* (2020) 39(9):859–67. doi:10.1016/j.healun.2020.06.006
11. Ulvestad M, Durheim MT, Kongerud JS, Hansen BH, Lund MB, Edvardsen E. Cardiorespiratory Fitness and Physical Activity Following Lung Transplantation: A National Cohort Study. *Respiration* (2020) 99(4):316–24. doi:10.1159/000506883
12. Braccioni F, Bottigliengo D, Ermolao A, Schiavon M, Loy M, Marchi MR, et al. Dyspnea, Effort and Muscle Pain During Exercise in Lung Transplant Recipients: An Analysis of Their Association with Cardiopulmonary Function Parameters Using Machine Learning. *Respir Res* (2020) 21(1):267. doi:10.1186/s12931-020-01535-5
13. Trájer E, Bosnyák E, Komka ZS, Kováts T, Protzner A, Szmodis M, et al. Retrospective Study of the Hungarian National Transplant Team's Cardiorespiratory Capacity. *Transpl Proc* (2015) 47(6):1600–4. doi:10.1016/j.transproceed.2015.02.022
14. Orlandi M, Pinnarò MS, Corsi M, Borchi B, Cavallo A, Guarducci S, et al. Exercise Prescription in Lung-Transplanted Cystic Fibrosis Adults. *J Funct Morphol Kinesiol* (2025) 10(2):212. doi:10.3390/jfmk10020212
15. Mühlbacher J, Slama A, Hötzenecker K, Flick H, Dzubur F, Hilty M, et al. What Is Possible for Patients After Lung Transplantation? The Highest Reported Altitude Achieved by a Lung Transplant Recipient Without Supplemental Oxygen - Climbing Mount Aconcagua (6.961M). *Transpl Int* (2026) 39:16591. doi:10.3389/ti.2026.16591

FUNDING

The author(s) declared that financial support was not received for this work and/or its publication.

GENERATIVE AI STATEMENT

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Copyright © 2026 Zajacova, Annema, Pilat and Berney. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

ESOT | Transplant International

LETTER TO THE EDITOR
published: 12 May 2026
doi: 10.3389/ti.2026.16591

What Is Possible for Patients After Lung Transplantation? The Highest Reported Altitude Achieved by a Lung Transplant Recipient Without Supplemental Oxygen - Climbing Mount Aconcagua (6.961m)

Jakob Mühlbacher[1], Alexis Slama[2], Konrad Hoetzenecker[3], Christina Jelly[3], Holger Flick[4], Fedja Dzubur[5], Matthias P. Hilty[6,7], Paul Fellinger[8], Rodrigo Duplessis[9], Lukas Furtenbach[10], Ida Valerie Wedenig[1], Wilfried Wisser[11], Clemens Aigner[2] and Peter Jaksch[2]*

[1]Department of Surgery, Division of Visceral Surgery, Medical University of Vienna, Vienna, Austria, [2]Department of Thoracic Surgery, Comprehensive Center for Chest Diseases, Medical University of Vienna, Vienna, Austria, United States, [3]Vanderbilt Lung Transplant, Vanderbilt Thoracic Surgery, Vanderbilt University Medical Center, Nashville, TN, United States, [4]Clinical Department of Pulmonology, Medical University of Graz, Graz, Austria, [5]Clinic for Respiratory Diseases Jordanovac, University Hospital Centre Zagreb, Zagreb, Croatia, [6]Institute of Intensive Care Medicine, University Hospital Zurich, Zurich, Switzerland, [7]Faculty of Medicine, University of Zurich, Zurich, Switzerland, [8]Department of Medicine III, Medical University of Vienna, Vienna, Austria, [9]Extreme Medicine, Medical Service of Aconcagua Provincial Park, Mendoza, Argentina, [10]Furtenbach Adventures, Innsbruck, Austria, [11]Department of Cardiac and Thoracic Aortic Surgery, Medical University of Vienna, Vienna, Austria

Keywords: extreme environments, high altitude, hypoxia, lung transplant, physical activity

OPEN ACCESS

***Correspondence**
Jakob Mühlbacher,
jakob.muehlbacher@meduniwien.ac.at

Received: *16 March 2026*
Revised: *16 March 2026*
Accepted: *15 April 2026*
Published: *12 May 2026*
Corrected: *14 May 2026*

Citation:
Mühlbacher J, Slama A, Hoetzenecker K, Jelly C, Flick H, Dzubur F, Hilty MP, Fellinger P, Duplessis R, Furtenbach L, Wedenig IV, Wisser W, Aigner C and Jaksch P (2026) What Is Possible for Patients After Lung Transplantation? The Highest Reported Altitude Achieved by a Lung Transplant Recipient Without Supplemental Oxygen - Climbing Mount Aconcagua (6.961m). Transpl. Int. 39:16591. doi: 10.3389/ti.2026.16591

Dear Editors,

Lung transplantation (LuTX) is an established and effective therapeutic option for patients with end-stage lung disease [1]. Over the past decades, advances in surgical techniques, perioperative management, immunosuppressive strategies, and long-term follow-up care have resulted in significant improvements in survival rates, health-related quality of life, and functional capacity after lung transplantation [2]. Consequently, many recipients are able to resume a broad range of physical activities, including high-intensity and endurance sports. Early publications on this topic are available from other solid organ transplant recipients [3]. In this context, participation in high-altitude mountaineering has been documented in carefully selected liver transplant recipients under close medical supervision [4]. In 2015 a transplanted patient reached the highest mountain peak (6.189m, Island Peak, Nepal) ever [5]. Also, lung transplant recipients are able to adapt to altitude and capable of performing prolonged exercise at high altitude after slow ascent [6, 7]. In 2017 eight lung transplanted patients successfully summited Mount Kilimanjaro (5.895 m, Tanzania) under guidance of the Vienna lung transplant team [7, 8]. Available evidence suggests that transplanted lungs retain the capacity to physiologically adapt to hypobaric hypoxia and can sustain prolonged physical exertion at high altitude, provided that ascent is gradual and appropriate acclimatization is ensured [7]. Eleven lung transplant recipients reached the summit of Mount Jebel Toubkal (4.167 m, Morocco) in 2019 without any adverse events, despite poorer cardiopulmonary performance compared to healthy volunteers [9]. In addition, they show stable immunosuppressive drug trough levels and stable Torque Teno virus loads suggest good immunologic tolerance relative to physical stress (Mühlbacher, accepted for publication in Scientific Reports, April 2026) [10].

As part of an international medical expedition under guidance of the Vienna lung transplant team and the respective national team leaders, nine transplanted patients (8 patients after lung transplantation, one patient after liver transplantation) were included to climb Mount Aconcagua

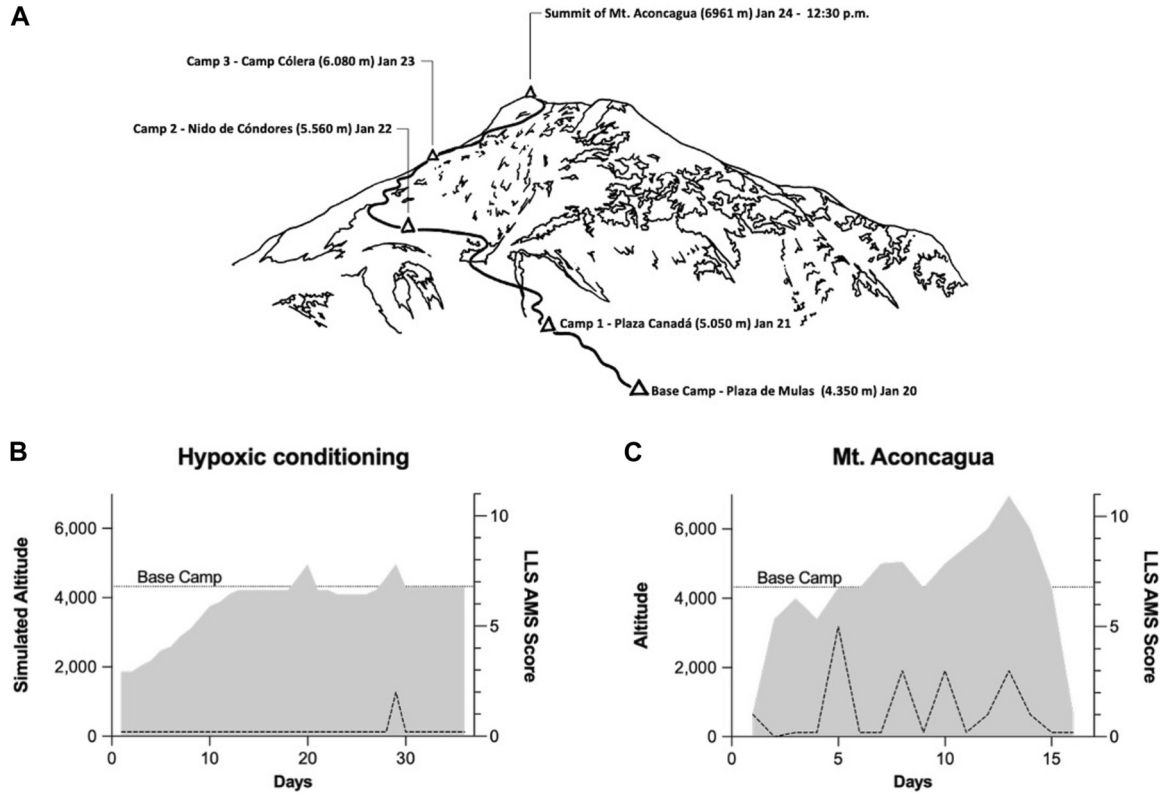


FIGURE 1 | Schedule and route for the Mount Aconcagua expedition, times are given in local time **(A)**. Hypoxic pre-conditioning performed at home, illustrating the progression of simulated altitude exposure over time and the corresponding Lake Louise Score (LLS) for acute mountain sickness (AMS) **(B)**. Elevation profile during the Aconcagua expedition illustrating altitude exposure over time together with the corresponding AMS score **(C)**, all altitudes are reported in meters above sea level (m a.s.l.).

(6.961m, Argentina) in January 2026. The expedition was supported by an accompanying team of physicians and professional guides. The actual tour planning was carried out by a professional expedition provider (Furtenbach Adventures GmbH, Rum, Austria) in cooperation with a local expedition provider (Grajales Expeditions, Los Penitentes, Mendoza Province), both of whom have many years of experience in planning and safely conducting expeditions. The selection of possible candidates was based on lung function and spiroergometry and was done in accordance with the included transplant centers in Austria, Switzerland, Croatia, Denmark and the USA.

Hypoxic conditioning (HC) applied at home as a pre-acclimatization strategy prior to high-altitude exposure may facilitate high-altitude ascents with a reduced risk of developing acute mountain sickness (AMS) [11, 12]. However, standardized protocols remain insufficiently defined, and robust scientific data are limited, although pre-acclimatization appears to be a key determinant in the success of rapid ascent expeditions [13]. It is currently unknown how this form of pre-acclimatization affects patients after lung transplantation. To maximize participant safety during the expedition, however, all participants completed a structured home-based HC program comprising at least 200 h of exposure prior to departure [11]. Participants completed mandatory safety and first aid training prior to the expedition; high flow oxygen systems (Summit Elite System, Summit Oxygen International Ltd) and carbon oxygen cylinders (4L, working pressure 300 bar; Armotech, Czech Republic) where available throughout the expedition for safety reasons.

The expedition to Mount Aconcagua (6.961 m, Argentina), followed a structured 19-day schedule organized by experienced professional providers. Accordingly, the ascent followed a standard acclimatization protocol *via* the normal route: approach to Plaza de Mulas Base Camp (BC) (4.350 m) over 4 days, followed by progressive establishment of higher camps at Plaza Canadá (5.050 m), Nido de Cóndores (5.560 m), and Camp Cólera (6.080 m). The summit attempt (6.961 m) was performed from High Camp Cólera (**Figure 1A**). Additional days were reserved for weather contingency and descent. Physiological monitoring, including heart rate and peripheral oxygen saturation, was performed using wearable devices provided within the framework of the project. In addition, the Lake Louise Acute Mountain Sickness (AMS) score was assessed daily based on self-reported symptoms documented by the mountaineers [14].

The majority of transplanted participants (7 patients after lung transplantation, one patient after liver transplantation) were unable to reach the summit due to a combination of altitude-related symptoms, reduced tolerance to physical demands at higher altitude, and precautionary decisions based on safety

considerations, resulting in descent at various stages between base camp and the higher camps.

On January 24, a lung transplant recipient successfully reached the summit of Mount Aconcagua (6,961 m, Argentina) together with the accompanying expedition team (8 participants), all without the use of supplemental oxygen. The ascent and descent were completed without adverse clinical events. In particular, no signs or symptoms consistent with high-altitude pulmonary edema (HAPE) or high-altitude cerebral edema (HACE) were observed during high-altitude exposure.

This 51-year-old male lung transplant recipient (BMI 18.3 kg/m^2), transplanted in 2002 for cystic fibrosis, resided at 407 m above sea level. Relevant comorbidities included diabetes mellitus and chronic kidney disease (creatinine: 2.57 mg/dL, November 2025); maintenance immunosuppression consisted of once-daily 0.75 mg extended-release tacrolimus in combination with everolimus 0.5 mg twice daily. He had prior high-altitude exposure, including Mount Kilimanjaro (5,895 m, Tanzania) [7], without any history of AMS, HAPE, or HACE. Baseline functional assessment demonstrated a maximal oxygen uptake (VO_2max) of 30.9 mL·kg^{-1}·min^{-1} (90% predicted; maximal workload 140 W) and an FEV_1 of 2.7 L (86% predicted), indicating preserved exercise capacity and stable graft function prior to the expedition. As part of the pre-acclimatization strategy, the lung transplant recipient completed 311 h of HC over 36 days (**Figure 1B**). Following HC, hemoglobin levels remained stable (from 13.7 to 13.8 g/dL). As simulated altitude increased during the pre-acclimatization phase, the participant experienced only mild symptoms, which was accompanied by a corresponding elevation in AMS scores (maximum AMS-Score of 2, **Figure 1B**). On the mountain he reported only mild to moderate symptoms of AMS (maximum AMS-Score of 5), and no instances of HAPE or HACE occurred at any point during the expedition (**Figure 1C**). For mild gastrointestinal problems, he took one tablet of Metoclopramide (10 mg) daily for 5 days as the only additional medication during the expedition. Arterial PaO_2 decreased by approximately 50%, from 82 mmHg in Mendoza (760 m) to 42 mmHg at Plaza de Mulas Base Camp (4,350 m), while arterial pH remained stable. Resting SpO_2 values progressively declined with increasing altitude from of 89% at BC to 75% at Camp 3. In contrast, heart rate remained relatively stable throughout the stay on the mountain, with average values ranging from 90 bpm at BC to 95 bpm at Camp 3.

These findings should be interpreted cautiously, as such high-altitude performance is likely restricted to a highly selected subgroup of transplant recipients under exceptional medical supervision and is not generalizable to the broader transplant population. Although the observed VO_2max of 31 mL·kg^{-1}·min^{-1} is lower than values suggested in the literature for successful high-altitude mountaineering [15, 16], summit attainment in this case may potentially be explained by a combination of factors, including HC, a very slow ascent rate, minimal additional load supported by porter assistance, favorable environmental conditions and potentially also by psychological factors such as resilience and motivation in this highly selected patient population. Currently, evidence regarding VO_2max thresholds for lung transplant recipients at high altitude remains limited.

In summary, selected patients after lung transplantation are able to tolerate and physiologically adapt to high-altitude exposure when preceded by normobaric hypoxic pre-acclimatization, without experiencing severe high-altitude–associated complications. Moreover, one lung transplant recipient successfully summited Mount Aconcagua without supplemental oxygen, which, to our knowledge, constitutes the highest reported altitude reached following lung transplantation.

DATA AVAILABILITY STATEMENT

Raw data are available from the authors upon request.

ETHICS STATEMENT

The studies involving humans were approved by Ethics Committee of the Medical University of Vienna (2105/2025). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

PJ and JM conceived the study and developed the study concept. JM coordinated the project and drafted the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

The author(s) declare that financial support was received for the research and/or publication of this article. This expedition was supported by the non-profit association Lungaktiv (https://www.lungeaktiv.at).

CONFLICT OF INTEREST

Author RD was employed by the company Extreme Medicine. Author LF was employed by the company Furtenbach Adventures.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

GENERATIVE AI STATEMENT

The author(s) declared that generative AI was used in the creation of this manuscript. This manuscript was reviewed with the assistance generative AI solely for linguistic correction and clarity of expression. The intellectual content, study design, data interpretation, and conclusions are entirely the responsibility of the authors.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

CORRECTION NOTE

This article has been corrected with minor changes. These changes do not impact the scientific content of the article.

REFERENCES

1. Arcasoy SM, Kotloff RM. Lung Transplantation. *N Engl J Med* (1999) 340(14): 1081–91. doi:10.1056/NEJM199904083401406
2. Seijo LL, Gao Y, Huang CY, Betancourt L, Venado A, Hays SR, et al. Improvements in Patient-Reported Functioning After Lung Transplant Is Associated with Improved Quality of Life and Survival. *Transpl Direct* (2025) 11(6):e1811. doi:10.1097/TXD.0000000000001811
3. Luks AM. Travel to High Altitude Following Solid Organ Transplantation. *High Alt Med Biol* (2016) 17(3):147–56. doi:10.1089/ham.2016.0060
4. Pirenne J, Van Gelder F, Kharkevitch T, Nevens F, Verslype C, Peetermans WE, et al. Tolerance of Liver Transplant Patients to Strenuous Physical Activity in High-Altitude. *Am J Transpl* (2004) 4(4):554–60. doi:10.1111/j.1600-6143.2004.00363.x
5. Suh KS, Kim T, Yi NJ, Hong G. Preparation for High Altitude Expedition and Changes in Cardiopulmonary and Biochemical Laboratory Parameters with Ascent to High Altitude in Transplant Patients and Live Donors. *Clin Transpl* (2015) 29(11):1013–20. doi:10.1111/ctr.12623
6. van Adrichem EJ, Siebelink MJ, Rottier BL, Dilling JM, Kuiken G, van der Schans CP, et al. Tolerance of Organ Transplant Recipients to Physical Activity During a High-Altitude Expedition: Climbing Mount Kilimanjaro. *PLoS One* (2015) 10(11):e0142641. doi:10.1371/journal.pone.0142641
7. Weber U, Schiefer J, Muhlbacher J, Bernardi MH, Ortner CM, Jaksch P. High Altitude Trekking After Lung Transplantation: A Prospective Study Using Lung Ultrasound to Detect Comets Tails for Interstitial Pulmonary Edema in Lung Transplant Recipients and Healthy Volunteers. *Transpl Int* (2018) 31(11): 1245–53. doi:10.1111/tri.13307
8. Gieszer B, Radeczky P, Farkas A, Csende K, Mészáros L, Török K, et al. Lung Transplant Patients on Kilimanjaro. *Transpl Proc* (2019) 51(4):1258–62. doi:10.1016/j.transproceed.2019.04.004
9. Schrutka L, Slama A, Muehlbacher J, Bessa V, Lichtenegger P, Ghimessy Á, et al. Cardiopulmonary Response to High-Altitude Mountaineering in Lung Transplant Recipients-the Jebel Toubkal Experience. *Scand J Med Sci Sports* (2021) 31(10):1941–8. doi:10.1111/sms.14008
10. Mühlbacher J, Kapps S, Fabriova J, Walenta K, Slama A, Schrutka L, et al. Impact of high-altitude exposure on Torque Teno virus and immunosuppression levels in lung transplantation recipients: climbing Mount Jebel Toubkal. *Sci Rep* (2026). doi:10.1038/s41598-026-46800-7
11. Burtscher J, Hufner K, Gatterer H, Pichler-Hefti J, Hefti U, Tannheimer M, et al. Time Requirements of Pre-Acclimatization at Simulated Altitude to Prevent Acute Mountain Sickness: A Mini Review. *J Trav Med* (2026) 33: taag009. doi:10.1093/jtm/taag009
12. Tannheimer M, Lechner R. Rapid Ascents of Mt Everest: Normobaric Hypoxic Preacclimatization. *J Trav Med* (2020) 27(6). doi:10.1093/jtm/taaa099
13. Burtscher M, Millet GP, Burtscher J. Hypoxia Conditioning for High-Altitude Pre-Acclimatization. *J Sci in Sport and Exercise* (2022) 4(4):331–45. doi:10.1007/s42978-021-00150-0
14. Roach RC, Hackett PH, Oelz O, Bärtsch P, Luks AM, MacInnis MJ, et al. The 2018 Lake Louise Acute Mountain Sickness Score. *High Alt Med Biol* (2018) 19(1):4–6. doi:10.1089/ham.2017.0164
15. Burtscher M. VO(2)max, an Important Determinant of Success when Climbing High Mountains. *High Alt Med Biol* (2025) 26(4):382–4. doi:10.1089/ham.2025.0015
16. Seiler T, Nakas CT, Brill AK, Hefti U, Hilty MP, Perret-Hoigné E, et al. Do Cardiopulmonary Exercise Tests Predict Summit Success and Acute Mountain Sickness? A Prospective Observational Field Study at Extreme Altitude. *Br J Sports Med* (2023) 57(14):906–13. doi:10.1136/bjsports-2022-106211

Copyright © 2026 Mühlbacher, Slama, Hoetzenecker, Jelly, Flick, Dzubur, Hilty, Fellinger, Duplessis, Furtenbach, Wedenig, Wisser, Aigner and Jaksch. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

ESOT | Transplant International

TYPE Letter to the Editor
PUBLISHED 01 May 2026
DOI 10.3389/ti.2026.16512

Check for updates

OPEN ACCESS

*CORRESPONDENCE
Julien Branchereau,
julien.branchereau@chu-nantes.fr

RECEIVED 03 March 2026
REVISED 15 April 2026
ACCEPTED 22 April 2026
PUBLISHED 01 May 2026
CORRECTED 17 June 2026

CITATION
Mesnard B, Scalea JR, Shah J and Branchereau J (2026) Aerial drones for graft transport — ready for takeoff? *Transpl. Int.* 39:16512.
doi: 10.3389/ti.2026.16512

COPYRIGHT
© 2026 Mesnard, Scalea, Shah and Branchereau. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Aerial drones for graft transport — ready for takeoff?

Benoit Mesnard [1,2], Joseph R. Scalea[3], Jaimeen Shah[3] and Julien Branchereau [1,2]*

[1]Department of Urology and Transplantation Surgery, Nantes University Hospital, Nantes, France, [2]Nantes Université, CHU Nantes1, INSERM, Centre for Research in Transplantation and Translational Immunology, UMR 1064, ITUN5, Nantes, France, [3]Division of Transplantation, Department of Surgery, University of Maryland, Baltimore, MD, United States

KEYWORDS
aircraft, organ transplantation, tissue and organ procurement, transportation, unmanned aerial vehicles

Dear editors,

The transport of grafts between the donor site and the recipient center remains a critical link in organ transplantation. It raises major organizational challenges and involves numerous professionals—physicians, nurses, procurement coordinators, and transport teams—and represents one of the determinants of cold ischemia time [1]. Cold ischemia itself is the most important modifiable predictor of short-, mid-, and long-term graft function. In kidney transplantation, cold ischemia is an independent factor significantly associated with delayed graft function [2] as well as long-term graft survival [3]. This issue is crucial, as it concerns not only the transport of organs from deceased donors but also potentially high-risk, high-stakes activities such as living-donor kidney transplantation, particularly within kidney exchange programs.

Organ transport currently relies on three main modalities: road networks using ambulances and taxis; rail transport; and air transport, often involving private jets. Aerial drones, and particularly uncrewed aircraft systems, defined as drones flown either by remote radio control or guided autonomously via GPS, could become an ideal solution in the future, as they offer several advantages.

Regarding clinical impact, long-distance ground transport may result in prolonged transport times. Ambulances are constrained by road networks and traffic conditions, while train transport depends on commercial lines and is therefore subject to scheduling constraints and limited flexibility. Organizational impact on clinical team: Automated drone transport offers improved logistical predictability and allows for around-the-clock organ reception. This increased fluidity could enable surgical teams to optimize operating room scheduling and reduce delays related to local logistics. Similarly, reducing the number of intermediaries involved in the transport of transplants is an important factor in minimizing logistical errors that may occur along the transportation chain. Public health and medicoeconomic impact: Drones represent a reliable, rapid, and less costly alternative to private jets and emergency road transport. Moreover, reductions in cold ischemia time, given its major prognostic value for short and long term graft function, carry significant medico-economic implications. Improved graft survival reduces the need for dialysis, which represents a major financial burden on healthcare systems. Environmental impact: Drone transport has a low carbon footprint compared with conventional air transport. Drones operate using either fully electric or hybrid propulsion systems. Their use could help reduce greenhouse gas emissions in alignment with ecological transition objectives. Occupational health: Replacing prolonged nighttime road trips (ambulance teams) with automated transport systems would reduce professional exposure to fatigue and accident risk while easing the logistical burden on on-call teams. In 2006, in France,

FIGURE 1
Fully electric aerial drone taking off for kidney graft transport during a preclinical experiment in France. The propulsion system consists of four rotors positioned vertically during takeoff and landing, which tilt horizontally during cruising flight. Image courtesy of Dufour Aerospace (Dübendorf, Switzerland).

two surgeons died in the crash of the aircraft that was transporting them to perform an organ procurement in a nearby city.

The first implementation of aerial drones for organ transport occurred in 2018 in Baltimore (USA) [4–6]. These early trials demonstrated stable thermal conditions during transport, reduced vibrations compared with traditional transport modes and minimized changes in spatial orientation. This work culminated in the first clinical kidney transplantation using drone transport, published in 2019, with an unremarkable postoperative course and good 30-day graft function. The drone used a six-rotor vertical propulsion system and flew at a cruising speed of approximately 32 km/h. These early experiments demonstrated technical feasibility but were constrained by the technological limitations of that time.

The use of uncrewed aircraft systems is now increasingly feasible thanks to technological advances. Current fully electric drone models achieve cruising speeds of around 100 km/h with ranges slightly surpassing 100 km. Larger hybrid-propulsion drones are more substantial models with wingspans exceeding 6 m, capable of reaching cruising speeds of approximately 120 km/h, ranges greater than 500 km, and payload capacities of around 40 kg. These drones, with increased payload capacity and volume, allow the use of clinically validated preservation containers, whether for static cold storage or hypothermic machine perfusion. Depending on the model, navigation may rely on radio-controlled guidance from a ground operator or on autonomous GPS-based flight along predefined trajectories. These devices represent the next-generation of drones, enabling transport with the lowest possible level of risk while minimizing the potential for human error. These new-generation fully autonomous drones are undergoing testing and have been evaluated in preclinical kidney transplantation experiments. In June 2025, the first preclinical experiments were conducted in France (Figure 1) using an allotransplantation model. Early results demonstrate stable thermal conditions and minimal vibration during 1-h transports, with further studies planned to confirm these findings over distances greater than 500 km.

These technological advances suggest that drone transport is becoming a mature modality for graft transportation, offering the technical possibility of connecting distant cities via direct fly routes [7]. While technological challenges are diminishing, new political and regulatory challenges are emerging. In most countries, drones intended for medical transport are regulated under civilian drone legislation. Numerous flight restrictions exist depending on population density, overflight of sensitive infrastructure, and proximity to critical zones. Establishing transfer routes between transplant centers requires the drafting and approval of flight plans meeting quality and safety standards equivalent to those of civil aviation. These regulations are nonetheless necessary and serve as a reminder that drones, by definition, are modes of transport more susceptible to hacking and diversion attempts.

Current regulations and the need to establish an aerial network dedicated to medical drone transport represent a major and labor-intensive challenge [8]. Clinical implementation will likely require future updates and adaptations to regulations specifically tailored to medical drone operations. Strong political engagement will be necessary to ease restrictions and enable the development of aerial drones for organ transport. It is up to us to make this technology the mode of organ transport for today and the future. The development of aerial drones could become a crucial logistical component in the future of organ preservation, particularly in the context of emerging normothermic perfusion hubs and the need for rapid transfer of grafts from the procurement site to strategic locations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was approved by Ministère de l'enseignement supérieur, de la recherche et de l'espace - APAFIS. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

BM: Writing – original article, conceptualization, methodology. JRS: Writing – review and editing, Validation. JS: Writing – review and editing, Validation. JB – original article, conceptualization, methodology, validation, Project administration.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Acknowledgements

We extend our sincere thanks to LEEFT (Avignon, France), Dufour Aerospace (Dübendorf, Switzerland), IGL (Lisieux, France) for their expertise and scientific collaboration. The authors thank the Center for Research in Transplantation and Translational immunology for their scientific expertise (S. Le Bas-Bernardet, D. Minault, J. Herouvet).

Conflict of interest

The authors(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Correction note

This article has been corrected with minor changes. These changes do not impact the scientific content of the article.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

References

1. Placona AM, Humphries C, Curran C, Ambroise W, Orlowski JP, Gauntt K, et al. Association of transit time with cold ischemic time in kidney transplantation. *JAMA Netw Open* (2021) 4(12):e2141108. doi:10.1001/jamanetworkopen.2021.41108

2. Husain SA, Khanna S, Yu M, Adler JT, Cron DC, King KL, et al. Cold ischemia time and delayed graft function in kidney transplantation: a paired kidney analysis. *Transplantation* (2024) 108(9):e245–e253. doi:10.1097/TP.0000000000005006

3. Debout A, Foucher Y, Trébern-Launay K, Legendre C, Kreis H, Mourad G, et al. Each additional hour of cold ischemia time significantly increases the risk of graft failure and mortality following renal transplantation. *Kidney Int* (2015) 87(2):343–9. doi:10.1038/ki.2014.304

4. Scalea JR, Restaino S, Scassero M, Blankenship G, Bartlett ST, Wereley N. An initial investigation of unmanned aircraft systems (UAS) and real-time organ status measurement for transporting human organs. *IEEE J Transl Eng Health Med* (2018) 6:4000107. doi:10.1109/JTEHM.2018.2875704

5. Scalea JR, Pucciarella T, Talaie T, Restaino S, Drachenberg CB, Alexander C, et al. Successful implementation of unmanned aircraft use for delivery of a human organ for transplantation. *Ann Surg* (2021) 274(3):e282–e288. doi:10.1097/SLA.0000000000003630

6. Scalea JR, Restaino S, Scassero M, Bartlett ST, Wereley N. The final frontier? Exploring organ transportation by drone. *Am J Transpl* (2019) 19(3):962–4. doi:10.1111/ajt.15113

7. Karpstein R, Brolli J, Stiegler P, Sucher R, Holzapfel F, Biberthaler P. Evaluation of the advanced air mobility potential for organ transplantation in Austria and Germany. *Sci Rep* (2024) 14(1):29782. doi:10.1038/s41598-024-81045-2

8. Gilmour RG, Hoff M. Beyond feasibility: critical steps toward drone-based organ transport. *Transplantation* (2026) 110(1):e4–e7. doi:10.1097/TP.0000000000005527

ESOT | Transplant International

TYPE Review
PUBLISHED 07 May 2026
DOI 10.3389/ti.2026.15786

Check for updates

OPEN ACCESS

*CORRESPONDENCE
Alessandro Furlanetto,
alessandro.furlanetto@unipd.it

RECEIVED 22 October 2025
REVISED 22 October 2025
ACCEPTED 20 April 2026
PUBLISHED 07 May 2026

CITATION
Cillo U, Furlanetto A, Lanari J, Nieddu E, Rosso E, D'Amico FE, Bassi D and Gringeri E (2026) Present and future of liver transplantation for cholangiocellular carcinoma: moving toward personalized multiparametric transplantability patterns. *Transpl. Int.* 39:15786.
doi: 10.3389/ti.2026.15786

COPYRIGHT
© 2026 Cillo, Furlanetto, Lanari, Nieddu, Rosso, D'Amico, Bassi and Gringeri. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Present and future of liver transplantation for cholangiocellular carcinoma: moving toward personalized multiparametric transplantability patterns

Umberto Cillo[1,2], Alessandro Furlanetto[1,2]*, Jacopo Lanari[1,2], Eleonora Nieddu[1,2], Eugenia Rosso[1,2], Francesco Enrico D'Amico[1,2], Domenico Bassi[2] and Enrico Gringeri[1,2]

[1]Department of Surgery, Oncology and Gastroenterology (DiSCOG), University of Padua, Padua, Italy, [2]Hepato-Bilio-Pancreatic Surgery and Liver Transplantation Unit, Azienda Ospedale Universita Padova, Padua, Italy

Liver transplantation for cholangiocarcinoma (CCA) shifted from a contraindication to a promising therapeutic option for selected patients. Advances in neoadjuvant therapy and refined selection criteria resulted in long-term outcomes comparable to other accepted oncologic indications, particularly in perihilar CCA managed with standardized protocols and in intrahepatic CCA with favorable tumor biology. The future challenge is to develop a multiparametric biological selection, blending clinical, functional, histopathologic, molecular, and radiologic parameters to identify candidates with indolent disease behavior, thus maximizing oncologic benefit while ensuring appropriate use of limited graft resources.

KEYWORDS
cholangiocarcinoma, liver transplant, transplant oncology, transplant assessment, tumor biomarkers

Introduction

Liver transplantation (LT) for cholangiocarcinoma (CCA) emerged as a critical area of inquiry due to the limited curative options in a context of a rapidly evolving transplant oncology [1–3]. Although resection remains the standard of care (SOC), many patients are ineligible due to tumor burden, anatomical constraints, or insufficient future liver remnant [4–6]. On a speculative basis, LT may provide a valuable alternative, allowing complete oncologic resection with wide margins, eliminating the pro-oncogenic hepatic microenvironment, and restoring liver function often compromised by underlying disease or prior treatments.

Aside from the excellent outcomes observed in revisited HCC indications, LT is now employed for hepatoblastoma, hemangioendothelioma, and unresectable, well-differentiated neuroendocrine tumors, and selected unresectable colorectal liver metastases patients [7–10]. All these indications share an intrinsic favorable tumor biology. On the contrary, CCA has an aggressive behavior, and LT evolved from a contraindication to a therapeutic possibility only after patient superselection. This

review will present current results in the field of LT for CCA, with particular focus on available evidence to improve patient selection based on biological aggressiveness.

Current landscape of CCA management

CCA is a biologically and clinically heterogeneous malignancy of biliary epithelial cells, characterized by an aggressive course and high recurrence risk. Although rare, its global incidence and mortality increased, ranging from 0.3 to 6/100,000 in Western countries and exceeding 6/100,000 in East Asia, reflecting geographic variability in genetic, environmental, and infectious risk factors [11–13]. CCA is classified anatomically into intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA), each with distinct risk associations: iCCA with chronic liver disease, cirrhosis, viral hepatitis, and obesity; pCCA with primary sclerosing cholangitis; dCCA with choledocholithiasis. Beyond anatomy, CCA shows marked biological heterogeneity in molecular pathogenesis, tumor microenvironment, histology, and growth patterns. Diagnosis is challenging due to asymptomatic early stages and nonspecific imaging. Contrast-enhanced CT is the standard for staging, MRI provides detailed assessment of local and biliary extension, and PET-CT is useful for lymph node and distant staging. Serum CEA and CA19-9 elevation is associated with advanced disease [11, 13–15]. While preoperative histology is not currently required for pCCA due to risk of dissemination, it is recommended that all iCCA candidates for LT undergo liver biopsy to confirm diagnosis, exclude mixed HCC-CCA and to identify poorly differentiated tumors with high risk of recurrence [16–18].

Hepatic resection is considered the main curative treatment for both pCCA and iCCA, with 5-year survival ranging from 25% to 45% [19–21]. Despite innovative and extreme approaches [22, 23], most patients remain ineligible for surgery and can only receive systemic therapies, with median OS not exceeding 12 months [24].

A registry-based study by ENSCCA [19] showed that most favorable outcomes were achieved after radical (R0), node-negative (N0) resection, with a median OS of 52.2 months and a relapse rate of 59.9%. In contrast, patients with positive margins or nodal involvement had 21%–29% 5-year OS, with a 77.4% relapse rate. Resection was performed in only 50.3% of patients, and R0 margin in 35.8%. Among the 49.6% of patients with unresectable disease, median OS was 10.6 months in those treated with active palliative therapy and 4.0 months in those receiving best supportive care.

Gemcitabine/cisplatin (GemCis) has long been first-line therapy for advanced biliary tract cancers [24], but recently the addition of immune checkpoint inhibitors became the new SOC [25, 26]. Despite these developments, the clinical benefit remains modest. In the updated TOPAZ-01 trial [27], durvalumab improved median OS by 1.6 months, while pembrolizumab extended OS by 1.8 months in the KEYNOTE-966 trial [28], compared to Gem-Cis alone. However, the association of Gem-Cis and Durvalumab showed excellent disease control rates (85%), with a 59% rate of sustained response after 6 months, making it a promising candidate as neoadjuvant treatment [25, 29, 30].

These unfavorable outcomes underscore two critical considerations. First, patient selection is crucial, focusing on biological aggressiveness and extrahepatic spread. Performance status, CA19-9, vascular involvement, and tumor size may serve as predictors of futility for both resection and transplantation [31, 32]. Second, although R0 resections are fundamental prerequisites for relevant survival benefit, the risk of recurrence remains high even after oncologically sound interventions. This infers directly to the transplant oncology setting, where total hepatectomy overcomes the problem of positive margins in liver-limited disease, while in cases of direct involvement of adjacent structures pancreaticoduodenectomy or total upper-abdominal exenteration is considered to ensure radicality.

LT for pCCA

From early experiences to "standard approaches"

Early reports described dismal outcomes, with 20%–38% 5-year OS and 53%–84% recurrence rates, despite anecdotal cases of long-term survival in early-stage node-negative patients, and a controversial role of primary sclerosing cholangitis (PSC) [33–36].

In 1993, the Mayo Clinic [37] described a novel protocol proposing LT for pCCA after thorough selection and aggressive neoadjuvant chemo-radiotherapy (Figure 1; Table 1). The first large case series [38] demonstrated excellent outcomes. Of 184 enrolled patients, 172 completed chemoradiation and underwent staging surgery, and 126 ultimately received LT. The 5-year intention-to-treat (ITT) survival was 54%, reaching 61% in patients with underlying PSC and 42% in those with *de novo* pCCA. Recurrence occurred in 21 patients (18%) after a mean time of 25 months.

These findings were confirmed by a multicenter study [41] involving 287 patients from 12 high-volume transplant centers across the USA. In this cohort, 71 patients dropped out before undergoing LT, 5-year ITT survival was 53%, and the recurrence-free survival (RFS) was 65%.

Following these encouraging results several groups in Europe and the US started following the Mayo protocol or Mayo-like protocols with similar inclusion criteria and slight modifications in the neoadjuvant treatment. However, rather small case series were reported.

A long-term analysis from the Mayo Clinic [42] reported 349 patients (1993–2018), of whom only 60% ultimately underwent LT. OS at 5- and 10-year was 69% and 62% in the per-protocol analysis and 51%, and 46% in the ITT analysis. Interestingly, a significant difference in survival was observed between patients with PSC-associated and those with *de novo* pCCA (5-year OS 76% vs. 58%).

A recent meta-analysis [43] of 20 studies comprising 428 patients reported a 31.6% pooled 5-year OS following LT without neoadjuvant therapy, compared to 65.1% in patients who completed neoadjuvant chemoradiation. Furthermore, 3-year recurrence was significantly lower among those who received neoadjuvant therapy (24% vs. 51.7%). However, despite the Mayo Clinic cohort being the largest (152 patients), marked heterogeneity was observed in the application of the protocol across studies. While most studies selected patients with unresectable tumors smaller than

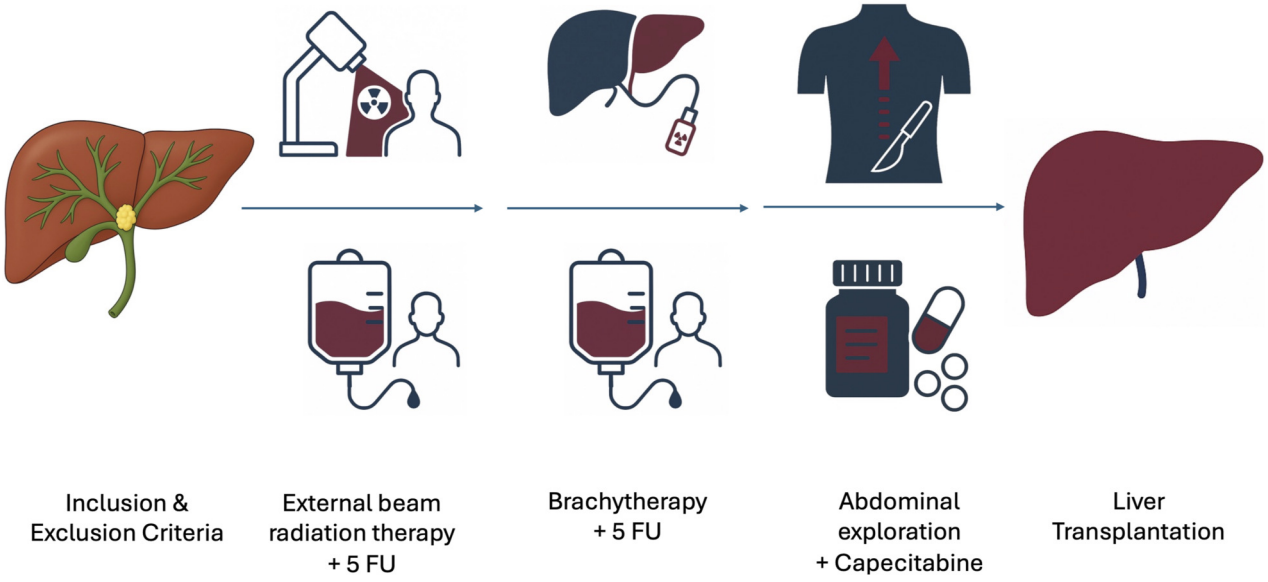


FIGURE 1
The Mayo Clinic protocol: the neoadjuvant chemoradiation regimen consists of external beam radiation (40–45 Gy), followed by transcatheter brachytherapy (20–30 Gy) using iridium wires. Intravenous 5-fluorouracil is administered concurrently as a radiosensitizer during radiation therapy, and capecitabine-based chemotherapy is given while patients await transplantation. Staging surgery with lymph node biopsies is always performed prior to LT, via laparoscopy, hand-assisted surgery, or laparotomy.

TABLE 1 Mayo clinic protocol [3, 37–39].

Inclusion criteria	Exclusion criteria
- Diagnosis of pCCA (transcatheter biopsy or brush cytology, CA 19–9 > 100 mg/mL and/or a mass on cross-sectional imaging with a malignant appearing stricture on cholangiography) - Unresectable tumor above cystic duct (pancreatoduodenectomy for microscopic involvement of CBD) or resectable pCCA arising in PSC - Radial tumor diameter <3 cm - Absence of intrahepatic and extrahepatic metastases - Candidate for liver transplantation	- Intrahepatic cholangiocarcinoma - Uncontrolled infection - Prior radiation or chemotherapy - Prior biliary resection or attempt resection - Intrahepatic metastases - Evidence of extrahepatic disease - History of other malignancy within 5 years - Transperitoneal biopsy (including percutaneous and EUS-guided FNA)
Mayo clinic protocol: neoadjuvant chemo-radiotherapy	
- External beam radiation therapy (45 Gy in 30 fractions, 1.5 Gy twice daily) + 5FU for 3 days at initiation - Brachytherapy (20 Gy at 1 cm in approximately 20–25 h) + 5FU - administered 2 weeks following completion of external beam radiation therapy - Capecitabine - administered until the time of transplantation, held during perioperative period for staging - Abdominal exploration for staging - Liver transplantation	

Unresectability is defined as bilateral segmental ductal involvement, encasement of the main portal vein, unilateral segmental ductal involvement with contralateral vascular encasement, or unilateral hepatic atrophy combined with contralateral segmental ductal or vascular involvement, particularly in the presence of underlying liver disease (PSC). Transperitoneal biopsy was introduced as exclusion criteria due to the reported high risk of tumor seeding [40]. As a result, diagnosis of pCCA within this protocol must rely on identification of a malignant-appearing biliary stricture on cholangiography, along with at least one of the following: pathological confirmation by transcatheter biopsy or brush cytology; CA 19–9 level >100 mg/mL; mass visible on cross-sectional imaging; or detection of biliary aneuploidy by fluorescence *in situ* hybridization (FISH) [38].

3 cm and excluded those with prior resection or biopsy, only a subset included patients with PSC, elevated CA19-9 levels, or malignant stricture in the absence of positive cytology. Furthermore, some groups (including the Mayo Clinic during its early experience) excluded patients with tumor extension beyond the origin of the cystic duct, to avoid pancreaticoduodenectomy. Although preoperative staging was universally performed, the extent of lymph node sampling varied considerably. Only three studies strictly followed the original Mayo chemoradiation regimen, while others introduced modifications such as substituting 5-fluorouracil with capecitabine or gemcitabine/cisplatin, or omitting chemotherapy or brachytherapy altogether.

In line with these principles, the recent Milan consensus [6] recommended LT only after neoadjuvant treatment with Mayo chemo-radiation regimen, and in presence of an unresectable pCCA <3.0 cm, with no evidence of nodal or distant metastases, no previous surgical manipulation nor transperitoneal biopsy. Interestingly, the jury supports LT also in case of borderline or dubious preoperative resectability.

Neoadjuvant, multimodal approach or simple patient selection?

The strength of the Mayo Protocol lies in rigorous criteria and locally-aggressive neoadjuvant treatment. However, the relative contribution of these two components to the overall success remains uncertain. An ELITA-ELTR study showed that a subgroup of patients who met Mayo criteria but did not receive neoadjuvant treatment before LT had similar excellent long-term oncological results (5-year OS 59%) and fared significantly better than patient outside criteria (5-year OS 21%) [44].

Although some centers [45], question the utility of neoadjuvant treatment, available data suggest that this approach increases the risk of positive margins and disease recurrence, meanwhile preventing a test of time on biological aggressiveness.

An Italian survey [39] showed that several patients underwent LT for pCCA without receiving neoadjuvant therapy, due to concerns regarding the use of radiotherapy and its short- and long-term complications, along with the requirement to deviate from current SOC chemotherapy.

These concerns are shared by the Mayo Clinic group [46], who, despite reporting excellent outcomes in the per-protocol cohort, also observed a worrisomely high 31% dropout rate (41% for *de novo* and 15% for PSC-associated pCCA). They further highlight the high toxicity of chemoradiation: nearly all patients develop recurrent cholangitis, while vascular friability often results in ischemic cholangiopathy and strictures, frequently progressing to liver failure in the absence of transplantation [38, 42, 47].

Even assuming a therapeutic effect of the neoadjuvant regimen, the considerable dropout rate implies that a several patients who ultimately did not undergo transplantation received suboptimal chemotherapy while being exposed to treatment-related complications, without any survival benefit [45]. It has been argued that radiotherapy (and consequently radiosensitizing fluorouracil) could be avoided unless their role in improving post-transplant outcomes is definitively established, as they are not currently included among standard treatments for advanced pCCA [4, 5].

The underlying disease issue

Primary sclerosing cholangitis (PSC) is a major predisposing condition for pCCA. Management is particularly challenging due to diffuse biliary involvement, impaired liver function, and a pro-oncogenic field that favors multifocal and synchronous neoplastic transformation [48]. Surgical resection is technically demanding and often associated with high morbidity and incomplete oncologic clearance [49]. When performed according to the Mayo Clinic protocol, LT yields superior outcomes in PSC-associated pCCA compared to *de novo* cases, reflecting earlier diagnosis, less aggressive tumor biology, and the concurrent treatment of both the malignancy and the underlying cholangiopathy [42, 43]. Reported results show 5-year overall survival of 65%–70% and recurrence rates of 20%–24%, making neoadjuvant therapy and LT the treatment of choice in candidable patients with PSC-associated pCCA [48].

Role of pancreaticoduodenectomy

Hepatopancreatoduodenectomy (HPD) is an extremely complex and technically demanding procedure associated with high morbidity. The technique has been mainly developed and reported by Japanese groups [50–54], who also provided most of the available outcome data [52, 55–59]. A recent meta-analysis [60] reports a 90-day mortality of 10% and morbidity of 64%, although mortality can approach zero in highly experienced centers [61]. Outcomes show marked geographic variability, with 90-day mortality of 26% in North America [62], 13%–17% in Europe [63], and <5% in Japan [58, 61].

The combination of total hepatectomy, pancreaticoduodenectomy (PD) and LT has been poorly explored. PD may be performed simultaneously with transplantation or delayed by weeks to months, but evidence is limited to small series and case reports [35, 42, 64–68], with long-term survival mainly driven by CCA recurrence [64]. The addition of pancreaticoduodenectomy increases morbidity, particularly due to technical complexity and to the impact of immunosuppression on pancreatic healing. Pancreatic fistula, reported in up to 24% of cases [64], is especially critical in the transplant setting because of the risk of vascular anastomotic injury or compression; total pancreatectomy or a two-stage approach may be considered in case of complications.

Living donor liver transplantation (LDLT)

Although potentially advantageous for optimizing transplant timing in the neoadjuvant setting, LDLT was limited by concerns regarding the risk of arterial thrombosis related to perihilar irradiation. Although jump-grafts to the aorta can be used, and the middle-colic or right gastroepiploic artery were employed to avoid performing anastomoses in the irradiated field, these strategies remain technically demanding [69, 70]. Recent neoadjuvant protocols that omit pre-transplant radiotherapy [39, 71, 72] have renewed interest in the use of LDLT for pCCA.

A retrospective analysis [73] by the Mayo Clinic compared 73 cases of LDLT performed for pCCA (66% PSC-associated) with 173 LDLTs for other indications. The pCCA group showed higher requirement for arterial or portal vein reconstruction and Roux-en-Y choledochojejunostomy. Rates of early hepatic artery thrombosis were similar between the two groups (5.4% vs. 7.6%), whereas late arterial (18.9% vs. 4.1%) and portal (37.8% vs. 8.7%) complications were more frequent in the pCCA group, although these did not affect long-term survival. 5-year OS was significantly lower in the overall pCCA cohort (66.5% vs. 87%), and differed between *de novo* (47.5%) and PSC-associated (75.9%) cases. The Mayo Clinic tried to address the issue of operating in an irradiated field by introducing technical modifications, particularly within LDLT protocols [73]. These include nonstandard arterial reconstruction (avoiding irradiated hepatic artery, use alternative

inflow sources with interposition grafts, anastomosis to the infrarenal or supraceliac), portal reconstruction (using jump grafts or anastomosis to the superior mesenteric vein or splenic vein confluence below the irradiated field) and systematic biliary reconstruction with Roux-en-Y choledochojejunostomy [42, 47].

The University of Kyoto [70] drafted a modified protocol for LDLT in pCCA, consisting of GCS chemotherapy administered for more than 2 months, followed by external-beam radiotherapy only in case of disease stability. In their initial report on 10 patients, only five proceeded to LT, achieving 100% 1-year survival rate, with one recurrence after 10 months. Hepatic artery thrombosis and delayed gastric emptying occurred in two and three patients, respectively.

Comparing resection and transplantation

The excellent long-term outcomes after LT, contrasting with persistently poor results after liver resection, raised the issue whether LT should be extended beyond unresectable disease to include borderline-resectable or even resectable cases. Only few studies addressed this issue, and case series are small and heterogeneous. A 2019 systematic review and metanalysis [74] of studies comparing LT and LR suggested a trend towards longer OS after LT, although not statistically significant. Their analysis, however, showed comparable mortality rates, but shorter hospital stay and higher rates of R0 margins after LT. In contrast, the most recent report from the Mayo Clinic [46] focusing on *de novo* pCCA, demonstrated superior results of LT compared with resection (with or without vascular resection) in terms of OS (78 vs. 25.8 vs. 58.2 months) and perioperative mortality (4% vs. 8% vs. 7%) in the per-protocol analysis. However, the high dropout rate (31% in the LT group, 28% in the surgical group) had a substantial impact on the ITT analysis, which failed to demonstrate a significant survival advantage of LT over resection.

Dropout rate is a crucial and underestimated factor. The randomized TRANSPHIL trial (NCT02232932), comparing neoadjuvant chemoradiation and LT with liver resection for resectable pCCA, reported poor long-term survival and a dropout rate exceeding 50%, ultimately leading to early termination for ethical reasons. Exposing resectable patients to both the toxicity of chemoradiation and the high likelihood of dropout and futility may ultimately condemn them to poor outcomes associated with chemotherapy alone, rather than the still unfavorable but comparatively better results of resection. These findings warrant caution and at the same time support efforts to improve consistency in preoperative management, favoring SOC chemotherapy over chemoradiation [39].

Benchmarking surgical therapeutic options

A benchmark study [75] involving 134 patients from 17 high-volume centers provided several important insights. Ideal cases were defined as treated at high-volume centers (≥50 LT/year), who underwent neoadjuvant chemoradiotherapy, had tumors <3 cm, negative lymph nodes, and no significant comorbidities. Benchmark thresholds included 90-day mortality rate ≤5.2%, 1-year Comprehensive Complication Index (CCI) ≤33.7, ≤66.7% grade ≥3 complications, and R0 resection margins rate ≥80.0%. For long-term outcomes, the benchmarks for 5-year disease-free survival (DFS) and OS were ≥43.8% and ≥60.0%, respectively. Authors advocate for recognizing unresectable pCCA treated with neoadjuvant chemoradiotherapy as a formal indication for LT, and propose extending its use to resectable cases based on the observation that benchmark outcomes of LT for pCCA not only exceed those of LT for other indications [76] but also those of surgical resection [21]. In this study, benchmark LT cases were also directly compared with a matched cohort of curatively resected, node-negative Bismuth IV patients, demonstrating significantly superior 5-year DFS (50.2% vs. 17.4%) and OS (56.3% vs. 39.9%) in the LT group, with no significant difference in major complications (72.7% vs. 74.6%) and a higher 3-month mortality rate in the resection group.

Future directions

To address the limitations of the Mayo protocol, several groups shifted to a neoadjuvant treatment based on SOC chemotherapy, with various adoption of radiotherapy or transarterial radioembolization (Figure 2).

An undergoing Italian trial (LITALHICA, NCT06125769) maintains Mayo selection criteria but replaces neoadjuvant radiochemotherapy with SOC chemotherapy to avoid altering the patient's therapeutic pathway solely due to trial inclusion [77].

Ongoing trials are summarized in Table 2, the main clinical studies and their key outcomes are reported in Table 3, and the main statements with supporting studies, corresponding levels of evidence, and relevant guideline recommendations are provided in Supplementary Table 1.

LT for iCCA

Historically, LT for iCCA was associated with poor outcomes (10%–18% 5-year OS) and high recurrence. However, recent developments identified two subsets of patients with potential high transplant benefit [16]:

1. Cirrhotic patients with unresectable (due to impaired liver function) "very early stage" iCCA (single tumor, ≤2 cm)
2. Locally advanced iCCA after good response to neoadjuvant chemotherapy

LT for "very early" iCCA in cirrhosis

In cirrhotic patients with severe portal hypertension and small unresectable iCCA, LT may simultaneously treat the tumor and the chronic liver disease.

A 2014 Spanish retrospective study [83] reported 62% 5-year OS after transplantation among cirrhotic patients with small incidental iCCA. A subsequent international study [84] showed that similarly defined "very early" iCCA (<2 cm) had better outcomes compared to "advanced (multiple or >2 cm) tumors (5-year OS 65% vs. 45%). Risk of recurrence at 5 years was also lower in the very early group (18% vs. 65%), although tumor size was not a predictor of tumor recurrence at multivariate analysis.

A metanalysis [85] of 18 studies including 355 cases, showed that cirrhosis, was positively associated with RFS, and at subgroup

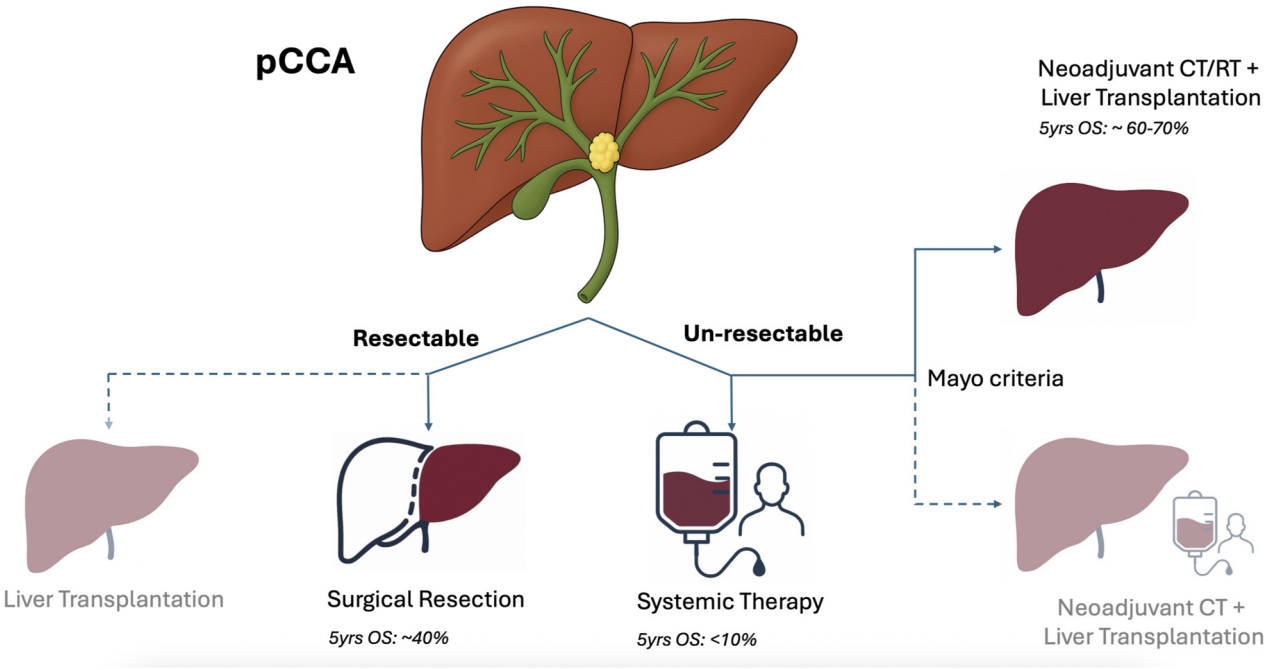


FIGURE 2
Current landscape of pCCA treatment (shaded indications are investigational).

analysis patients with very early iCCA had superior pooled 5-year RFS compared to advanced iCCA (67% vs. 34%). To be noticed, incidental diagnosis was not associated with either prolonged OS or RFS.

However, real life applicability of the 2 cm cutoff may be difficult, as pre-transplant confirmation such small unresectable iCCA is quite uncommon. Both HCC and CCA can develop on cirrhosis, as long as mixed HCC-CCA forms, and preoperative differential diagnosis can be challenging [86–88]. Indeed, a prospective trial on LT for early iCCA (NCT02878473) by the Toronto group was terminated because of low accrual.

LT for locally advanced iCCA after neoadjuvant chemotherapy

Attaining R0 resection for locally advanced iCCA can be challenging even in the non-cirrhotic [20]. To this respect, total hepatectomy followed by LT represents a resection with the highest potential for radicality, provided that there are no lymphnode involvement and extrahepatic spread. Evidence suggest, however, that patients should be selected based on surrogates of favorable tumor biology, namely response to neoadjuvant chemotherapy and test of time of disease control.

The group from UCLA [89, 90] in a 24-year single center experience on 35 cases, highlighted how patients receiving LT had significantly better outcomes than those receiving resection (5-year RFS 33% vs. 0%). Moreover, in the LT group, patients receiving neoadjuvant and adjuvant chemotherapy had better survival compared to those receiving no therapy or adjuvant therapy alone (5-year RFS 47% vs. 20% vs. 33%). On multivariate analysis, recurrence was not associated with tumor size, but rather with factors biology-related factors like multifocality, infiltrative pattern, pernieural and lymphovascular invasion, history of PSC, neoadjuvant and adjuvant therapy. In 2022, the same group reported their 30-year experience [91] (19 pCCA and 30 iCCA), confirming excellent oncological results for LT even for large size CCAs compared to patients not receiving preoperative treatment, particularly when adopting a multimodal chemotherapy and loco-regional neoadjuvant approach (5-year OS 100% vs. 41%).

The Houston Methodist-MD Anderson group developed a protocol offering LT to patients with unresectable iCCA, without evidence of macrovascular or lymph node involvement, who had sustained tumor stability with gemcitabine-based neoadjuvant therapy for more than 6 months [92]. Their latest series [93] (18 patients) showed post-LT OS of 71%, and 57% at 3 and 5 years respectively. Tumor recurred in 39% of patients after a median time of 11 months after LT, being treated with further systemic therapy and surgery. Interestingly, transplanted patients had a median number of 2 iCCA tumors and a median cumulative tumor diameter of 10.4 cm, confirming that acceptable OS can be achieved independently from size in presence of good response to therapy and disease stability. Next-generation sequencing was performed in most cases, using liquid biopsy, percutaneous biopsy, or explant tumor tissue. Known genetic alterations were identified, including FGFR (27%), CDKN2A (7%), IDH1 (35%), BRAF (19%), and TP53 (19%), but univariate analysis showed no association with outcomes. In selected patients, the presence of targetable alterations enabled the use of targeted therapies, including the FGFR inhibitor pemigatinib (1 case), the IDH1 inhibitor ivosidenib (2 cases), and the PARP inhibitor olaparib (4 cases).

TABLE 2 LT for pCCA ongoing trials.

Study	Study title	Inclusion criteria	Neoadjuvant treatment	Outcomes	Center	Start date
NCT01549795	Liver transplantation for hilar cholangiocarcinoma in association with neoadjuvant radio- and chemo-therapy	UpCCA<3 cm, PSC, no prior chemotherapy or surgery	Radiotherapy + brachytherapy + caepcitabine	Recurrence rate, time to recurrence, DFS, OS, morbidity	Padova University Hospital, Padova (Italy)	2012
NCT02178280	Phase 1 study of liver transplantation combined with neoadjuvant radiochemotherapy for unresectable hilar cholangiocarcinoma	UpCCA <3 cm, N0 M0, <65yo	Brachytherapy (I-125 stents) followed by external beam radiotherapy + capecitabine	OS, RFS, acute and chronic rejection rate	The Affiliated Nanjing Drum Tower Hospital of Nanjing University Medical School, Nanjing (China)	2014
NCT04378023	Liver transplant combined with neoadjuvant chemo-radiotherapy in the treatment of unresectable hilar cholangiocarcinoma. A prospective multicenter study	UpCCA, <3 cm, N0 M0, no prior surgery, <70 yo	External radiotherapy + capecitabine, followed by gemcitabine + cisplatin	OS, RFS, ITT OS, drop out rate	Hospital Vall d'Hebron, Barcelona (Spain)	2020
TESLA II (NCT04993131)	Liver transplantation for non-resectable perihilar cholangiocarcinoma	UpCCA (even with portal or arterial infiltration), N0 M0, 6 months SD or PR, 12 months from diagnosis	Chemotherapy	OS, OS after recurrence, DFS, morbidity, QoL	Oslo University Hospital, Oslo (Norway)	2021
LITALHICA (NCT06125769)	LIver TrAnspLantation for non-resectable Peri-HIlar cholangioCArcinoma (LITALHICA)	UpCCA <3 cm, N0 M0, 6 months SD or PR, no prior surgery or biopsy, <70 yo	SOC chemotherapy	OS, DFS, drop out, QoL, patient stratification, role of PET-MRI	Padova University hospital, Padova (Italy)	2024
EMPHATIC (NCT06434493)	Evaluation of combined Modality Protons and hepatic transplantation for hilar cholangiocarcinoma	PSC, UpCCA<3 cm, N0 M0, no prior surgery or radiation	Proton beam therapy (PBT) + capecitabine, followed by chemotherapy (GemCis)	Toxicity, rate of LT, morbidity, cancer-related mortality, graft survival, OS, RFS, recurrence, recruitment rates	University College London Hospitals, London (UK)	2024
SURE-LT (NCT06850753)		UpCCA beyond Mayo clinic criteria (including arterial and portal infiltration), M0 (including distant lymph nodes); pCCA recurrence in PSC 2 years after resection (N0R0). 6 months SD or PR	Chemotherapy + radiation followed by en bloc resection of the liver and Pancreas with a "non-touch" technique	OS (1, 3, 5 years), DFS, survival after recurrence, QoL, morbidity	Oslo University Hospital, Oslo (Norway)	2025

UpCCA, unresectable perihilar cholangiocarcinoma; PSC, primary sclerosing cholangitis; SD, stable disease; SOC, standard of care; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; ITT, intention to treat; PR, partial response; QoL, quality of life.

LDLT in iCCA

Patients with iCCA were traditionally excluded from LDLT because of insufficient expected OS and RFS to justify the donor's risk. However, the evolving diffusion of the concept of transplant benefit as gain in life-years quality-adjusted over alternative available therapies is now changing such a perception, provided the achievement of a minimal 5-year survival to avoid futility.

Literature remains limited [94, 95]. A multicenter study from Japan [96] on 19 LDLT recipients incidentally diagnosed with iCCA showed 46% 5-year OS. A similar study from Pakistan [97] including

TABLE 3 results from key studies about LT for pCCA.

Authors	Study design	Population	N	Key findings	Survival	Main prognostic factors
Meyer et al. [33]	Retrospective study Multicenter 1968–1997	LT for CCA	207	High rate recurrence. LT is not the standard. Neoadjuvant therapy are necessary for LT implementation	1-, 2-, and 5-year OS 72, 48, and 23%; recurrence 51%, 84% recurrence within 2 years. Survival after recurrence rarely more than 1 year	Survival: Tumor recurrence Recurrence; tumor spread at time of surgery
Robles et al. [34]	Multicenter retrospective (Spain) 1988–2001	LT for iCCA/pCCA	36	LT has favourable outcomes, especially with early stage tumors. High selection of patients is required	1-, 3-, and 5-year OS 82%, 53%, and 30%	Survival: Lymphnodes involvement, metastatic disease, advanced stage, vascular invasion, perineural invasion
Heimbach et al. [37]	Prospectic single center 1993–2003	Mayo clinic protocol LT for pCCA	56	Neoadjuvant CRT before LT is essential in LT protocol for pCCA.	1- and 5-year OS = 88% and 82%	
Ghali et al. [36]	Retrospective single center 1996–2003	LT for incidental iCCA/ pCCA	10	Outcomes for transplanted incidental CCA are not better than known CCA. Aggressive investigation pre LT is mandatory	Recurrence in 8/10 patients, 7/10 died because of recurrence. mRFS = 26 months, mOS = 30 months. 3-year OS = 30%	
Heimbach et al. [78]	Prospectic single center 1993–2006	Mayo clinic protocol LT for pCCA	65	Older patients and those with high CA-19.9 levels, and larger tumors are more likely to develop recurrent disease. Prolonged waiting time may emerge as a significant risk factor	5 years OS 76%, DFS 60%	Predictors of recurrence: older age, pretransplant cancer antigen (CA) 19–9,100 U/mL, prior cholecystectomy, mass on cross-sectional imaging, residual tumor in explant 2 cm, tumor grade and perineural invasion in explant
Seehofer et al. [35]	Retrospective single center/cohort study 1992–2007	LT and extended bile duct resection for pCCA	16	Extended surgical procedures in combination with LT are related to significantly increased perioperative mortality. Adjuvant or neoadjuvant therapy protocol are required to improve outcomes after LT.	1-, 5-, and 10-year OS rates after EBDR + LT 63%, 38%, and 38%	Survival: Metastatic disease, positive lymph nodes, CA19-9 levels >1000, preoperative PTCD (instead of ERCP)
Darwish Murad et al. [41]	Multricenter (12 centers) retrospective study 1993–2010	Mayo clinic protocol LT for pCCA	287	Neoadjuvant CRT is highly effective in LT protocol for CCA. There is a variability in neoadjuvant protocols (variable administration of brachytherapy). Strict patient selection is recommended	2- and 5-year Intent-to-treat = 68% and 53%. 2- and 5-year RFS after LT rates = 78% and 65%	Recurrence: metastatic disease, tumor size >3 cm, direct tumor biopsy, other malignancy in the previous 5 years

(*Continued*)

TABLE 3 Continued

Authors	Study design	Population	N	Key findings	Survival	Main prognostic factors
Darwish Murad et al. [79]	Multricenter retrospective study 1993–2010	Mayo clinic protocol LT for pCCA	199 (137 LT)	Risk of dropout is related to patient and tumor characteristics. Recurrence risk is mostly associated with presence of residual cancer on explant. PSC patients do not have an Independent survival advantage over *de novo* patients, but present with more favorable tumor Characteristics		Predictors of dropout: CA 19–9≥ 500 U/mL, mass ≥3 cm, malignant brushing or biopsy and MELD score ≥20 Predictors of recurrence: Elevated CA 19–9, portal vein encasement and residual tumor on explant
Croome et al. [80]	Retrospective single center (Mayo) 1993–2013	LT vs. LR for pCCA	LT 90, LR 124	Patients with clearly resectable *de novo* pCCA should be treated with LR because there is no evidence that they would fare better with LT.	1-, 3-, and 5-year OS 90%, 71%, and 59% for LTX and 81%, 53%, and 36% for LR. Survival was not different after adjusting for prognostic factors	Survival: Resection (vs. transplantation) age, lymph node metastases, tumor grade and tumor size
Mantel et al. [44]	Multicenter retrospective (ELTR 21 centers) 1990–2010	LT for pCCA	147	LT for pCCA has favourable outcomes with strict selection of patients, according to Mayo clinic criteria	5-year OS after LT for pCCA = 32%. 5-year OS in stricted selected patients (Mayo clinic criteria) = 59%. 90-day mortality rate = 15%. 5-year recurrence probability in stricted selected patients = 46%, in not selected patients 79%	Survival: Lymphnodes involvement
Ethun et al. [81]	Multicenter (USEBMC database) 10 centers (USA) 2000–2015	LT for pCCA	LR 234, LT 70	LR for pCCA that meets criteria for LT (<3 cm, lymph-node negative disease) is associated with substantially decreased survival compared to LT for the same criteria with unresectable disease	OS LT vs. LR 3-yr: 72% vs33%; 5-yr: 64% vs. 18% ($p < 0.001$); for tumors <3 cm, n-, non PSC, OS LT vs. LR 3-yr: 54% vs44%; 5-yr: 54% vs. 29% ($p = 0.03$)	
Moris et al. [74]	Meta-analysis (5 studies)	LT vs. resection for pCCA		OS is not inferior after LT in non metastatic unresectable tumors compared to LR. No differences in post operative mortality. Trend towards better OS in LT		
Tan et al. [73]	Retrospective LDLT study Single center 2000–2017	LDLT for pCCA (Mayo clinic)	74	The incidence of early hepatic artery thromboses was similar in LT for pCCA and non-pCCA patients. Late hepatic artery and portal vein complication were more common in the pCCA group	1-, 5- and 10- year OS = 84.9%, 66.5%, and 55.6%. Cancer recurred in 12.3%	Survival: *de novo* pCCA (vs. PSC-associated pCCA), residual tumor

(*Continued*)

TABLE 3 Continued

Authors	Study design	Population	N	Key findings	Survival	Main prognostic factors
Zaborowski et al. [82]	Prospective single-center (Ireland) 2004–2016	LT for pCCA after NCR	37 ITT (26 LT)	NCR followed by LT substantially increases the survival of patients with unresectable pCCA. Achieving a pathologic complete response confers a significant survival benefit	Overall median survival was 53 months and 1-, 3-, and 5-year OS was 81%, 69%, and 55%	Survival: Complete response
Cambridge et al. [43]	Meta-analysis (20 studies) 2000–2019	LT for pCCA	428	Better OS in LT for pCCA after completed NCT. Better results in LT for PSC-associated pCCA compared to pCCA alone	1, 3-, and 5-year OS rates after LT = without NCT 71.2%, 48.0%, and 31.6%; with NCT 82.8%, 65.5%, and 65.1%. 3-year RFS = 24.1% with NCT and 51.7% without NCR therapy	
Breuer et al. [75]	Benchmark study, multicenter (17 centers) 2014–2018	LT for pCCA (Mayo-like protocol, tumor 3 cm, node-negative)	134	NCT + LT for pCCA must be considered in selected patients with unresectable tumor (negative nodes and size < 3 cm). LT should be considered also in selected resectable patients, even considering LDLT.	Benchmark 5 years OS >60% DFS >48.3%; superior compared with a matched group of nodal negative patients undergoing LR	
Hoogwater et al. [45]	Multicenter retrospective, cohort study 2011–2020	LT for pCCA	49	NCT before LT is related to a higher complication rate (vascular), higher survival rate and lower recurrence rate after LT.	1-, 3-, and 5-year OS after LT with NCT = 65%, 51% and 41%; after LT without NCT = 91%, 68% and 53%. Hepatic vascular complications are more frequent after NCT	Recurrence: neoadjuvant therapy before LT, patients BMI, tumor size in final pathology, vascular invasion, perineural invasion
Dong et al. [46]	Retrospective cohort study Single center 1993–2023	LT (Mayo protocol) vs. liver resection (with or w/o vascular reconstruction) for pCCA	191	NCT + LT offers best outcomes for unresectable patients. LR + VR remains the preferred approach for resectable patients. Key factors are high drop out rates in LT and high perioperative mortality after LR.	Matched cohorts: 5-year OS rate in LR w/o VR = 60.8%, in RT + LT = 44.2% and LR + VR = 23.6%. Median RFS in RT + LT = 46.7 months, in LR w/o VR = 32.3 months, in LR + VR = 17.7 months. After matching the LR w/o VR group remained the most favorable group with the highest RFS, followed by RT + LT and LR + VR	
Ito et al. [70]	Prospective single-center 2018–2024	LDLT after CRT for pCCA	10 (5 LDLT)	LDLT for pCCA is feasible and effective but it is the last treatment option	1- and 5-year OS 100%, 27.4%. High frequency of HAT	

patients with incidental pCCA and iCCA, collected 16 patients, reporting 47% 3-year RFS (64% for well differentiated tumors). The largest series [98], focusing on LDLT outcomes for primary sclerosing cholangitis, included 55 out of 805 cases with iCCA, with OS reaching 81.9%.

The 2024 ILTS–ILCA Consensus [16] recommends considering LDLT for iCCA within institutional study protocols, particularly for patients with early-stage disease. At the same time, the Toronto group is currently leading a multicentric trial (NCT04195503) to validate LDLT's efficacy for advanced iCCA.

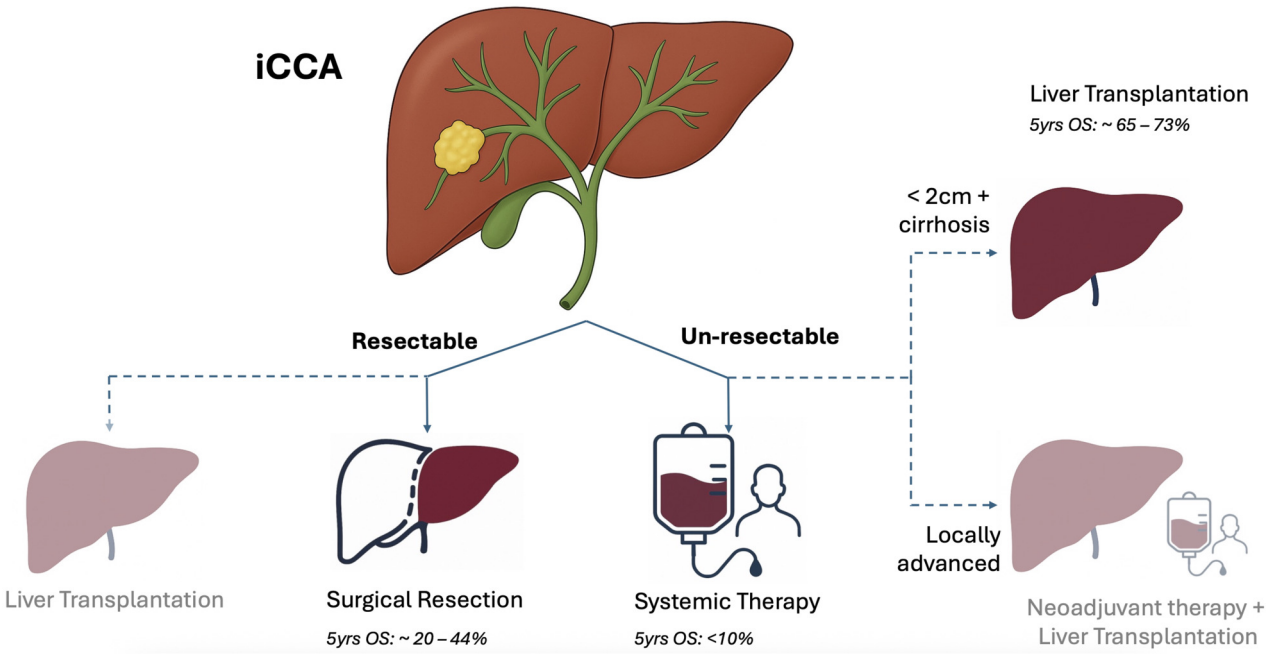


FIGURE 3
Current landscape of iCCA treatment (shaded indications are investigational).

Comparative efficacy of resection versus transplantation

Early reports showed markedly worse survival after LT compared with resection [99, 100], although patient matching was frequently biased [94].

A propensity score–matched (PSM) analysis by Jung et al., (16 LT vs. 100 resections), showed comparable OS and recurrence rates [101]. Several groups subsequently analyzed data from the US-NCDB [102–105], consistently reporting similar OS between LT and resection. However, in a multivariate analysis [104], LT was associated with a significantly reduced risk of death compared with matched resection cases.

Huang [106] recently analyzed the US-SEER database, including 2538 patients with iCCA treated with curative surgery (2425 resections, 113 LT) and 5048 LT for HCC. PSM between resected and transplanted iCCA groups corrected the baseline imbalance, since patients with early stage, smaller tumors, well-differentiated histology, and cirrhosis were more likely to be selected for LT. LT patients had significantly longer survival than those who underwent LR in the matched cohorts (median OS: 23 vs. 18 months; 5-year OS 52.8% vs. 29.9%). Interestingly, a subgroup analysis showed that patients who met recommended selection criteria (i.e. very early iCCA on cirrhosis or locally advanced iCCA after chemotherapy) had a 5-year OS of 43.8% and 61.7% respectively.

Future directions

Preliminary data [107] from the TESLA trial report 5 patients showing excellent perioperative course after LT after neoadjuvant treatment, although two experienced disease recurrence within 12 months (Figure 3; Table 4).

In Italy, the LIRICA trial, is enrolling patients with unresectable iCCA after 6 months of SOC chemotherapy. As for LITALHICA trial, unresectability is assessed by a dedicated multidisciplinary tumor board and patients are listed for LT only after 6 months of documented disease stability.

The Milan-INT group is investigating the neoadjuvant combination of chemotherapy and transarterial radioembolization (Y90-TARE). Preliminary data from 13 patients revealed a 69% dropout rate due to disease progression or inadequate response. Only four patients proceeded to transplantation, showing favorable early outcomes [108].

Ongoing trials are summarized in Table 4, the main clinical studies and their key outcomes are reported in Figure 3 and Table 5, and the main statements with supporting studies, corresponding levels of evidence, and relevant guideline recommendations are provided in Supplementary Table 2.

Looking to the future: patient selection through the lens of biological agressiveness

The most challenging task in transplant oncology [17] is not to "extend criteria" for transplantation but, on the contrary, to improve their predictive capabilities by moving beyond static morphological parameters towards dynamic, biology-driven multiparametric decision-making (Figure 4). Understanding tumor biology remains a significant challenge due to its inherent complexity and heterogeneity, complicating the identification of consistent

TABLE 4 LT for iCCA ongoing trials.

Study	Study title	Inclusion criteria	Neoadjuvant treatment	Outcomes	Center	Start date
NCT04195503	Liver transplant for stable, advanced intrahepatic cholangiocarcinoma	UiCCA, N0 M0, 6 months SD - LDLT	6 months SOC chemotherapy	OS, DFS (5 years)	University Health Network, Toronto (Canada)	2019
TESLA trial (NCT04556214)	Liver transplantation for non-resectable intrahepatic cholangiocarcinoma: a prospective Exploratory trial	UiCCA, N0 M0, 6 months SD	Chemotherapy or locoregional therapy	OS, DFS, morbidity, QoL, retransplantation	Oslo University Hospital, Oslo (Norway)	2020
NCT06140134	Liver transplantation in intrahepatic cholangiocarcinoma	UiCCA, N0 M0, 6 months SD	Systemic therapy	OS, RFS, ITT OS, morbidity	State University of New Jersey, Newark (USA)	2023
LIRICA (NCT06098547)	LIver transplantation for non-resectable intrahepatic CholAngiocarcinoma (LIRICA)	UiCCA, N0 M0, 6 months SD or PR	SOC chemotherapy	OS, DFS, drop out, QoL, patient stratification, role of PET-MRI	Padova University Hospital, Padova (Italy)	2024
LIVINCA (NCT06539377)	Living donor liver transplantation for intrahepatic cholangiocarcinoma	UiCCA, G1-2, M0, SD or PR afetrr neoadj therpay, LDLT	Any chemotherapy regime + mandatory local-ablative therapy (SIRT)	OS, RFS, donor and recipient morbidity	Jena University Hospital, Jena (Germany)	2024
RIS-TH (NCT06910722)	Liver transplantation for locally advanced intrahepatic cholangiocarcinoma after SIRT and chemotherapy	Pauci nodular (≤5 lesions) UiCCA M0, infiltration <50% of liver, <65 yo	Selective internal radiation therapy (SIRT) + chemotherapy	OS (3 years), drop out, recurrence, tolerance, QoL, complications	Assistance Publique - Hôpitaux de Paris, Paris (France)	2025
iCOLA (NCT06862934)	Liver transplantation for unresectable intrahepatic colangiocarcinoma after sustained response to neoadjuvant treatments	UiCCA, N0 M0, 6 months SD or PR	Chemotherapy+/- immunotherapy and transarterial radioembolization (Y90-TARE)	OS, RFS, morbidity, QoL, comparison with resectable patients	Istituto Nazionale dei Tumori, Milan (Italy)	2025

UiCCA, unresectable intrahepatic cholangiocarcinoma; SD, stable disease; LDLT, living donor liver transplantation; SOC, standard of care; OS, overall survival; DFS, disease-free survival; RFS, recurrence-free survival; ITT, intention to treat; PR, partial response; SIRT, Selective Internal Radiation Therapy; QoL, quality of life.

prognostic patterns. Both tumor-related and patient-specific factors contribute to posttransplant clinical outcomes. In synthesis, seven key pillars can be identified as indicators of biological aggressiveness: 1) tumor burden, 2) tumor histology, 3) molecular profile 4) circulating biomarkers 5) functional radiology 6) response to treatment 7) test of time. When corroborated by sufficient evidence, data related to these pillars will be integrated with prognostically relevant patient variables impacting on post-transplant survival to draw a personalized, multidisciplinary driven, pattern of transplantability aimed at guiding the decision making process. AI will be critical in such an evolution [109, 110].

Histology and molecular profiling

Tumor burden cutoffs and patterns are already included in most LT protocols for patient selection, both in pCCA [6, 38] and iCCA [84].

Even though not yet integrated in patient selection processes, molecular biology might play a crucial role. In particular, iCCA exhibits marked heterogeneity, with significant diagnostic, prognostic, and therapeutic implications. Small-duct and large-duct subtypes, differ in morphology, cellular origin, clinical behavior, and molecular characteristics. Small-duct subtype generally confers better prognosis and is often associated with targetable genetic alterations (IDH1/IDH2, FGFR2). In contrast, large-duct iCCA more commonly harbors classical adenocarcinoma genetic alterations, such as in KRAS and TP53 [11]. Next-generation sequencing enables detection of actionable mutations, and is gradually transforming oncologic care [111]. A large meta-analysis of 1,481 resected iCCA cases demonstrated that patients with tumors harboring KRAS, TP53, and/or SMAD4 mutations had significantly worse OS and RFS compared to those with FGFR2 fusions, IDH mutations, BAP1 mutations, or no major genetic abnormalities [112]. Additional mutations in RB1, ERBB2, and BAP1 are also frequently observed in iCCA, and up to 70% of patients harbor potentially targetable genetic alterations [113]. Pemigatinib and infigratinib, showed progression-free survival (PFS) of 6.9 and 5.8 months, respectively, in patients with FGFR2 fusions [114–116]. Ivosidenib (IDH1 inhibitor) improved both PFS and OS in the ClarIDHy trial and was approved as palliative treatment [117, 118].

TABLE 5 results from key studies about LT for iCCA.

Authors	Study design	Population	N	Key findings	Survival	Prognostic factors
Pichlmayr et al. [99]	Retrospective study (historical) Single center 1980–1993	LT and LR for iCCA	18 LT	LR is indicated in resectable situations. LT for unresectable lesions seems not to be indicated unless adjuvant protocols appear promising	mOS = 12.8 months after LR, = 5.0 months after LT. Longest survival after transplantation was 25 months. After LR 4 patients survived >5 years. 1-year OS = 13.9% after LT.	Surival: Tumor size, tumor stage
Weimann et al. [100]	Retrospective cohort study Single center 1978–1996	LT and LR for CCA	162 (24 LT)	Therapeutic efforts should therefore be directed towards achieving resectability. Data rule out LT as a treatment option for advanced unresectable CCC	1-, 2- and 5-year survival rates after LR (resectable tumors) = 64%, 43% and 21%, after LT = 21%, 8% and 0%	Survival: Age, jaundice, N and M category, and UICC tumour stage (tumor number, tumor size, treatment modality, vascular invasion, CEA)
Hong et al. [89]	Single-center retrospective Single center (UCLA) 1985–2009	LT vs. resection in locally advanced iCCA/ pCCA	57 (38 LT, 19 LR)	LT associated with neoadjuvant and adjuvant therapies is superior to LR with adjuvant therapy in locally advanced iCCA and pCCA	5-year RFS 33% after LT. 5-year OS after neoadjuvant and adjuvant therapies = 47%, with no therapy 20%, with adjuvant therapy only 33%	Survival: hilar CCA (vs. intrahepatic), multifocal tumors, perineural invasion, treatment modality (resection vs. LT), adjuvant and/or neoadjuvant therapy
Hong et al. [90]	Single-center retrospective 1985–2010	Recurrence after LT for iCCA/pCCA	40	Model highly predictive of long term outcomes according to risk stratification after LT for locally advanced iCCA and pCCA	5-year RFS was significantly higher in low-risk (78%) compared with intermediate- (19%) and high-risk (0%) groups	Recurrence: Multifocal tumor, perineural invasion, infiltrative growth pattern, lack of neoadjuvant and adjuvant therapy, history of primary, and sclerosing cholangitis
Sapisochin et al. [83]	Multicenter retrospective cohort study 16 centers (Spain) 2000–2010	LT for incidental CCA/ HCC-CC	42	Patients with uninodular tumors 2 cm or smaller had similar OS compared to HCC	Patients with uninodular tumors 2 cm or smaller had similar 1-, 3-, and 5-year survival rate (92%, 83%, 62% vs. 100%, 80%, 80%; P = 0.4)	
Sapisochin et al.2016 [84]	Multicenter retrospective cohort study 17 centers 2000–2013	LT for very early CCA (incidental or not)	81	Favorable long-term survival after LT for very early intrahepatic cholangiocarcinoma (≤2 cm)	1-, 3-, and 5-year recurrence risk 7%, 18%, and 18% in very early iCCA, 30%, 47%, and 61% in advanced iCCA. 1-, 3-, and 5-year OS 93%, 84%, and 65% in very early iCCA, 79%, 50%, and 45% in advanced iCCA	Recurrence: Microvascular invasion, poor differentiation, tumor size, advanced stage, out of UCSF criteria

(*Continued*)

TABLE 5 Continued

Authors	Study design	Population	N	Key findings	Survival	Prognostic factors
Jung et al. [101]	Retrospective cohort study Single center 2003–2014	LT and LR for incidental iCCA	16 LT, 100 LR	The prognosis of incidentally detected ICC following LT is as poor as that following LR.	1-, 3-, and 5-year recurrence rates = 56.2%, 56.2%, and 78.1%. 1-, 3-, and 5-year OS rates were 81.3%, 52.4%, and 52.4%	
Lunsford et al. [92]	Prospective case series Single center (MD Anderson) 2010–2017	Neoadjuvant therapy followed by LT for locally advanced iCCA	6	Selected patients with locally advanced iCCA who show pre-transplant disease stability on neoadjuvant therapy might benefit from liver transplantation	1-, 3-, 5-year OS = 100%, 83.3%, and 83.3%. Median RFS of 7.6 months after LT. 1-, 3- and 5-year RFS = 50%	
De Martin et al. [88]	Multicenter retrospective cohort study 3 centers (France) 2002–2015	LT vs. LR for CCA in cirrhosis	75	LT may offer a benefit for highly selected patients with cirrhosis and unresectable iCCA/cHCC-CCA having tumors ≤5 cm	5-year RFS = 75%, 5-year OS = 69% in patients with tumors ≤2 cm and and 65% in patients with tumors >2–5 cm	Recurrence: Tumor size, tumor differentiation, resection (vs. LT)
Ziogas et al. [85]	Meta-analysis 18 studies	LT for iCCA	355	Cirrhotics with very early iCCA or carefully selected patients with advanced iCCA after neoadjuvant therapy may benefit from LT	1-, 3-, and 5-year OS rates = 75%, 56%, and 42%. 1-, 3-, and 5-year RFS rates = 70%, 49%, and 38%. Recurrence rate = 43%	Recurrence: Cirrhosis (protective)
Hara et al. [96]	Multicenter retrospective 45 centers (Japan) 2001–2015	Incidental iCCA in LDLT	19	Incidental iCCA at LT is associated with a high risk of recurrence and poor prognosis	1-, 3-, and 5-year RFS rates = 79%, 45%, and 45%. Tumor recurrence after LT = 53%. 1-, 3-, and 5-year OS rates = 79%, 63%, and 46%	
Hue et al. [102]	Retrospective registry study cohort Multicenter (national cancer database) 2010–2016	LT and LR for incidental iCCA	1879 LR, 74 LT	LR and LT were associated with similar postoperative outcomes and survival. Hepatectomy is preferable for localized ICC.	1-, 3-, 5-year OS after LT = 89.4%, 53.0,% 40.8%. 1-, 3-, 5-year OS after LR = 82.6%, 50.2%, 33.0%	
Ito et al. [91]	Single-center retrospective Single center (UCLA) 1985–2019	LT for iCCA/pCCA	19 pCCA, 30 iCCA	Multimodal NAT is associated with improved survival in LT for both iCCA and hCCA regardless of tumor size	5-year OS after LT (2008–2019) for pCCA = 88% with NCT, 9% without NCT, for iCCA = 100% with NCT, 41% without NCT.	Survival: Neoadjuvant treatment, era of treatment, multifocal tumors, grading
McMillan et al. [93]	Retrospective cohort Single center (MD Anderson) 2010–2021	MD Anderson LT protocol for locally advanced iCCA	18	LT could be a treatment for highly selected patients with locally advanced, unresectable iCCA, after NCT with disease stability for at least 6 months	1-, 3-, and 5-year OS = 100%, 71%, and 57%. 1-, 3-year RFS = 70% and 52%	

(*Continued*)

TABLE 5 Continued

Authors	Study design	Population	N	Key findings	Survival	Prognostic factors
Kim et al. [103]	Retrospective Multicenter (national cancer database) 2004–2016	LT and LR for incidental iCCA	66	LT is effective in select patients with localized iCCA. No difference in OS and RFS between LT and LR.	5-year OS after LT = 36.1%, after LR = 32.7%, after CT alone = 5.3%	
Lee et al. [104]	Multicenter (database) 2004–2018	Disparities in treatment for early iCCA	62 LT	LT had a trend toward improved OS compared to LR.	1-, 3-, and 5-year OS after LT = 88.9%, 72.9% and 67.9% (95% CI: 55.8%–82.5%)	
Huang et al. [106]	Retrospective, Multicenter, SEER database analysis 2000–2019	LT for iCCA vs. LR for iCCA vs. LT for HCC	113 LT; 2425 LR; 5048 LT HCC	Patients with ICC after LT had a better prognosis than those after LR but inferior to HCC after LT	5-y OS: LT iCCA = 52.8%, LR iCCA = 29.9%; LT iCCA = 61.7% in patients with local advanced ICC after NCT.	
Howell et al. [105]	Multicenter (national cancer database; UNOS STAR) 2010–2018	LT and LR for iCCA	153 LT	LR remains the standard of care for patients with resectable disease. Highly selected patients with unresectable iCCA may achieve favorable outcomes after LT.	5-year OS after LT = 59.8%, after LR = 39.9%. mOS after LT = 105.7 months	Survival: older age, other race (vs. White), stage II and III disease (vs. stage I), and presence of comorbidities, receiving surgery at an academic center, more recent year of diagnosis

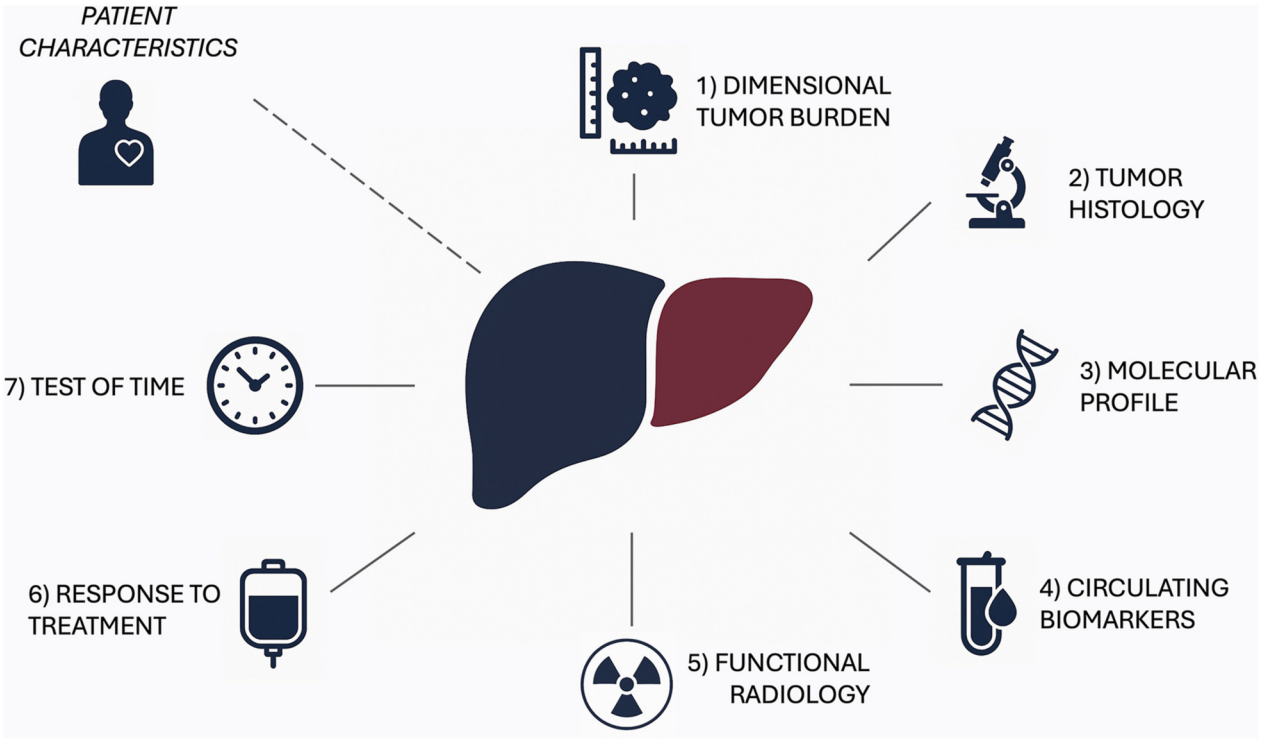


FIGURE 4
The seven pillars of biological aggressiveness.

Circulating biomarkers and liquid biopsy

Ca19-9 is elevated in 60%–80% [19, 119] of cases, and its diagnostic accuracy is limited by false positives in biliary obstruction and cholangitis. High preoperative and postoperative values of CA19-9, particularly when associated with increased carcinoembryonic antigen (CEA), are linked with advanced disease and worse OS and RFS [120–122]. On the contrary, a >50% reduction in CA19-9 after systemic therapy is strongly associated with radiologic response [120] and improved survival, and could serve as therapeutic objective.

Liquid biopsy is a non-invasive technique [2, 123] enabling detection of circulating tumor-derived material, including circulating tumor cells, ctDNA, ctRNA, microRNAs, and extracellular vesicles. ctDNA has emerged as a key biomarker for genomic profiling and tumor burden assessment [123–125], showing high concordance with tissue mutation profiles [126–128], with variant allele frequencies correlating with tumor load and supporting its role as a dynamic indicator of disease status [124, 129, 130]. ctDNA is detectable across all disease stages and carries prognostic value, with ctDNA-positive patients showing poorer progression-free survival both pre- and postoperatively. During surveillance, ctDNA detection is associated with significantly worse relapse-free survival and identifies recurrence in 93.8% of cases, with a mean lead time of 3.7 months over imaging [131].

Bile-derived cfDNA appears particularly promising due to direct tumor contact, detecting driver mutations in 54% of cases compared with 17% in plasma [132, 133].

However, limitations include lower sensitivity for gene fusions compared with tissue RNA-based assays, variability in ctDNA shedding depending on tumor burden and site, lack of standardization in extraction methods, platforms and timing, need for prospective interventional validation, and cost and reimbursement issues [123–125]. ctDNA remains complementary rather than a replacement for tissue testing, increasing actionable variant detection by 14.3% when used concurrently, and is particularly valuable when tissue is insufficient, unavailable, or when rapid or serial assessment is required [126, 128, 134].

Functional radiology

Radiomics-based machine learning shows excellent diagnostic accuracy [135, 136] in CCA, particularly when integrated into clinical–radiomic models [137], often achieving performance comparable to postoperative pathology. Its main strength lies in improving diagnosis and preoperative prediction of microvascular invasion [138–140], gene mutations, perineural invasion [141], and lymph node metastasis [142, 143]. This stratification may guide surgical decision-making and enable prediction of early recurrence [144, 145] and survival [146]. Emerging deep learning models enable multimodal integration of radiology, pathology, and molecular data, but remain limited by data heterogeneity, poor interpretability, lack of standardization, and the need for prospective multicenter validation. Despite expert-level performance, clinical translation is hindered by regulatory constraints, cost sustainability, algorithmic bias, and insufficient validation [137, 147, 148].

Functional and metabolic assessment could provide useful insights as shown in CRLM transplantation setting [149]. PET is not recommended [48] for tumor diagnosis due to limited accuracy, but shows good performance in detecting lymph node and distant metastases [150–154]. SUVmax is an independent prognostic factor for disease-free and overall survival [155–159]. While 18F-FDG PET/CT is established for detecting metastatic disease and recurrence with high specificity, PET/MRI provides superior staging accuracy, particularly for T and N staging [160–162]. A new tracer 68Ga-FAPI PET/CT, targeting cancer-associated fibroblasts in the tumor microenvironment, shows high positive predictive value, high detection rates and better outcomes compared to 18F-FDG in terms of detection of primary tumors, lymph nodes, and distant metastases [163–168].

Response to therapy and test of time

Integrating the patient's clinical trajectory into the selection algorithm provides a longitudinal perspective on disease behavior [169]. The "test of time" itself reflects an indolent tumor biology, characterized by disease confinement within the liver and the absence of systemic or circulating tumor spread. Similarly, response to therapy serves as a surrogate marker of favorable tumor biology and informs postoperative management, as patients who respond to treatment before transplantation are more likely to maintain therapeutic sensitivity thereafter. For these reasons, as in the setting of CRLM [170], these principles have been incorporated into most modern neoadjuvant protocols, emphasizing refined patient selection over procedural acceleration [39, 93].

Conclusion

Liver transplantation for cholangiocarcinoma has evolved from contraindication to a viable option in highly selected patients, with outcomes comparable to other oncologic indications when strict criteria are applied. Interpretation of the available evidence is limited by the predominance of retrospective studies, small and highly selected cohorts, and significant heterogeneity in neoadjuvant strategies and selection criteria across centers. In addition, most data derive from highly specialized institutions reporting limited case volumes over prolonged periods, and prospective validation of emerging biomarkers remains scarce, further restricting the generalizability of current findings. Evidence indicates that prognosis is driven primarily by tumor biology, response to therapy, and disease stability rather than anatomical factors alone. While standardized protocols define current practice in pCCA and selected indications are emerging in iCCA, recurrence risk, dropout rates, and organ scarcity remain major limitations.

The field is shifting toward a multiparametric, biology-driven model of transplantability integrating clinical, radiologic, and molecular data, although prospective validation is still required. We envision a future in which patient selection is guided by an integrated assessment of validated morpho-biologic prognostic parameters together with general preoperative predictors emerging from the pretransplant evaluation. The development of such complex "transplantability patterns", rather than simplistic in/out criteria, will be crucial and will most likely be co-piloted by AI-based decision support. Overall, future progress will depend on refining selection, validating ongoing trials, and balancing oncologic benefit with equitable graft allocation. At the same time, the potential for an increase of oncologic indications for

LT enhances competition for the limited organ supply [171]. To address this, further efforts should be made on expanding the donor pool through extended-criteria donors, LDLT and techniques of liver splitting and graft mitigation/manipulation [71, 72, 172–174].

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. The authors acknowledge the use of ChatGPT (OpenAI, GPT-5) for language editing and stylistic refinement of the manuscript, as well as for the generation of illustrative images. All AI-assisted outputs were carefully reviewed, verified, and, where necessary, modified by the authors to ensure accuracy and appropriateness. The authors take full responsibility for the content of the manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2026.15786/full#supplementary-material

References

1. Allkushi E, Wehrle CJ, Kim JK, Khalil M, Kwon DCH, Fujiki M, et al. Expanding indications in transplant oncology. *Cancers (Basel)* (2025) 17(5):773. doi:10.3390/cancers17050773

2. Karageorgos FF, Karakasi KE, Kofinas A, Antoniadis N, Katsanos G, Tsoulfas G. Evolving transplant oncology: evolving criteria for better decision-making. *Diagnostics* (2025) 15(7):820. doi:10.3390/diagnostics15070820

3. Krendl FJ, Bellotti R, Sapisochin G, Schaefer B, Tilg H, Scheidl S, et al. Transplant oncology –Current indications and strategies to advance the field. *JHEP Rep*. (2023). 6(2):100965. doi:10.1016/j.jhepr.2023.100965

4. European Association for the Study of the Liver. EASL-ILCA clinical practice guidelines on he management of intrahepatic cholangiocarcinoma. *J Hepatol*. (2023) 79(1):181–208. doi:10.1016/j.jhep.2023.03.010

5. Vogel A, Bridgewater J, Edeline J, Kelley RK, Klümpen HJ, Malka D, et al. Biliary tract cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up ☆. *Ann Oncol* (2023) 34(2):127–40. doi:10.1016/j.annonc.2022.10.506

6. Pfister M, Ratti F, Gores GJ, Lesurtel M, Chiche L, Ebata T, et al. Recommendations on perihilar cholangiocarcinoma. The milan jury-based consensus. *Ann Surg* (2025). doi:10.1097/SLA.0000000000006773

7. Sapisochin G, Hibi T, Toso C, Man K, Berenguer M, Heimbach J, et al. Transplant oncology in primary and metastatic liver tumors: principles, evidence, and opportunities. *Ann Surg* (2021) 273(3):483–93. doi:10.1097/SLA.0000000000004071

8. Hibi T, Rela M, Eason JD, Line PD, Fung J, Sakamoto S, et al. Liver transplantation for colorectal and neuroendocrine liver metastases and hepatoblastoma. Working group report from the ILTS transplant oncology consensus conference. *Transplantation* (2020) 104(6):1131–5. doi:10.1097/TP.0000000000003118

9. Adam R, Piedvache C, Chiche L, Adam JP, Salamé E, Bucur P, et al. Liver transplantation plus chemotherapy versus chemotherapy alone in patients with permanently unresectable colorectal liver metastases (TransMet): results from a multicentre, open-label, prospective, randomised controlled trial. *The Lancet* (2024) 404(10458):1107–18. doi:10.1016/S0140-6736(24)01595-2

10. Cillo U, Gringeri E, D'Amico FE, Lanari J, Furlanetto A, Vitale A. Hepatocellular carcinoma: revising the surgical approach in light of the concept of multiparametric therapeutic hierarchy. *Dig Liver Dis* (2025) 57(4):809–18. doi:10.1016/j.dld.2024.12.003

11. Banales JM, Marin JJG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* (2020) 17(9):557–88. doi:10.1038/s41575-020-0310-z

12. Vithayathil M, Khan SA. Current epidemiology of cholangiocarcinoma in Western countries. *J Hepatol* (2022) 77(6):1690–8. doi:10.1016/j.jhep.2022.07.022

13. Rimassa L, Lamarca A, O'Kane GM, Edeline J, McNamara MG, Vogel A, et al. New systemic treatment paradigms in advanced biliary tract cancer and variations in patient access across Europe. *The Lancet Reg Health - Europe* (2025) 50:101170. doi:10.1016/j.lanepe.2024.101170

14. Malik AK, Davidson BR, Manas DM. Surgical management, including the role of transplantation, for intrahepatic and peri-hilar cholangiocarcinoma. *Eur J Surg Oncol* (2025) 51(2):108248. doi:10.1016/j.ejso.2024.108248

15. Esmail A, Badheeb M, Alnahar B, Almiqlash B, Sakr Y, Khasawneh B, et al. Cholangiocarcinoma: the current status of surgical options including liver transplantation. *Cancers (Basel)* (2024) 16(11):1946. doi:10.3390/cancers16111946

16. Kodali S, Kulik L, D'Allessio A, De Martin E, Hakeem AR, Lewinska M, et al. The 2024 ILTS-ILCA consensus recommendations for liver transplantation for HCC and intrahepatic cholangiocarcinoma. *Liver Transplant* (2025) 31(6):815–31. doi:10.1097/LVT.0000000000000589

17. Connor AA, Kodali S, Abdelrahim M, Javle MM, Brombosz EW, Ghobrial RM. Intrahepatic cholangiocarcinoma: the role of liver transplantation, adjunctive treatments, and prognostic biomarkers. *Front Oncol* (2022) 12:996710. doi:10.3389/fonc.2022.996710

18. Cillo U, Fondevila C, Donadon M, Gringeri E, Mocchegiani F, Schlitt HJ, et al. Surgery for cholangiocarcinoma. *Liver Int* (2019) 39(Suppl. 1):143–55. doi:10.1111/LIV.14089

19. Izquierdo-Sanchez L, Lamarca A, La Casta A, Buettner S, Utpatel K, Klümpen HJ, et al. Cholangiocarcinoma landscape in Europe: diagnostic, prognostic and therapeutic insights from the ENSCCA registry. *J Hepatol* (2022) 76(5):1109–21. doi:10.1016/j.jhep.2021.12.010

20. Alaimo L, Endo Y, Catalano G, Ruzzenente A, Aldrighetti L, Weiss M, et al. Benchmarks in liver resection for intrahepatic cholangiocarcinoma. *Ann Surg Oncol* (2024) 31(5):3043–52. doi:10.1245/s10434-023-14880-8

21. Mueller M, Breuer E, Mizuno T, Bartsch F, Ratti F, Benzing C, et al. Perihilar cholangiocarcinoma – novel benchmark values for surgical and oncological outcomes from 24 expert centers. *Ann Surg* (2021) 274(5):780–8. doi:10.1097/SLA.0000000000005103

22. Cillo U, Furlanetto A, Nieddu E, Polacco M, Boetto R, Bassi D, et al. Ante situm liver surgery using machine perfusion liver preservation: pilot human experience. *Br J Surg* (2021) 108:e235–e236. doi:10.1093/bjs/znab095

23. Cillo U, D'Amico FE, Furlanetto A, Perin L, Gringeri E. Robotic hepatectomy and biliary reconstruction for perihilar cholangiocarcinoma: a pioneer western case series. *Updates Surg Springer Sci Business Media Deutschland GmbH* (2021) 73(3):999–1006. doi:10.1007/s13304-021-01041-3

24. Weigt J, Malfertheiner P. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *Expert Rev Gastroenterol Hepatol* (2010) 4(4):395–7. doi:10.1586/egh.10.45

25. Oh DY, Ruth He A, Qin S, Chen LT, Okusaka T, Vogel A, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. *NEJM Evid* (2022) 1(8):EVIDoa2200015. doi:10.1056/evidoa2200015

26. Li Z, Aliseda D, Jones O, Rajendran L, Magyar C, Grant R, et al. Recent advances in systemic therapy for advanced biliary tract cancer: a systematic review and meta-analysis using reconstructed RCT survival data. *JHEP Rep* (2025) 7(3):101290. doi:10.1016/j.jhepr.2024.101290

27. Oh DY, He AR, Bouattour M, Okusaka T, Qin S, Chen LT, et al. Durvalumab or placebo plus gemcitabine and cisplatin in participants with advanced biliary tract cancer (TOPAZ-1): updated overall survival from a randomised phase 3 study. *Lancet Gastroenterol Hepatol* (2024) 9(8):694–704. doi:10.1016/S2468-1253(24)00095-5

28. Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet* (2023) 401(10391):1853–65. doi:10.1016/S0140-6736(23)00727-4

29. Wilbur HC, Soares HP, Azad NS. Neoadjuvant and adjuvant therapy for biliary tract cancer: advances and limitations. *Hepatology* (2024) 82:1287–302. doi:10.1097/HEP.0000000000000760

30. Goetze TO, Vogel A, Pratschke J, Behrend M, Reim D, Schnitzbauer AA, et al. Neoadjuvant chemotherapy with gemcitabine plus cisplatin followed by radical liver resection versus immediate radical liver resection alone followed adjuvant therapy in biliary tract cancer: final results from the phase III AIO/CALGP/ACO-GAIN-Trial. *J Clin Oncol* (2025) 43(16_Suppl. l):4008. doi:10.1200/JCO.2025.43.16_SUPPL.4008

31. Ratti F, Marino R, Olthof PB, Pratschke J, Erdmann JI, Neumann UP, et al. Predicting futility of upfront surgery in perihilar cholangiocarcinoma: machine learning analytics model to optimize treatment allocation. *Hepatology* (2024) 79(2):341–54. doi:10.1097/HEP.0000000000000554

32. Bhat M, Hathcock M, Kremers WK, Darwish Murad S, Schmit G, Martenson J, et al. Portal vein encasement predicts neoadjuvant therapy response in liver transplantation for perihilar cholangiocarcinoma protocol. *Transpl Int* (2015) 28(12):1383–91. doi:10.1111/tri.12640

33. Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation* (2000) 69(8):1633–7. doi:10.1097/00007890-200004270-00019

34. Robles R, Figueras J, Turrión VS, Margarit C, Moya A, Varo E, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. *Ann Surg* (2004) 239(2):265–71. doi:10.1097/01.sla.0000108702.45715.81

35. Seehofer D, Thelen A, Neumann UP, Veltzke-Schlieker W, Denecke T, Kamphues C, et al. Extended bile duct resection and [corrected] liver and transplantation in patients with hilar cholangiocarcinoma: long-term results. *Liver Transpl* (2009) 15(11):1499–507. doi:10.1002/lt.21887

36. Ghali P, Marotta PJ, Yoshida EM, Bain VG, Marleau D, Peltekian K, et al. Liver transplantation for incidental cholangiocarcinoma: analysis of the Canadian experience. *Liver Transpl* (2005) 11(11):1412–6. doi:10.1002/lt.20512

37. Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Nyberg SL, Ishitani MB, et al. Liver transplantation for unresectable perihilar cholangiocarcinoma. *Semin Liver Dis* (2004) 24(2):201–7. doi:10.1055/s-2004-828896

38. Rosen CB, Heimbach JK, Gores GJ. Liver transplantation for cholangiocarcinoma. *Transpl Int* (2010) 23(7):692–7. doi:10.1111/j.1432-2277.2010.01108.x

39. Gringeri E, Furlanetto A, Billato I, Cescon M, De Carlis L, Mazzaferro V, et al. The Italian experience on liver transplantation for unresectable peri-hilar cholangiocarcinoma: a national survey and future perspectives. *Updates Surg* (2024) 76(7):2505–13. doi:10.1007/s13304-024-01889-1

40. Heimbach JK, Sanchez W, Rosen CB, Gores GJ. Trans-peritoneal fine needle aspiration biopsy of hilar cholangiocarcinoma is associated with disease dissemination. *Hpb* (2011) 13(5):356–60. doi:10.1111/j.1477-2574.2011.00298.x

41. Darwish MS, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology* (2012) 143(1):88–98. doi:10.1053/j.gastro.2012.04.008

42. Tan EK, Taner T, Heimbach JK, Gores GJ, Rosen CB. Liver transplantation for perihilar cholangiocarcinoma. *J Gastrointest Surg* (2020) 24(11):2679–85. doi:10.1007/s11605-020-04721-4

43. Cambridge WA, Fairfield C, Powell JJ, Harrison EM, Søreide K, Wigmore SJ, et al. Meta-analysis and meta-regression of survival after liver transplantation for unresectable perihilar cholangiocarcinoma. *Ann Surg* (2021) 273(2):240–50. doi:10.1097/SLA.0000000000003801

44. Mantel HTJ, Westerkamp AC, Adam R, Bennet WF, Seehofer D, Settmacher U, et al. Strict selection alone of patients undergoing liver transplantation for hilar cholangiocarcinoma is associated with improved survival. *PLoS One* (2016) 11(6):e0156127. doi:10.1371/journal.pone.0156127

45. Hoogwater FJH, Kuipers H, De Meijer VE, Maulat C, Muscari F, Polak WG, et al. Role of neoadjuvant chemoradiotherapy in liver transplantation for unresectable perihilar cholangiocarcinoma: Multicentre, retrospective cohort study. *BJS Open* (2023) 7(2):1–8. doi:10.1093/bjsopen/zrad025

46. Dong Y, Li Z, Podrascanin V, Eaton JE, Ilyas SI, Gores GJ, et al. Liver resection with and without vascular resection versus transplantation for *de novo* perihilar cholangiocarcinoma. *Hepatology* (2025) 83:1128–42. doi:10.1097/HEP.0000000000001449

47. Mantel HTJ, Rosen CB, Heimbach JK, Nyberg SL, Ishitani MB, Andrews JC, et al. Vascular complications after orthotopic liver transplantation after neoadjuvant therapy for hilar cholangiocarcinoma. *Liver Transpl* (2007) 13(10):1372–81. doi:10.1002/lt.21107

48. Bowlus CL, Arrivé L, Bergquist A, Deneau M, Forman L, Ilyas SI, et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. *Hepatology* (2023) 77(2):659–702. doi:10.1002/HEP.32771

49. Jansson H, Olthof PB, Bergquist A, Ligthart MAP, Nadalin S, Troisi RI, et al. Outcome after resection for perihilar cholangiocarcinoma in patients with primary sclerosing cholangitis: an international multicentre study. *HPB* (2021) 23(11):1751–8. doi:10.1016/j.hpb.2021.04.011

50. Are C, Dhir M, Ravipati L. History of pancreaticoduodenectomy: early misconceptions, initial milestones and the pioneers. *HPB* (2011) 13(6):377–84. doi:10.1111/j.1477-2574.2011.00305.x

51. Miyagawa S, Makuuchi M, Kawasaki S, Hayashi K, Harada H, Kitamura H, et al. Outcome of major hepatectomy with pancreatoduodenectomy for advanced biliary malignancies. *World J Surg* (1996) 20(1):77–80. doi:10.1007/s002689900014

52. Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, Nimura Y, et al. Hepatopancreatoduodenectomy for cholangiocarcinoma: a single-center review of 85 consecutive patients. *Ann Surg* (2012) 256(2):297–305. doi:10.1097/SLA.0b013e31826029ca

53. Ishii T, Seo S, Ito T, Ogiso S, Fukumitsu K, Masui T, et al. Liver transection-first approach in hepatopancreatoduodenectomy for hilar cholangiocarcinoma: a safe and secure technique for the early assessment of curable resection and vascular reconstruction. *Ann Surg Oncol* (2021) 28(6):2988–9. doi:10.1245/s10434-020-09303-x

54. Chiba N, Abe Y, Yokozuka K, Hikita K, Kobayashi T, Sano T, et al. Surgical technique of pancreatic parenchyma transection-delayed approach (PPTDA) in hepatopancreatoduodenectomy for hilar cholangiocarcinoma. *J Gastrointest Surg* (2019) 23(3):613–6. doi:10.1007/s11605-018-3923-6

55. Yoshimi Y, Noji T, Okamura K, Tanaka K, Matsui A, Nakanishi Y, et al. The Short- and long-term surgical results of consecutive hepatopancreaticoduodenectomy for wide-spread biliary malignancy. *Ann Surg Oncol* (2023) 31(1):90–6. doi:10.1245/s10434-023-14406-2

56. Sugiura T, Ohgi K, Ashida R, Yamada M, Kato Y, Otsuka S, et al. Hepatopancreatoduodenectomy for extrahepatic cholangiocarcinoma: a series of 100 consecutive cases from an expert center in Japan. *Ann Surg Oncol* (2025) 32(9):6531–40. doi:10.1245/s10434-025-17515-2

57. Shimizu A, Motoyama H, Kubota K, Notake T, Fukushima K, Ikehara T, et al. Safety and oncological benefit of hepatopancreatoduodenectomy for advanced extrahepatic cholangiocarcinoma with horizontal tumor spread: shinshu university experience. *Ann Surg Oncol* (2021) 28(4):2012–25. doi:10.1245/s10434-020-09209-8

58. Endo I, Hirahara N, Miyata H, Yamamoto H, Matsuyama R, Kumamoto T, et al. Mortality, morbidity, and failure to rescue in hepatopancreatoduodenectomy: an analysis of patients registered in the national clinical database in Japan. *J Hepatobiliary Pancreat Sci* (2021) 28(4):305–16. doi:10.1002/jhbp.918

59. Kiritani S, Kawaguchi Y, Nishioka Y, Mihara Y, Ichida A, Takamoto T, et al. Long-term outcomes of hepatopancreatoduodenectomy for perihilar cholangiocarcinoma: a comparative study with conventional hepatectomy. *Eur J Surg Oncol* (2025) 51(5):109633. doi:10.1016/j.ejso.2025.109633

60. Yasukawa K, Shimizu A, Kubota K, Notake T, Hosoda K, Sakai H, et al. Reassessing the role of hepatopancreatoduodenectomy in advanced biliary tract cancer: a systematic review and single-arm meta-analysis of modern case series. *Ann Surg Oncol* (2026) 33(2):1515–25. doi:10.1245/s10434-025-18665-z

61. Aoki T, Sakamoto Y, Kohno Y, Akamatsu N, Kaneko J, Sugawara Y, et al. Hepatopancreaticoduodenectomy for biliary cancer: strategies for near-zero operative mortality and acceptable long-term outcome. *Ann Surg* (2018) 267(2):332–7. doi:10.1097/SLA.0000000000002059

62. Welch JC, Gleeson EM, Karachristos A, Pitt HA. Hepatopancreatoduodenectomy in North America: are the outcomes acceptable? *HPB* (2020) 22(3):360–7. doi:10.1016/j.hpb.2019.08.010

63. D'Souza MA, Valdimarsson VT, Campagnaro T, Cauchy F, Chatzizacharias NA, D'Hondt M, et al. Hepatopancreatoduodenectomy –a controversial treatment for bile duct and gallbladder cancer from a European perspective. *HPB* (2020) 22(9):1339–48. doi:10.1016/j.hpb.2019.12.008

64. Stauffer JA, Steers JL, Bonatti H, Dougherty MK, Aranda-Michel J, Dickson RC, et al. Liver transplantation and pancreatic resection: a single-center experience and a review of the literature. *Liver Transpl* (2009) 15(12):1728–37. doi:10.1002/lt.21932

65. Soejima Y, Ueda S, Sanefuji K, Kayashima H, Yoshizumi T, Ikegami T, et al. Sequential pancreaticoduodenectomy after living donor liver transplantation for cholagiocacinoma. *Am J Transplant* (2008) 8(10):2158–62. doi:10.1111/j.1600-6143.2008.02346.x

66. Varotti G, Gondolesi GE, Roayaie S, Suriawinata A, Soltys K, Fishbein TM, et al. Combined adult-to-adult living donor right lobe liver transplantation and pancreatoduodenectomy for distal bile duct adenocarcinoma in a patient with primary sclerosing cholangitis. *J Am Coll Surg* (2003) 197(5):765–9. doi:10.1016/j.jamcollsurg.2003.06.001

67. Gringeri E, Bassi D, D'Amico FE, Boetto R, Polacco M, Lodo E, et al. Neoadjuvant therapy protocol and liver transplantation in combination with

pancreatoduodenectomy for the treatment of hilar cholangiocarcinoma occurring in a case of primary sclerosing cholangitis: case report with a more than 8-year disease-free surviva. *Transpl Proc* (2011) 43(4):1187–9. doi:10.1016/j.transproceed.2011.01.140

68. Wu Y, Johlin FC, Rayhill SC, Jensen CS, Xie J, Cohen MB, et al. Long-term, tumor-free survival after radiotherapy combining hepatectomy-whipple *en bloc* and orthotopic liver transplantation for early-stage hilar cholangiocarcinoma. *Liver Transplant* (2008) 14(3):279–86. doi:10.1002/lt.21287

69. Moon DB, Lee SG, Kim KH. Total hepatectomy, pancreatoduodenectomy, and living donor liver transplantation using innovative vascular reconstruction for unresectable cholangiocarcinoma. *Transpl Int* (2015) 28(1):123–6. doi:10.1111/tri.12401

70. Ito T, Taura K, Fukumitsu K, Okumura S, Ogiso S, Anazawa T, et al. Safety and efficacy of living donor liver transplantation for unresectable perihilar cholangiocarcinoma: a single center prospective study. *J Hepatobiliary Pancreat Sci* (2025) 32(4):276–86. doi:10.1002/jhbp.12121

71. Cillo U, Furlanetto A, Gringeri E, Bertacco A, Marchini A, Rosso E, et al. Advocating for a " shift - to - left " in transplant oncology: left grafts, RAPID and dual graft. *Updates Surg* (2024) 77(0123456789):1889–902. doi:10.1007/s13304-024-01919-y

72. Gringeri E, Furlanetto A, Polacco M, Perin L, Nieddu E, Rosso E, et al. Exploring auxiliary liver transplantation in the era of transplant oncology-A proposal for a new liver splitting program (ALERT-50). *Liver Transpl* (2025) 31(9):1176–82. doi:10.1097/LVT.0000000000000574

73. Tan EK, Rosen CB, Heimbach JK, Gores GJ, Zamora-Valdes D, Taner T. Living donor liver transplantation for perihilar cholangiocarcinoma: outcomes and complications. *J Am Coll Surg* (2020) 231(1):98–110. doi:10.1016/j.jamcollsurg.2019.12.037

74. Moris D, Kostakis ID, Machairas N, Prodromidou A, Tsilimigras DI, Ravindra KV, et al. Comparison between liver transplantation and resection for hilar cholangiocarcinoma: a systematic review and meta-analysis. *PLoS One* (2019) 14(7):1–13. doi:10.1371/journal.pone.0220527

75. Breuer E, Mueller M, Doyle MB, Yang L, Darwish Murad S, Anwar IJ, et al. Liver transplantation as a new standard of care in patients with perihilar cholangiocarcinoma? Results from an international benchmark study. *Ann Surg* (2022) 276(5):846–53. doi:10.1097/SLA.0000000000005641

76. Muller X, Marcon F, Sapisochin G, Marquez M, Dondero F, Rayar M, et al. Defining benchmarks in liver transplantation: a multicenter outcome analysis determining best achievable results. *Ann Surg* (2018) 267(3):419–25. doi:10.1097/SLA.0000000000002477

77. Gringeri E, Furlanetto A, Nieddu E, Romagnoli R, Gruttadauria S, Ghinolfi D, et al. From clinical heterogeneity to national standardization in liver transplantation for perihilar cholangiocarcinoma: the LITALHICA protocol. *Transplantation* (2026). in press.

78. Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Pedersen R, Kremers W, et al. Predictors of disease recurrence following neoadjuvant chemoradiotherapy and liver transplantation for unresectable perihilar cholangiocarcinoma. *Transplantation* (2006) 82(12):1703–7. doi:10.1097/01.tp.0000253551.43583.d1

79. Murad SD, Kim WR, Therneau T, Gores GJ, Rosen CB, Martenson JA, et al. Predictors of pretransplant dropout and posttransplant recurrence in patients with perihilar cholangiocarcinoma. *Hepatology* (2012) 56(3):972–81. doi:10.1002/hep.25629

80. Croome KP, Rosen CB, Heimbach JK, Nagorney DM. Is liver transplantation appropriate for patients with potentially resectable *de novo* hilar cholangiocarcinoma? *J Am Coll Surg* (2015) 221(1):130–9. doi:10.1016/j.jamcollsurg.2015.01.064

81. Ethun CG, Lopez-Aguiar AG, Anderson DJ, Adams AB, Fields RC, Doyle MB, et al. Transplantation versus resection for hilar cholangiocarcinoma: an argument for shifting treatment paradigms for resectable disease. *Ann Surg* (2018) 267(5):797–805. doi:10.1097/SLA.0000000000002574

82. Zaborowski A, Heneghan HM, Fiore B, Stafford A, Gallagher T, Geoghegan J, et al. Neoadjuvant chemoradiotherapy and liver transplantation for unresectable hilar cholangiocarcinoma: the Irish experience of the Mayo protocol. *Transplantation* (2020) 104(10):2097–104. doi:10.1097/TP.0000000000003114

83. Sapisochin G, De Lope CR, Gastaca M, de Urbina JO, López-Andujar R, Palacios F, et al. Intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma in patients undergoing liver transplantation: a spanish matched cohort multicenter study. *Ann Surg* (2014) 259(5):944–52. doi:10.1097/SLA.0000000000000494

84. Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, et al. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: international retrospective study supporting a prospective assessment. *Hepatology* (2016) 64(4):1178–88. doi:10.1002/hep.28744

85. Ziogas IA, Giannis D, Economopoulos KP, Hayat MH, Montenovo MI, Matsuoka LK, et al. Liver transplantation for intrahepatic cholangiocarcinoma: a meta-analysis and meta-regression of survival rates. *Transplantation* (2021) 105(10):2263–71. doi:10.1097/TP.0000000000003539

86. Tham EKJ, Lim RY, Koh B, Tan DJH, Ng CH, Law M, et al. Prevalence of chronic liver disease in cholangiocarcinoma: a meta-analysis. *Clin Gastroenterol Hepatol* (2025) 23(10):1710–8. doi:10.1016/J.CGH.2024.09.028

87. Thakral N, Gonzalez T, Nano O, Shin SH, Samuels S, Hussein A. Cirrhosis in intrahepatic cholangiocarcinoma: prognostic importance and impact on survival. *BMC Gastroenterol* (2023) 23(1):151. doi:10.1186/S12876-023-02710-W

88. De Martin E, Rayar M, Golse N, Dupeux M, Gelli M, Gnemmi V, et al. Analysis of liver resection *versus* liver transplantation on outcome of small intrahepatic cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma in the setting of cirrhosis. *Liver Transplant* (2020) 26(6):785–98. doi:10.1002/lt.25737

89. Hong JC, Jones CM, Duffy JP, Petrowsky H, Farmer DG, French S, et al. Comparative analysis of resection and liver transplantation for intrahepatic and hilar cholangiocarcinoma: a 24-year experience in a single center. *Arch Surg* (2011) 146(6):683–9. doi:10.1001/ARCHSURG.2011.116

90. Hong JC, Petrowsky H, Kaldas FM, Farmer DG, Durazo FA, Finn RS, et al. Predictive index for tumor recurrence after liver transplantation for locally advanced intrahepatic and hilar cholangiocarcinoma. *J Am Coll Surg* (2011) 212(4):514–20. doi:10.1016/j.jamcollsurg.2010.12.005

91. Ito T, Butler JR, Noguchi D, Ha M, Aziz A, Agopian VG, et al. A 3-Decade, single-center experience of liver transplantation for cholangiocarcinoma: impact of era, tumor size, location, and neoadjuvant therapy. *Liver Transpl* (2022) 28(3):386–96. doi:10.1002/LT.26285

92. Lunsford KE, Javle M, Heyne K, Shroff RT, Abdel-Wahab R, Gupta N, et al. Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. *Lancet Gastroenterol Hepatol* (2018) 3(5):337–48. doi:10.1016/S2468-1253(18)30045-1

93. McMillan RR, Javle M, Kodali S, Saharia A, Mobley C, Heyne K, et al. Survival following liver transplantation for locally advanced, unresectable intrahepatic cholangiocarcinoma. *Am J Transplant* (2022) 22(3):823–32. doi:10.1111/ajt.16906

94. Kodali S, Connor AA, Thabet S, Brombosz EW, Ghobrial RM. Liver transplantation as an alternative for the treatment of intrahepatic cholangiocarcinoma: past, present, and future directions. *Hepatobiliary Pancreat Dis Int Elsevier (Singapore) Pte Ltd.* (2024) 23(2):129–38. doi:10.1016/j.hbpd.2023.07.007

95. Rauchfuß F, Ali-Deeb A, Rohland O, Dondorf F, Ardelt M, Settmacher U. Living donor liver transplantation for intrahepatic cholangiocarcinoma. *Curr Oncol* (2022) 29(3):1932–8. doi:10.3390/curroncol29030157

96. Hara T, Eguchi S, Yoshizumi T, Akamatsu N, Kaido T, Hamada T, et al. Incidental intrahepatic cholangiocarcinoma in patients undergoing liver transplantation: a multi-center study in Japan. *J Hepatobiliary Pancreat Sci* (2021) 28(4):346–52. doi:10.1002/JHBP.896

97. Hafeez Bhatti AB, Tahir R, Qureshi NR, Mamoon N, Khan NY, Zia HH. Living donor liver transplantation for intra hepatic cholangiocarcinoma. *Ann Med Surg* (2020) 57(June):82–4. doi:10.1016/j.amsu.2020.07.028

98. Sierra L, Barba R, Ferrigno B, Goyes D, Diaz W, Patwardhan VR, et al. Living-donor liver transplant and improved post-transplant survival in patients with primary sclerosing cholangitis. *J Clin Med* (2023) 12(8):2807. doi:10.3390/JCM12082807

99. Pichlmayl R, Lamesch P, Weimann A, Tusch G, Ringe B. Surgical treatment of cholangiocellular carcinoma. *World J Surg* (1995) 19(1):83–8. doi:10.1007/BF00316984

100. Weimann A, Varnholt H, Schlitt HJ, Lang H, Flemming P, Hustedt C, et al. Retrospective analysis of prognostic factors after liver resection and transplantation for cholangiocellular carcinoma. *Br J Surg* (2000) 87(9):1182–7. doi:10.1046/j.1365-2168.2000.01532.x

101. Jung DH, Hwang S, Song GW, Ahn CS, Moon DB, Kim KH, et al. Clinicopathological features and prognosis of intrahepatic cholangiocarcinoma after liver transplantation and resection. *Ann Transpl* (2017) 22:42–52. doi:10.12659/AOT.901504

102. Hue JJ, Rocha FG, Ammori JB, Hardacre JM, Rothermel LD, Chavin KD, et al. A comparison of surgical resection and liver transplantation in the treatment of intrahepatic cholangiocarcinoma in the era of modern chemotherapy: an analysis of the national cancer database. *J Surg Oncol* (2021) 123(4):949–56. doi:10.1002/jso.26370

103. Kim P, Littau M, Baker TB, Abdelsattar Z, Tonelli C, Bunn C, et al. Intrahepatic cholangiocarcinoma: is there a role for liver transplantation? *Surgery (United States)* (2022) 171(3):741–6. doi:10.1016/j.surg.2021.09.034

104. Lee YT, Singal AG, Lauzon M, Agopian VG, Luu M, Noureddin M, et al. Disparities in curative treatments and outcomes for early stage intrahepatic cholangiocarcinoma in the United States. *Cancer* (2022) 128(20):3610–9. doi:10.1002/cncr.34436

105. Howell TC, Rhodin KE, Shaw B, Bao J, Kanu E, Masoud S, et al. Contemporary trends and outcomes after liver transplantation and resection for intrahepatic cholangiocarcinoma. *J Gastrointest Surg* (2024) 28(5):738–45. doi:10.1016/j.gassur.2024.02.029

106. Huang G, Song W, Zhang Y, Yu J, Lv Y, Liu K. Liver transplantation for intrahepatic cholangiocarcinoma: a propensity score-matched analysis. *Sci Rep* (2023) 13(1):10630. doi:10.1038/s41598-023-37896-2

107. Yaqub S, Busund S, Smedman TM, Syversveen T, Khan A, Solheim JM, et al. Liver transplantation for locally advanced non-resectable intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: early results from the TESLA trial. *Br J Surg* (2025) 112(3):znaf054. doi:10.1093/bjs/znaf054

108. Maspero M, Sposito C, Bongini MA, Cascella T, Flores M, Maccauro M, et al. Liver transplantation for intrahepatic cholangiocarcinoma after chemotherapy and radioembolization: an intention-to-treat study. *Transpl Int* (2024) 37:13641. doi:10.3389/ti.2024.13641

109. Deeb M, Gangadhar A, Rabindranath M, Rao K, Brudno M, Sidhu A, et al. The emerging role of generative artificial intelligence in transplant medicine. *Am J Transplant* (2024) 24(10):1724–30. doi:10.1016/J.AJT.2024.06.009

110. Loupy A, Preka E, Chen X, Wang H, He J, Zhang K. Reshaping transplantation with AI, emerging technologies and xenotransplantation. *Nat Med* (2025) 31(7):2161–73. doi:10.1038/S41591-025-03801-9

111. Young SE, Sritharan R, Sia D. Genomic alterations in intrahepatic cholangiocarcinoma. *Hepatoma Res* (2023) 9(34):34. doi:10.20517/2394-5079.2023.37

112. Wang XY, Zhu WW, Wang Z, Huang JB, Wang SH, Bai FM, et al. Driver mutations of intrahepatic cholangiocarcinoma shape clinically relevant genomic clusters with distinct molecular features and therapeutic vulnerabilities. *Theranostics* (2022) 27(1): 260–76. doi:10.7150/THNO.63417

113. Sia D, Losic B, Moeini A, Cabellos L, Hao K, Revill K, et al. Massive parallel sequencing uncovers actionable FGFR2-PPHLN1 fusion and ARAF mutations in intrahepatic cholangiocarcinoma. *Nat Commun* (2015) 6:6087. doi:10.1038/NCOMMS7087

114. Javle M, Lowery M, Shroff RT, Weiss KH, Springfeld C, Borad MJ, et al. Phase II study of BGJ398 in patients with FGFR-altered advanced cholangiocarcinoma. *J Clin Oncol* (2018) 36(3):276–82. doi:10.1200/JCO.2017.75.5009

115. Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol* (2020) 21(5):671–84. doi:10.1016/S1470-2045(20)30109-1

116. Javle M, Roychowdhury S, Kelley RK, Sadeghi S, Macarulla T, Weiss KH, et al. Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. *Lancet Gastroenterol Hepatol* (2021) 6(10):803–15. doi:10.1016/S2468-1253(21)00196-5

117. Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* (2020) 21(6):796–807. doi:10.1016/S1470-2045(20)30157-1

118. Zhu AX, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, et al. Final overall survival efficacy results of ivosidenib for patients with advanced cholangiocarcinoma with IDH1 mutation: the phase 3 randomized clinical ClarIDHy trial. *JAMA Oncol* (2021) 7(11):1669–77. doi:10.1001/JAMAONCOL.2021.3836

119. Liang B, Zhong L, He Q, Wang S, Pan Z, Wang T, et al. Diagnostic accuracy of serum CA19-9 in patients with cholangiocarcinoma: a systematic review and meta-analysis. *Med Sci Monit* (2015) 21:3555–63. doi:10.12659/MSM.895040

120. Cai QY, Yang P, Yang XL, Zhang XH, Guo LP, Lu XY, et al. The association of carbohydrate antigen 19-9 response with radiologic response and survival in intrahepatic cholangiocarcinoma: a prospective cohort study. *Cancer* (2023) 129(19): 2999–3009. doi:10.1002/CNCR.34854

121. Endo Y, Kawashima J, Woldesenbet S, Akabane M, Ruzzente A, Aldrighetti L, et al. Characteristics of "Very Early" intrahepatic cholangiocarcinoma undergoing liver resection and its relationship with carbohydrate antigen 19-9. *J Surg Oncol* (2025) 132(5):924–34. doi:10.1002/JSO.70071

122. Okada K, Kobayashi T, Kuroda S, Mashima H, Hashimoto M, Tahara H, et al. Prognostic impact of pre- and postoperative tumor markers in patients with intrahepatic cholangiocarcinoma. *Surg Today* (2024) 54(2):177–85. doi:10.1007/S00595-023-02715-8

123. Kotsifa E, Saffioti F, Mavroeidis VK. Cholangiocarcinoma: the era of liquid biopsy. *World J Gastroenterol* (2025) 31(11):104170. doi:10.3748/wjg.v31.i11.104170

124. de Scordilli M, Bortolot M, Torresan S, Noto C, Rota S, Di Nardo P, et al. Precision oncology in biliary tract cancer: the emerging role of liquid biopsy. *ESMO Open* (2025) 10(5):105079. doi:10.1016/j.esmoop.2025.105079

125. Wang Y, Li Y, Liang Z, Zhang Y, Li T, Tian C, et al. Circulating tumor DNA in cholangiocarcinoma: current clinical applications and future perspectives. *Front Cell Dev Biol* (2025) 13:1616064. doi:10.3389/fcell.2025.1616064

126. Mahadevia H, Majeed U, Patel J, Ahmed AK, Elhariri A, Albelal D, et al. Circulating tumor DNA and tissue testing for pancreatobiliary tumors. *JAMA Netw Open* (2025) 8(9):e2531373. doi:10.1001/jamanetworkopen.2025.31373

127. Ettrich TJ, Schwerdel D, Dolnik A, Beuter F, Blätte TJ, Schmidt SA, et al. Genotyping of circulating tumor DNA in cholangiocarcinoma reveals diagnostic and prognostic information. *Scientific Rep* (2019) 9(1):13261. doi:10.1038/s41598-019-49860-0

128. Kanwar N, Campion MB, Schneider AR, Milosevic D, Sosa C, Wojcik AA, et al. Validation and clinical utility of a pan-cancer circulating tumor DNA assay as a first-approach test. *J Mol Diagn* (2025) 27(12):1213–23. doi:10.1016/j.jmoldx.2025.08.009

129. Dao J, Conway PJ, Subramani B, Meyyappan D, Russell S, Mahadevan D. Using cfDNA and ctDNA as oncologic markers: a path to clinical validation. *Int J Mol Sci* (2023) 24(17):13219. doi:10.3390/IJMS241713219

130. Rompianesi G, Martino MD, Gordon-Weeks A, Montalti R, Troisi R. Liquid biopsy in cholangiocarcinoma: current status and future perspectives. *World J Gastrointest Oncol* (2021) 13(5):332–50. doi:10.4251/WJGO.V13.I5.332

131. Yu J, He AR, Ouf M, Mehta R, Anaya DA, Denbo J, et al. Detecting early recurrence with circulating tumor DNA in stage I-III biliary tract cancer after curative resection. *JCO Precis Oncol* (2025) 9(9):e2400443. doi:10.1200/po-24-00443

132. Miura Y, Ohyama H, Mikata R, Hirotsu Y, Amemiya K, Mochizuki H, et al. The efficacy of bile liquid biopsy in the diagnosis and treatment of biliary tract cancer. *J Hepatobiliary Pancreat Sci* (2024) 31(5):329–38. doi:10.1002/jhbp.1432

133. Arechederra M, Rullán M, Amat I, Oyon D, Zabalza L, Elizalde M, et al. Next-generation sequencing of bile cell-free DNA for the early detection of patients with malignant biliary strictures. *Gut* (2022) 71(6):1141–51. doi:10.1136/gutjnl-2021-325178

134. Berchuck JE, Facchinetti F, DiToro DF, Baiev I, Majeed U, Reyes S, et al. The clinical landscape of cell-free DNA alterations in 1671 patients with advanced biliary tract cancer. *Ann Oncol* (2022) 33(12):1269–83. doi:10.1016/j.annonc.2022.09.150

135. Quan X, Huang X, Liu J, Yuan X, Shu J. Preoperative assessment of longitudinal extent in hilar cholangiocarcinoma using noninvasive enhanced MR radiomics: a multicenter study. *Front Oncol* (2025) 15:1632630. doi:10.3389/fonc.2025.1632630

136. Cheng M, Zhang H, Guo Y, Lyu P, Yan J, Liu Y, et al. Comparison of MRI and CT based deep learning radiomics analyses and their combination for diagnosing intrahepatic cholangiocarcinoma. *Scientific Rep* (2025) 15(1):9629. doi:10.1038/s41598-025-92263-7

137. Xu L, Chen Z, Zhu D, Wang Y. The application status of Radiomics-Based machine learning in intrahepatic cholangiocarcinoma: systematic review and meta-analysis. *J Med Internet Res* (2025) 27(1):e69906. doi:10.2196/69906

138. Jang HJ, Kim DH, Choi SH, Rhee H, Cho ES, Yeom SK, et al. Preoperative prediction of microvascular invasion in intrahepatic cholangiocarcinoma and its prognostic implications: a multicenter study. *Liver Cancer* (2026) 15(1):63–76. doi:10.1159/000547071

139. Miao G, Qian X, Zhang Y, Hou K, Wang F, Xuan H, et al. An MRI-based radiomics model for preoperative prediction of microvascular invasion and outcome in intrahepatic cholangiocarcinoma. *Eur J Radiol* (2025) 183:111896. doi:10.1016/j.ejrad.2024.111896

140. Fiz F, Rossi N, Langella S, Ruzzenente A, Serenari M, Ardito F, et al. Radiomic analysis of intrahepatic cholangiocarcinoma: non-invasive prediction of pathology data: a multicenter study to develop a clinical–radiomic model. *Cancers* (2023) 15(17):4204. doi:10.3390/cancers15174204

141. Zhan PC, Lyu PJ, Li Z, Liu X, Wang HX, Liu NN, et al. CT-Based radiomics analysis for noninvasive prediction of perineural invasion of perihilar cholangiocarcinoma. *Front Oncol* (2022) 12:900478. doi:10.3389/fonc.2022.900478

142. Zhan PC, Yang T, Zhang Y, Liu KY, Li Z, Zhang YY, et al. Radiomics using CT images for preoperative prediction of lymph node metastasis in perihilar cholangiocarcinoma: a multi-centric study. *Eur Radiol* (2024) 34(2):1280–91. doi:10.1007/s00330-023-10108-1

143. Pan YJ, Wu S, Zeng Y, Cao ZR, Shan Y, Lin J, et al. Intra- and peri-tumoral radiomics based on dynamic contrast Enhanced-MRI to identify lymph node metastasis and prognosis in intrahepatic cholangiocarcinoma. *J Magn Reson Imaging* (2024) 60(6): 2669–80. doi:10.1002/jmri.29390

144. Qin H, Hu X, Zhang J, Dai H, He Y, Zhao Z, et al. Machine-learning radiomics to predict early recurrence in perihilar cholangiocarcinoma after curative resection. *Liver Int* (2021) 41(4):837–50. doi:10.1111/liv.14763

145. Song Y, Zhou G, Zhou Y, Xu Y, Zhang J, Zhang K, et al. Artificial intelligence CT radiomics to predict early recurrence of intrahepatic cholangiocarcinoma: a multicenter study. *Hepatol Int* (2023) 17(4):1016–27. doi:10.1007/s12072-023-10487-z

146. Fiz F, Rossi N, Langella S, Conci S, Serenari M, Ardito F, et al. Radiomics of intrahepatic cholangiocarcinoma and peritumoral tissue predicts postoperative survival: development of a CT-Based clinical-radiomic model. *Ann Surg Oncol* (2024) 31(9): 5604–14. doi:10.1245/s10434-024-15457-9

147. Koku D, Agarwala Y, Vithayathil M, Tait P, Aboagye EO, Sharma R. Radiomics of hepatopancreatobiliary cancer diagnosis, management, and future prospects. *Clin Radiol* (2026) 92:107167. doi:10.1016/j.crad.2025.107167

148. Ronot M, Calderado J. Incorporating artificial intelligence into imaging for surveillance and diagnosis of liver cancer: innovations, challenges, and clinical translation. *Hepatology* (2026). doi:10.1097/HEP.0000000000001698

149. Dueland S, Smedman TM, Grut H, Syversveen T, Jørgensen LH, Line PD. PET-uptake in liver metastases as method to predict tumor biological behavior in patients transplanted for colorectal liver metastases developing lung recurrence. *Cancers (Basel)* (2022) 14(20):5042. doi:10.3390/CANCERS14205042

150. Huang X, Yang J, Li J, Xiong Y, Abd-Elsalam S. Comparison of magnetic resonance imaging and 18-fludeoxyglucose positron emission tomography/computed tomography in the diagnostic accuracy of staging in patients with cholangiocarcinoma: a meta-analysis. *Medicine (United States)* (2020) 99(35): E20932. doi:10.1097/MD.0000000000020932

151. Lamarca A, Barriuso J, Chander A, McNamara MG, Hubner RA, Óreilly D, et al. 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) for patients with biliary tract cancer: systematic review and meta-analysis. *J Hepatol* (2019) 71(1):115–29. doi:10.1016/j.jhep.2019.01.038

152. Hu JH, Tang JH, Lin CH, Chu YY, Liu NJ. Preoperative staging of cholangiocarcinoma and biliary carcinoma using 18F-fluorodeoxyglucose positron emission tomography: a meta-analysis. *J Invest Med* (2018) 66(1):52–61. doi:10.1136/jim-2017-000472

153. Pang L, Bo X, Wang J, Wang C, Wang Y, Liu G, et al. Role of dual-time point 18F-FDG PET/CT imaging in the primary diagnosis and staging of hilar cholangiocarcinoma. *Abdom Radiol* (2021) 46(9):4138–47. doi:10.1007/s00261-021-03071-2

154. Ma KW, Cheung TT, She WH, Chok KSH, Chan ACY, Dai WC, et al. Diagnostic and prognostic role of 18-FDG PET/CT in the management of resectable biliary tract cancer. *World J Surg* (2018) 42(3):823–34. doi:10.1007/s00268-017-4192-3

155. Hwang JP, Moon JH, Kim HK, Lee MH, Lim CH, Park SB, et al. Prognostic value of metabolic parameters measured by pretreatment dual-time-point 18F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with intrahepatic or perihilar cholangiocarcinoma A STROBE study. *Medicine (United States)* (2021) 100(21): e26015. doi:10.1097/MD.0000000000026015

156. Harimoto N, Hoshino K, Muranushi R, Hagiwara K, Yamanaka T, Ishii N, et al. Impact of metabolic parameters of 18F-Fluorodeoxyglucose positron-emission tomography after hepatic resection in patients with intrahepatic cholangiocarcinoma. *Anticancer Res* (2019) 39(2):971–7. doi:10.21873/anticanres.13201

157. Koca F, Petrova E, El Youzouri H, Heil J, Heise M, Sliwinski S, et al. Prognostic value of resection margin and lymph node status in perihilar cholangiocarcinoma. *HPB* (2025) 27(1):71–9. doi:10.1016/j.hpb.2024.09.012

158. Yin JX, Fan X, Chen QL, Chen J, He J. Progress in the application of fludeoxyglucose positron emission tomography computed tomography in biliary tract cancer. *World J Hepatol* (2025) 17(5):105446. doi:10.4254/WJH.V17.I5.105446

159. Cao J, Srinivas-Rao S, Mroueh N, Anand R, Kongboonvijit S, Sertic M, et al. Cholangiocarcinoma imaging: from diagnosis to response assessment. *Abdom Radiol (NY)* (2024) 49(5):1699–715. doi:10.1007/S00261-024-04267-Y

160. Pang L, Mao W, Zhang Y, Liu G, Hu P, Chen S, et al. Comparison of 18F-FDG PET/MR and PET/CT for pretreatment TNM staging of hilar cholangiocarcinoma. *Abdom Radiol (NY)* (2023) 48(8):2537–46. doi:10.1007/S00261-023-03925-X

161. Yoo J, Lee JM, Yoon JH, Joo I, Lee DH. Additional value of integrated 18F-FDG PET/MRI for evaluating biliary tract cancer: Comparison with contrast-enhanced CT. *Korean J Radiol* (2021) 22(5):714–24. doi:10.3348/kjr.2020.0689

162. Ferrone C, Goyal L, Qadan M, Gervais D, Sahani DV, Zhu AX, et al. Management implications of fluorodeoxyglucose positron emission tomography/magnetic resonance in untreated intrahepatic cholangiocarcinoma. *Eur J Nucl Med Mol Imaging* (2020) 47(8):1871–84. doi:10.1007/S00259-019-04558-3

163. Msherghi A, Abuajamieh M, Ekreer M, Alzlitni M, Hajalamin M, Aldieb E, et al. Comparative diagnostic performance of [68 Ga]Ga-FAPI PET/CT and [18 F]FDGPET/CT in biliary tract cancers: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging.* (2025) 52(11):4200–42. doi:10.1007/s00259-025-07264-5

164. Zhang Z, Cheng C, Jiang H, Pan G, Yu Y, Jin G, et al. 68Ga-FAPI-04 PET/CT for the evaluation of cholangiocarcinoma comparison with 18F-FDG PET/CT and abdominal 68Ga-FAPI-04 PET/MR. *Clin Nucl Med* (2024) 49(5):409–18. doi:10.1097/RLU.0000000000005112

165. Pabst KM, Trajkovic-Arsic M, Cheung PFY, Ballke S, Steiger K, Bartel T, et al. Superior tumor detection for 68Ga-FAPI-46 *versus* 18F-FDG PET/CT and conventional CT in patients with cholangiocarcinoma. *J Nucl Med* (2023) 64(7):1049–55. doi:10.2967/jnumed.122.265215

166. Pabst KM, Weber MM, Laschinsky C, Sandach P, Bartel T, Küper AT, et al. [68Ga]Ga-FAPI-46 PET accuracy for cancer imaging with histopathology validation: a single-centre, single-arm, interventional, phase 2 trial. *Lancet Oncol* (2025) 26(9):1204–14. doi:10.1016/S1470-2045(25)00299-2

167. Denizmen Zorba D, Arslan DF, Sanli Y, Kuyumcu S. Optimizing Intrahepatic cholangiocarcinoma staging: comparison of [18F]FDG, [68Ga]Ga-FAPI, and [68Ga]Ga-Trivehexin PET/CT imaging. *Clin Nucl Med* (2026). doi:10.1097/RLU.0000000000006310

168. Raeisi N, Saber Tanha A, Ghahraman M, Aryana K, Aghaee A. Comparable diagnostic value of 99mTc-FAPI-46 SPECT/CT and 18F-FDG PET/CT in cholangiocarcinoma: a case report. *Clin Nucl Med* (2025) 50:e695–e696. doi:10.1097/RLU.0000000000005877

169. Gorji L, Brown ZJ, Limkemann A, Schenk AD, Pawlik TM. Liver transplant as a treatment of primary and secondary liver neoplasms. *JAMA Surg* (2024) 159(2):211–8. doi:10.1001/JAMASURG.2023.6083

170. Dueland S, Smedman TM, Syversveen T, Grut H, Hagness M, Line PD. Long-term survival, prognostic factors, and selection of patients with colorectal cancer for liver transplant: a nonrandomized controlled trial. *JAMA Surg* (2023) 158(9):e232932. doi:10.1001/JAMASURG.2023.2932

171. Soubrane O, Scatton O. The development of transplant oncology may worsen the liver gap and needs new technical options in liver transplantation. *Ann Surg* (2023) 279(2):2023–4. doi:10.1097/sla.0000000000006086

172. Cillo U, Nalesso F, Bertacco A, Indraccolo S, Gringeri E. Normothermic perfusion of a human tumoral liver for 17 days with concomitant extracorporeal blood purification therapy: case description. *J Hepatol* (2024) 81(3):e96–e98. doi:10.1016/j.jhep.2024.04.024

173. Nalesso F, Bertacco A, Bettin E, Cacciapuoti M, Bogo M, Cattarin L, et al. The rationale for combining normothermic liver machine perfusion with continuous renal replacement therapy to maintain physiological perfusate during *Ex Vivo* organ perfusion. *J Clin Med* (2024) 13(17):5214. doi:10.3390/jcm13175214

174. Cillo U, Lauterio A, Furlanetto A, Canitano N, Polacco M, Buscemi V, et al. Full-left/full-right liver splitting with middle hepatic vein and caval partition during dual hypothermic oxygenated machine perfusion. *Transplantation* (2024) 108(6):1417–21. doi:10.1097/tp.0000000000005039

ESOT | Transplant International

TYPE Review
PUBLISHED 13 May 2026
DOI 10.3389/ti.2026.16295

Check for updates

OPEN ACCESS

*CORRESPONDENCE
Andrea Zajacova,
andrea.zajacova@kuleuven.be

RECEIVED 23 January 2026
REVISED 27 March 2026
ACCEPTED 27 April 2026
PUBLISHED 13 May 2026

CITATION
Saez-Gimenez B, Magnusson JM and Zajacova A (2026) Post–lung transplant surveillance in 2026: current practice, variability, and the need for standardization.
Transpl. Int. 39:16295.
doi: 10.3389/ti.2026.16295

COPYRIGHT
© 2026 Saez-Gimenez, Magnusson and Zajacova. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Post–lung transplant surveillance in 2026: current practice, variability, and the need for standardization

Berta Saez-Gimenez [1], Jesper M. Magnusson [2,3] and Andrea Zajacova [4]*

[1]Respiratory Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain, [2]Department of Pulmonology, Sahlgrenska University Hospital, Gothenburg, Sweden, [3]Transplant Institute, Gothenburg, Sweden, [4]Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), Department CHROMETA, KU Leuven, Leuven, Belgium

Post–lung transplant surveillance remains highly heterogeneous, with no universally accepted standard guiding organisation of care or the use of physiological testing, imaging, bronchoscopy, laboratory monitoring, and emerging biomarkers. This narrative review synthesises current surveillance practices across these domains and addresses key limitations, sources of inter-centre variability, and evidence gaps that hinder timely detection of allograft dysfunction. We summarize established and evolving approaches to organisation of care, lung function monitoring, radiological assessment, invasive diagnostics, and laboratory parameters, along with novel biomarkers, highlighting where evidence supports routine use and where tools remain investigational. Fragmentation of follow-up strategies, inconsistent interpretation of longitudinal data, and limited integration of novel diagnostics contribute to delayed recognition of graft injury and variable outcomes. Advancing post-transplant care will require consensus-driven definition of minimum surveillance standards, trajectory-based interpretation frameworks, and rational incorporation of validated biomarkers and digital technologies into harmonised follow-up pathways.

KEYWORDS
follow-up, graft survival, lung transplantation, outcome, surveillance

Introduction

Post–lung transplant (LTx) follow-up is complex, multidisciplinary, and highly variable across centres, with no universally adopted standard. Differences in the use of pulmonary function testing, imaging, laboratory testing, bronchoscopy, and emerging technologies result in substantial heterogeneity in clinical practice. In this narrative review, we summarise the current state-of-the-art approaches to LTx surveillance and highlight areas where practice varies and further harmonisation is needed. To inform this narrative review, we performed targeted PubMed searches between October 2025 and January 2026, focusing on available tools to monitor the graft after lung transplantation. Figure 1 provides a conceptual overview of the clinical trajectory from transplantation to graft failure, highlighting the key surveillance objectives that structure this review. The primary aim of our review is to highlight the existing variability in clinical practice and to identify the current gaps in standardization across surveillance strategies.

Post-lung transplant follow-up care organisation

The transplant pulmonologist as the central coordinator of care

LTx care is inherently a respiratory discipline and therefore must be anchored in specialised pulmonological follow-up. Transplant pulmonologists build on core respiratory training with dedicated expertise in lung allograft physiology, chest imaging, lung allograft-specific diagnostics including bronchoscopy, bronchoalveolar lavage (BAL), transbronchial biopsies (TBB), advanced lung-function interpretation, and chronic lung allograft dysfunction (CLAD) phenotyping. Because most post-LTx complications present with respiratory abnormalities, early recognition and effective management require specialised pulmonary expertise. While multidisciplinary care is essential, no other specialty integrates respiratory physiology, imaging, and procedural assessment throughout long-term follow-up. This central coordinating role is particularly critical when integrating multimodal surveillance data and resolving discrepant findings (e.g., discordance between imaging, bronchoscopy, and emerging biomarkers), where expert clinical judgment is required to guide management.

General pulmonologists may also contribute meaningfully—especially for patients distant from transplant centres—but optimal outcomes require a specialized transplant pulmonologist-coordinated care model [1] Figure 2.

Site of follow-up

Long-term surveillance is highly specialised, reflecting the interplay between complex allograft biology and substantial burden of extra-pulmonary comorbidities, and therefore requires coordinated multidisciplinary care within experienced transplant programmes [2]. LTx recipients frequently present with significant baseline multimorbidity—including cardiovascular, metabolic, and psychiatric conditions—which independently affects mortality and necessitates systematic assessment and follow-up [3, 4]. In parallel, increasing recognition of genetic and phenotypic heterogeneity in fibrotic lung disease underscores the need for centres capable of integrating molecular diagnostics, genetic screening, and precision-medicine approaches into post-transplant care [5–7].

Where follow-up is delivered also influences outcomes. In cystic fibrosis (CF), transplantation at centres hosting accredited CF programmes is associated with an approximately 33% lower risk of graft failure or death compared with non-CF centres, independent of centre volume [8]. More broadly, matched registry analyses demonstrate superior 5-year survival in European centres compared with North America despite similar early outcomes, suggesting that organisational structures and/or better access to long-term care meaningfully affect prognosis [9]. Advanced practice providers (nurse practitioners, physician assistants) are increasingly embedded within LTx programmes to enhance continuity, coordinate routine surveillance, and comorbidity management, and serve as a liaison between transplant centres and local clinicians [10, 11].

Documentation and monitoring

Comprehensive and longitudinal documentation is essential for qualitative post-LTx follow-up. Fragmentation inherent to paper-based records has driven adoption of electronic logbooks and transplant registries that consolidate clinical visits, investigations, and interventions. These systems facilitate audit, enable linkage with national registries, and support quality-improvement initiatives [12, 13]. From the patient perspective, personal logbooks—physical or digital—promote engagement and awareness of key health metrics, while integration of electronic alerts for test scheduling and abnormal results further strengthens safety in long-term transplant care [14, 15].

Patient-reported outcomes and experience measurements (PROMs and PREMs)

Structured post-LTx follow-up integrates subjective and objective assessment. Subjective evaluation captures patient-reported symptoms, medication side effects, and psychosocial wellbeing and can be standardised through validated PROMs, several of which are established in LTx [2, 16–18]. PROMs extend beyond conventional clinical data by capturing health status and quality of life, including symptoms, functional status, and psychological wellbeing [12, 19, 20]. PREMs complement PROMs by assessing patients' experience of care, including access, communication, coordination, and shared decision-making [21].

Both tools can be integrated into clinical workflows through digital pre-visit questionnaires or tablet-based assessments, enabling real-time identification of patient needs, individualisation of care, and longitudinal monitoring. Standardised use of PROMs and PREMs also facilitates benchmarking across transplant centres and supports quality improvement initiatives [22].

Role of telemedicine

Telemedicine is increasingly used to extend specialist follow-up after LTx. Telemonitoring, teleconsultation, telerehabilitation, and telespirometry can enhance surveillance, support patient-centred care, and promote self-management [23]. The INSPIRE-III randomised trial demonstrated that telehealth-delivered coping skills and exercise interventions are feasible after LTx and

Abbreviations: ACR, Acute Cellular Rejection; AMR, Antibody Mediated Rejection; AUC, Area Under the Curve; BAL, Bronchoalveolar Lavage; BLAD, Baseline Lung Allograft Dysfunction; BOS, Bronchiolitis Obliterans Syndrome; CF, Cystic Fibrosis; CLAD, Chronic Lung Allograft Dysfunction; CMV, Cytomegalovirus; CNI, Calcineurin Inhibitor; CT, Computed Tomography; Dd-cfDNA, Donor-derived Cell-free DNA; DLCO, Diffusing Capacity of the Lung for Carbon Monoxide; FEV1, Forced Expiratory Volume in 1 Second; FVC, Forced Vital Capacity; ISHLT, International Society for Heart and Lung Transplantation; LTx, Lung Transplantation; ML, Machine Learning; MRI, Magnetic Resonance Imaging; PET–CT, Positron Emission Tomography–Computed Tomography; PREMs, Patient-Reported Experience Measurements; PROMs, Patient-Reported Outcomes Measurements; qCT, Quantitative Computed Tomography; RAS, Restrictive Allograft Syndrome; SVC, Slow Vital Capacity; TBB, Transbronchial Biopsy; TDM, Therapeutic Drug Monitoring; TLC, Total Lung Capacity; ^{3}He-MRI, Helium-3 Hyperpolarized MRI; ^{19}F-MRI, Fluorine-19 MRI.

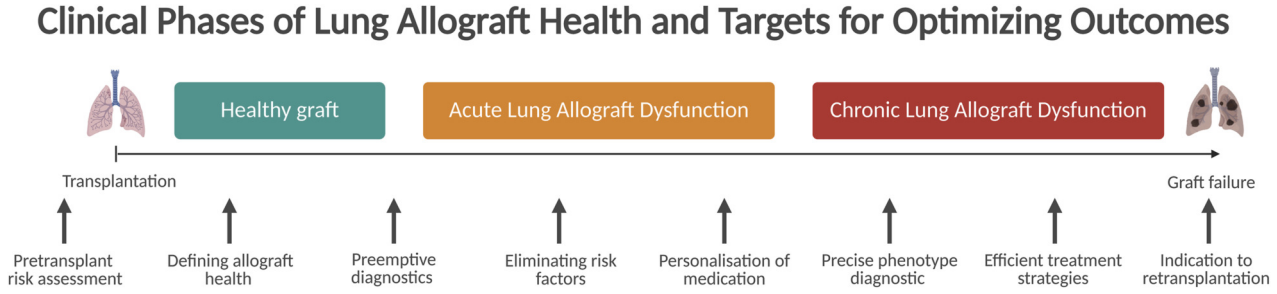


FIGURE 1
Clinical phases of lung allograft health and targets for optimizing outcomes.

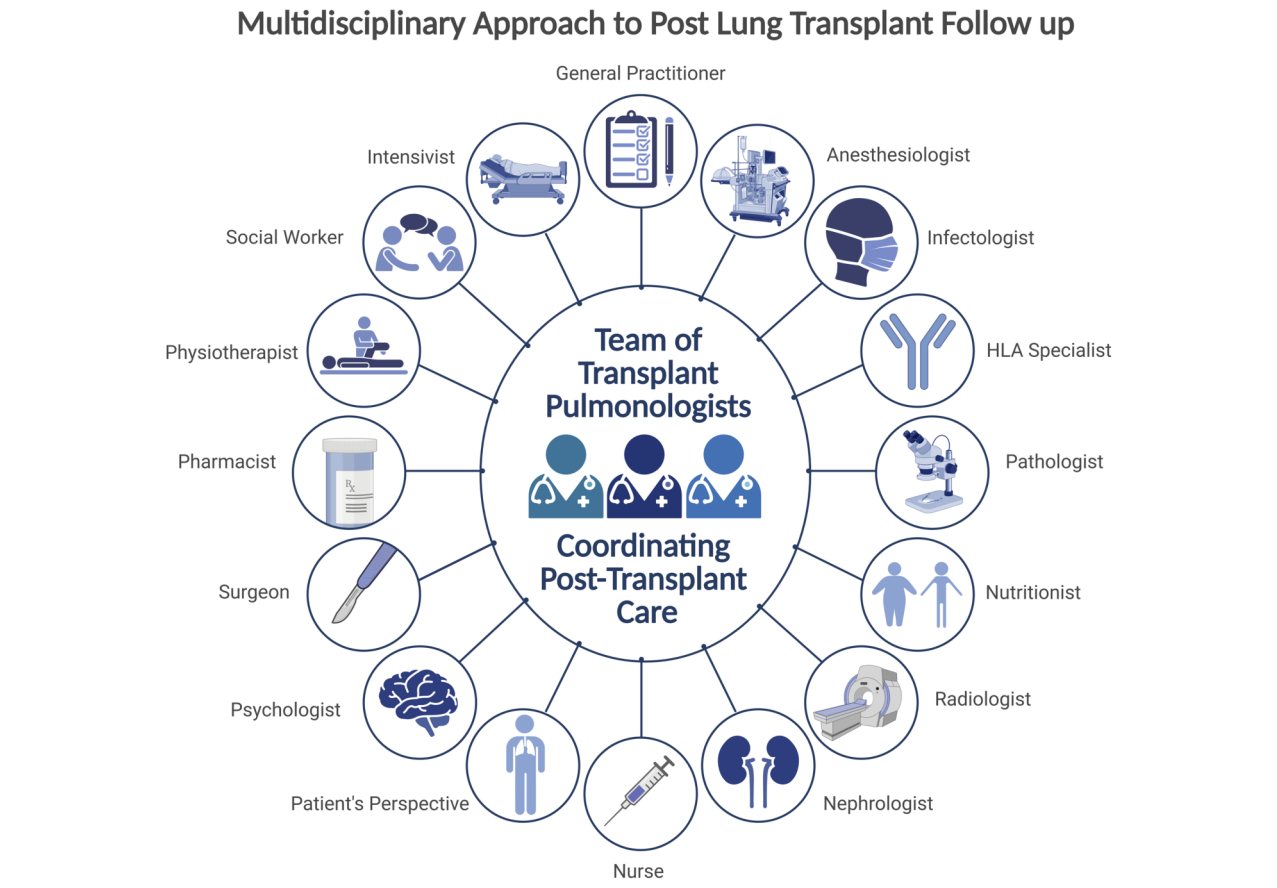


FIGURE 2
Central role of the transplant pulmonologist within a multidisciplinary post-transplant care team.

provide modest benefits in psychological distress and functional capacity, particularly among patients with baseline depression [24]. Observational studies report high patient satisfaction and reduced travel burden, although most patients prefer periodic in-person visits for complex assessments [15, 19, 25, 26]. Collectively, available evidence supports a hybrid care model in which regular in-person follow-up at specialised centres is augmented—but not replaced—by structured telemedicine.

Telemedicine may also support assessment of treatment adherence by enabling earlier detection of missed doses or behavioural barriers. As non-adherence is a major determinant of graft survival [20, 27, 28], integrating remote monitoring with in-person care may facilitate earlier intervention. Nevertheless, in-person visits remain essential for adherence reinforcement through pharmacy refill checks, drug-level variability indices, and validated self-report tools such as BAASIS [27–31].

Pulmonary function testing

Spirometry

Spirometry remains the cornerstone of physiological allograft monitoring, with forced expiratory volume in 1 second (FEV_1) serving as the basis for detecting and following lung allograft dysfunction. Percent-predicted thresholds are derived from healthy populations measurements, nevertheless, in complex post-transplant setting—heavily affected by size matching, thoracic wall disturbances (caused by both primary diagnosis and surgical approaches), respiratory muscle weakness, or receiving unilateral or lobar transplant—percent-predicted values are often misleading in assessing normality [32–37]. Accordingly, International Society for Heart and Lung Transplantation (ISHLT) guidelines define CLAD based on relative decline from an individualised post-transplant baseline using absolute FEV_1 values rather than population norms [38]. To contextualise lung function with standard population-based norms, the term baseline lung allograft dysfunction (BLAD) has been proposed to describe recipients who never achieve expected predicted values, awaiting the publication of a consensus document from the ISHLT [39–41].

Spirometry interpretation is further complicated by historical drift from the original Tiffeneau–Pinelli index (FEV_1/slow vital capacity; SVC) toward the forced expiratory ratio (FEV_1/forced vital capacity; FVC). FVC may be underestimated during forceful expiration due to dynamic airway collapse, particularly in bronchiolitis obliterans syndrome (BOS), thereby masking airflow obstruction [42, 43]. In contrast, SVC—measured during slow exhalation—more accurately reflects true vital capacity and minimises this artefact, as demonstrated in multiple studies [44–46]. Despite this, routine SVC measurement requires additional time, technical expertise, and transplant-specific reference values and current CLAD definitions therefore rely on FEV_1/FVC, which should be interpreted cautiously and contextualised (i.e., with flow–volume loops) [38, 47].

Machine learning (ML) introduces novel analytical approaches to spirometry, with preliminary data suggesting potential utility for CLAD prediction [48]. Digital home spirometry enables frequent remote monitoring with reliable FEV_1 measurements that correlate well with laboratory values and may improve early detection of lung function decline [35–37].

Body plethysmography

In post-LTx clinical monitoring, plethysmography has prognostic value and is required for establishing total lung capacity (TLC) baseline (at 6 and 12 months post-transplant) and for restrictive CLAD diagnosis and phenotyping, including restrictive allograft syndrome (RAS) and "mixed/undefined phenotypes" [38]. Despite this, a recent comprehensive European survey revealed that approximately 16% of centres managing CLAD do not routinely use this method [49]. Another limitation occurs in patients with severe dyspnoea, who may be unable to perform the panting manoeuvre, leading to discomfort and unreliable resistance and volume measurements [50]. Consequently, reliable plethysmographic TLC measurement in advanced CLAD can be challenging, underscoring that TLC assessment is most informative during stable follow-up and early CLAD phenotyping. While the optimal measurement interval is not well established, extending intervals relative to standard spirometry may help mitigate cost and availability constraints.

Lung diffusion capacity testing

Reduced diffusing capacity of the lung for carbon monoxide (DLCO) has independent prognostic value for survival, with declines associated with increased mortality even after adjustment for FEV_1 and FVC [51]. This suggests DLCO captures aspects of allograft health not reflected by spirometry or body plethysmography, likely related to gas exchange and pulmonary vascular integrity. DLCO is well-established for monitoring disease progression in interstitial lung diseases, where abnormalities often precede spirometric changes [52, 53], supporting its complementary role among pulmonary function tests, despite not being fully integrated into current post-transplant guidelines. Although TLC can be estimated using the single-breath helium dilution manoeuvre during DLCO testing, this method underestimates true TLC in the presence of ventilation inhomogeneity and is therefore less reliable than plethysmography [54].

Novel physiological methodology in lung transplant follow-up

Oscillometry measures distal airway resistance during tidal breathing and might be more sensitive than spirometry for detecting early rejection, although longitudinal data remain limited [38, 55–58]. Because it relies on normal tidal breathing, oscillometry is particularly useful in patients unable to perform forced manoeuvres reliably, including children and frail individuals.

Fractional exhaled nitric oxide provides a rapid, non-invasive marker of airway inflammation and is elevated in infection, lymphocytic bronchiolitis, and acute rejection. However, despite high sensitivity, it lacks specificity and does not predict functional decline, limiting its role to supportive use during routine visits [59–63].

Lung clearance index, obtained by multiple-breath washout, detects ventilation heterogeneity and is highly sensitive to small-airway dysfunction, often preceding spirometric changes [63, 64]. Evidence is strongest in paediatric recipients, while adult data remain limited [65, 66].

Novel biomarkers

Exhaled breath condensate analysis combined with ML has shown promise in discriminating between different forms of lung allograft dysfunction, however, further validation is required, although the practicality and rapidity of electronic-nose platforms suggest potential as a point-of-care diagnostic tool [67, 68].

Imaging

Chest X-ray

Chest X-ray remains an essential first-line screening tool after LTx due to its rapid availability, low radiation exposure, and utility

in detecting primary graft dysfunction and other post-transplant complications, including pneumothorax, pleural effusions, or pneumonia [69]. Acquisition of both posteroanterior and lateral projections is critical, as the lateral view improves detection of subtle pleural, parenchymal, and mediastinal abnormalities that may be missed on a single-plane projection [70].

Computed tomography (CT)

In contemporary practice, emphasis is better placed on CT protocol design than on older nomenclature such as high-resolution CT, because modern multidetector scanners generally provide high-resolution volumetric data. The clinically relevant distinction is whether appropriate non-contrast inspiratory and expiratory acquisitions are obtained, ideally using dose-optimized techniques [71]. Expiratory scans are particularly important, as it reveals air trapping—a hallmark feature of BOS—and frequently detects dysfunction earlier than inspiratory imaging [71–73]. However, its diagnostic utility depends strongly on acquisition quality, and inadequate expiratory effort can render studies non-diagnostic [71]. Standard CT retains a complementary role, particularly for assessing complications such as tree-in-bud, ground glass opacities, (sub)pleural consolidations, pulmonary embolism, vascular stenosis, large-airway pathology, or mediastinal abnormalities [73].

Surveillance CT

An initial baseline CT with both inspiratory and expiratory scans with a maximum width of 3-mm sections at 6 months post-LTx is recommended to enable a baseline for future comparison [38]. Among CT features, air-trapping is one of the most informative markers of BOS, outperforming mosaic perfusion, bronchiectasis, and bronchial wall thickening, although reported sensitivity varies [72, 74, 75]. Lung consolidations and pleural effusions have also been linked to subsequent BOS development and reduced survival [75].

Quantitative CT (qCT) techniques further enhance surveillance. Voxel-wise density mapping of paired inspiratory and expiratory scans at 6 months post-LTx outperformed conventional expiratory threshold-based methods and correlated with residual volume/TLC [76]. Longitudinal parametric response mapping links radiographic small-airway disease with peri-BOS FEV_1 decline, supporting its adjunctive prognostic value [77]. A consensus on the minimum frequency of imaging required for routine graft surveillance after LTx is still lacking.

Diagnostic CT

Beyond routine surveillance, CT is essential when new respiratory symptoms or lung-function decline raise suspicion of acute or chronic allograft dysfunction, as it aids in identifing underlying causes such as infection, acute rejection, CLAD, or malignancy. Several reviews provide detailed guidance on post-LTx radiologic assessment and CLAD imaging patterns [78, 79].

In unilateral LTx recipients with a ≥10% FEV_1 decline, combining pulmonary function testing with qCT metrics using supervised ML algorithms improved BOS detection compared with spirometry alone [80] and helped distinguish BOS from non-BOS causes of FEV_1 decline [81]. Among patients with a 10%–20% FEV_1 reduction, the presence of any abnormal parametric response mapping signature—functional small airway disease or parenchymal disease—was associated with shorter CLAD-free survival [82].

Although imaging contributes to CLAD subclassification, current ISHLT recommendations do not specify precise follow-up CT protocol that should be used [38]. Nevertheless, CT with paired inspiratory-expiratory scans could therefore be considered for all patients with suspected CLAD because of its phenotyping and prognostic value, and most European centres routinely acquire both inspiratory and expiratory scans at CLAD suspicion [49]. While air-trapping is frequently identified, it did not predict CLAD-free survival in a BOS cohort; in contrast, ground-glass opacities were associated with better outcomes, with deep neural networks demonstrating strong performance in BOS prediction [83]. Conversely, bronchiectasis, peribronchial thickening, and parenchymal changes were linked to inferior survival in BOS [84]. In RAS, prognostic interpretation of CT with expiratory scans remains heterogeneous, with some studies reporting no outcome correlation and others demonstrating prognostic value using inflammation-based scoring systems [85, 86]. qCT techniques—including texture analysis and CT density histograms—improve phenotyping and often predict BOS, RAS, or mixed phenotypes earlier, with clearer survival implications [87–89]. ML–enhanced radiology further refines prognostication; features such as reticulation and pulmonary vessel volume show strong diagnostic and prognostic performance, with pulmonary vessel volume emerging as a particular robust biomarker [90]. Although no formal guidelines define radiologic follow-up in established CLAD, serial CTs with expiratory scans may be appropriate in selected cases to assess phenotype transition from BOS to RAS, which may carry prognostic significance [91, 92].

Magnetic resonance

MRI is an emerging imaging tool in post-LTx follow-up. Hyperpolarised gas MRI—particularly ^{3}He-MRI—can detect early regional ventilation abnormalities in BOS but remains limited by cost, ^{3}He availability, and the need for specialised equipment [93, 94]. Consequently, more feasible non-hyperpolarised MRI techniques have gained interest. Oxygen transfer function MRI demonstrates reduced values in BOS [95], while functional approaches such as Fourier decomposition and phase-resolved functional lung (PREFUL) MRI enable assesment of regional ventilation without contrast agents. In a cohort a cohort of 141 recipients, PREFUL ventilation metrics, including reduced relative fractional ventilation, predicted retransplantation or CLAD-related death, whereas FEV_1 did not, with consistent threshold values reported across studies [96, 97]. Dynamic ^{19}F MRI has similarly demonstrated quantifiable regional ventilation differences between CLAD and non-CLAD recipients, particularly in regional lung clearance indices, with strong correlations between peripheral ventilation and FEV_1 [98].

Complementary imaging: ultrasound, PET–CT, and perfusion scintigraphy

Chest ultrasound after LTx is primarily used for bedside assessment of pleural effusions, diaphragmatic motion, and

procedural guidance for thoracentesis [99]. Nuclear imaging provides complementary information: PET–CT can help distinguish infection, malignancy, and inflammation, and support evaluation of suspected RAS by identifying metabolically active fibrotic or inflammatory regions [73, 100]. Perfusion scintigraphy remains useful when pulmonary vascular disease is suspected, aiding differentiation between vascular causes of functional decline and CLAD-related pathology [101], and may also support early BOS detection in single LTx recipients [102].

Novel biomarkers

Emerging molecular imaging with fibroblast activation protein–targeted tracers offers the potential to non-invasively visualize fibrotic remodelling in lung allografts, providing a "biological" radiologic biomarker that may enable earlier detection and phenotyping of CLAD, although its use remains largely investigational [103].

Bronchoscopy

Follow-up protocols

Bronchoscopy with BAL and TBB remains the current gold standard for both surveillance and for-cause evaluation after LTx, enabling detection, confirmation, or exclusion of subclinical infection, rejection, or anastomotic complications, although no consensus exists regarding optimal surveillance intervals.

Comparisons between surveillance and for-cause bronchoscopy have yielded mixed results. Current evidence does not demonstrate that surveillance bronchoscopies improve survival or reduce CLAD, although most centres still perform them to detect subclinical rejection [104]. Interpretation across studies is limited by inconsistent definitions of "for-cause" bronchoscopy, typically triggered by FEV_1 decline, new symptoms, hypoxaemia, or new radiological infiltrates. A recent meta-analysis including three small observational cohorts highlighted substantial heterogeneity in clinically indicated bronchoscopy use [105]. Detection rates for acute rejection were similar overall, although for-cause procedures yielded higher rates of grade A2–A4 acute cellular (ACR) rejection. Surveillance bronchoscopy nonetheless prompts therapeutic changes in 7%–31% of cases [106–108].

The goal of bronchoscopy strategies is to maximise diagnostic yield while minimising risk. Benefits include identification of infection and anastomotic complications and TBB remains the gold standard for diagnosing ACR and antibody-mediated rejection (AMR). These advantages must be balanced against procedure-related risks, including pneumothorax (0.1%–2%) and bleeding (1.9%–13%) [107, 109–111], mostly biopsy-related and more frequent in LTx recipients [112].

Transbronchial biopsy

TBB is a cornerstone for definitive histologic diagnosis of graft injury/rejection after LTx, but it is limited by procedural risk, inadequate tissue yield, interobserver variability, and patient discomfort. Diagnostic sensitivity remains uncertain: early studies reported high sensitivity with extensive sampling [113], whereas modern practice (typically ≤5 samples) achieves only ~30% sensitivity for acute rejection in both surveillance and for-cause procedures [107, 114, 115]. Interobserver agreement among pathologists is moderate to high for A-grade and fair for B-grade ACR [116, 117].

Surveillance TBB is supported by association between ACR or lymphocytic bronchiolitis and subsequent CLAD development [118–121], although correlations with overall survival are inconsistent [121, 122]. TBB has limited utility for CLAD detection [109] and it is not necessary for CLAD diagnosis [38]. Its diagnostic yield is highest within the first 12–16 weeks post-LTx, after which clinically significant findings decrease [106, 108].

Cryobiopsy remains investigational. A randomised study suggests comparable safety and diagnostic performance to forceps TBB, with higher specimen adequacy [123], and limited evidence indicates that four cryobiopsies may offer the best balance between diagnostic yield and safety [124], although the optimal number of samples required for ACR diagnosis remains undefined.

Endobronchial biopsies are an emerging, less invasive alternative to TBB, offering reproducible histologic and molecular markers of airway inflammation, ACR, and CLAD with a favourable safety profile, and may gain importance as molecular diagnostics evolve [125]. Additionally, airway brushing offers a minimally invasive means of sampling airway epithelial biology and has been used for molecular profiling of allograft injury—particularly CLAD—though its role in routine rejection surveillance remains investigational [126, 127].

Bronchoalveolar lavage

BAL samples the small airways and alveolar compartment, and remains essential for diagnosing infectious complications, a key contributor to CLAD development [16, 128]. The ISHLT published a consensus statement in 2020, standardising BAL technique in LTx [104]. Observational studies show that surveillance BAL detects asymptomatic infections in 12%–40% of procedures, while for-cause BAL identifies pathogens in 39%–50% of cases [129, 130]. However, despite higher detection rates, surveillance BAL has not been shown to improve CLAD-free survival or overall survival. An ISHLT survey reported universal bacterial cultures of BAL fluid, with most centres also performing fungal (89%), mycobacterial (86%), and non-cytomegalovirus (CMV) viral polymerase chain reaction testing (70.2%) [104].

Immunoprofiling

BAL lymphocyte differential profiles can support clinical interpretation of allograft status but are not diagnostic. In the ISHLT survey, 61% of centres routinely requested BAL cytology—most commonly for suspected infection (23%), malignancy (35%), or rejection (13%)—yet evidence remains insufficient to define diagnostic accuracy [104]. Assessment of cellular composition is performed in 72% of centres, and several studies have shown that BAL neutrophilia (cut-off ~15–20%) is associated with both concurrent and future CLAD, even in patients receiving azithromycin [131, 132]. Elevated BAL eosinophilia (1%–2%) has similarly been linked to reduced CLAD-free survival,

particularly in RAS [106, 133–135]. Accordingly, ISHLT consensus recommends inclusion of differential cell counts in all post-transplant BAL samples [104].

Novel biomarkers

BAL has been extensively explored for LTx monitoring, including donor-derived cell-free DNA (dd-cfDNA), inflammatory cytokines and chemokines (e.g., IL-8, CXCL9–11), and extracellular vesicles or exosomes, yet none have been adopted into routine clinical practice [136–139]. In parallel, transcriptomic profiling of BAL cells is emerging as a tool for allograft assessment and tissue-based transcriptomics (already standard-of-care in kidney and heart transplantation) may offer enhanced precision and identify subclinical but remains investigational and not yet approved for LTx [140–146].

Blood monitoring

Therapeutic drug monitoring

Most recipients are maintained on calcineurin inhibitor (CNI)–based regimens combined with an antimetabolite and corticosteroids [2, 147]. CNI have a narrow therapeutic index with substantial intra- and interindividual pharmacokinetic variability, making routine therapeutic drug monitoring (TDM) essential [147]. CNI trough levels—measured immediately before the next dose—remain the standard approach despite the absence of universally accepted targets or monitoring intervals [148]. For mTOR inhibitors (sirolimus/everolimus), routine TDM is also recommended because of substantial pharmacokinetic variability and drug–drug interaction [149]. Although pharmacokinetics favour AUC-based monitoring over trough levels for mycophenolate, the need for multiple timed samples limits routine implementation, and targeted AUC assessment is therefore mainly reserved for situations with uncertain absorption, suspected drug–drug interactions, or during CNI transitions [150, 151]. Dried blood spot sampling of tacrolimus has shown promising feasibility and may improve convenience and patient engagement, although current evidence remains insufficient to support routine use [152, 153]. TDM is also relevant for key anti-infective agents used in LTx care. Triazole antifungals require monitoring due to highly variable exposure and potent cytochrome P4503A4-mediated interactions that increase CNI levels, antivirals such as (val)ganciclovir require renal function-guided dosing to balance efficacy and marrow toxicity, while aminoglycosides warrant level-guided dosing to maintain efficacy and limit nephrotoxicity in patients already exposed to CNI-related nephrotoxicity [154–157].

Donor-specific antibody testing

Evaluation of donor-specific anti-HLA antibodies remains central to diagnosing AMR [158]. Practice patterns vary widely, ranging from low-sensitivity screening assays to routine use of high-resolution single-antigen bead platforms [159–161]. Some centres incorporate scheduled surveillance, whereas others reserve testing upon clinical deterioration [160–162]. Methodological rigour is essential: kidney transplant data indicate that nearly one-quarter of donor-specific antibodies may be misclassified using lower-resolution assays, underscoring the importance of high-fidelity testing in transplant recipients [163] Figure 3. Although evidence for non-HLA antibodies in allograft injury is increasing, it remains insufficient to justify their routine use in clinical decision-making after LTx [164, 165].

General haematological and biochemical monitoring

Comprehensive hematologic and biochemical evaluation provides valuable insight into immunologic and clinical status after LTx [2]. Leukopenia is common after LTx and has been associated with increased infectious complications and poorer clinical outcomes [166–168]. Immunophenotyping of lymphocytic subsets may help tailor immunosuppressive therapy, yet lung-transplant evidence remains scarce [169]. Eosinophilia, while nonspecific, may signal graft injury or early rejection [170]. Trends in haemoglobin and platelet counts can reveal marrow suppression, chronic disease anaemia, bleeding diatheses, or thrombotic microangiopathy [171–174].

Biochemical indices further refine clinical assessment. Elevations in C-reactive protein or procalcitonin may provide early, non-specific signals of inflammatory activity or systemic infection [175, 176]. Serum creatinine remains indispensable given well-recognised CNI nephrotoxicity, and liver enzyme abnormalities may indicate hepatotoxicity related to immunosuppressants, antifungals, or antivirals [177–180]. Broader metabolic screening is also important: dyslipidaemia is associated with post-transplant mortality, poor glycaemic control [181], and vitamin D deficiency is common and linked to higher rates of infection and adverse outcomes, and although lung-specific data are limited, routine thyroid function testing is often included to detect immunosuppression- or comorbidity-related endocrine disturbances [182–186].

From an immunologic perspective, hypogammaglobulinemia—particularly low IgG—correlates with increased infection burden, and while advanced immune phenotyping may offer additional insight into immunosuppressive intensity, current evidence does not support routine its clinical implementation [187–190].

Microbiological surveillance

Viral monitoring is now embedded in most follow-up pathways, although practices vary between centers. CMV viral load monitoring is widely used for surveillance and early detection of breakthrough viremia [191, 192]. Ebstein-Barr virus assessment is often pursued when evaluating the risk of post-transplant lymphoproliferative disorder and may also provide indirect insight into the net state of immunosupression [193, 194]. Although best characterised in the kidney transplantation, polyomavirus infection is increasingly recognised in LTx, particularly in patients with unexplained renal dysfunction, where viremia or nephropathy should be considered [195, 196].

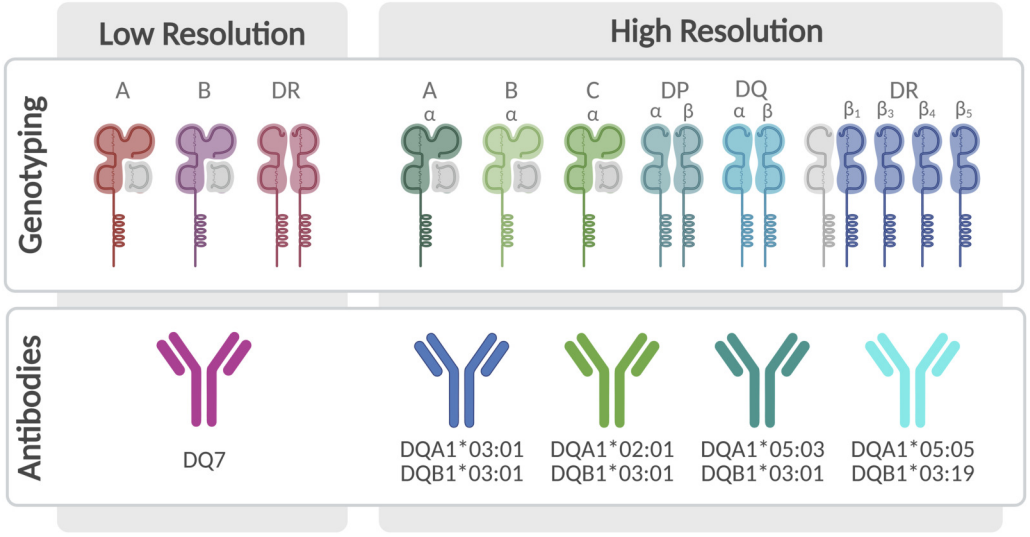


FIGURE 3
An overview of impact of resolution on HLA genotyping and anti-HLA antibodies assessment.

Novel biomarkers

Dd-cfDNA has emerged as a promising non-invasive biomarker of allograft health, with accumulating evidence and recent consensus statements from the European Society for Organ Transplantation highlighting its sensitivity for the early detection of allograft injury, including subclinical processes that may precede overt functional decline [197]. However, dd-cfDNA remains a non-specific marker of injury, as elevated levels do not differentiate between underlying causes such as acute rejection, infection, or other forms of graft damage, thereby necessitating correlation with clinical, functional, imaging, and histopathological findings [197, 198]. While these characteristics support its role as a complementary surveillance tool, its optimal integration into routine post-LTx care—including thresholds, timing, and clinical decision pathways—as well as its cost-effectiveness, remain to be defined. Ongoing prospective studies, including the LAMBDA-001 trial, are expected to provide important real-world data to better clarify its clinical utility and inform evidence-based implementation [197–199].

Torque teno virus load has emerged as a promising biomarker of the functional state of immunosuppression in LTx recipients, while epithelial injury markers such as club cell secretory protein, circulating extracellular vesicles/exosomes carrying lung self-antigens or immune-regulatory miRNAs, and cfDNA methylation–based tissue-of-origin mapping offer complementary insights into rejection biology, however, all remain investigational and lack sufficient validation for routine clinical implementation [139, 200–204].

Conclusion

Despite substantial advances in diagnostics and multidisciplinary care, post–LTx surveillance remains highly heterogeneous, with wide variation in organisational models, testing strategies, and integration of emerging tools. As summarised in Table 1, current follow-up practices are characterised by fragmented structures, inconsistent use of physiological, imaging, and procedural assessments, and a growing number of promising biomarkers that lack sufficient validation for routine clinical implementation. Moving the field forward will require practical, evidence-based, and consensus-driven guidance that defines minimum surveillance standards, emphasises trajectory-based interpretation of longitudinal data, and provides a clear framework for the stepwise incorporation of novel diagnostics and digital technologies into harmonised post-transplant care. Yet any meaningful standardization must acknowledge that surveillance practices are inevitably affected by geographical and logistical factors including healthcare system infrastructure, resource availability, reimbursement policies, and centre volume, which render a one-size-fits-all approach not desirable. Over-surveillance in low resource environments may divert capacity from higher-priority clinical needs which would be harmful for the overall program results. Ultimately, this highlights the critical gap where current clinical practice often reflects eminence-based rather than evidence-based decision-making; a gap that rigorous, consensus-driven standardisation can meaningfully close by establishing a minimum set of universal surveillance requirements, while offering an expanded framework of additional recommendations for higher-resourced centres with the capacity to implement them.

TABLE 1 Major gaps in current post–LTx surveillance, highlighting limitations of existing practices, sources of inter-centre variability, and priority areas for future standardisation and evidence generation.

Domain/ Section	Current practice/Strengths	Weak spots and limitations	Unmet needs/Future directions
Follow-Up Organisation	Transplant pulmonologists coordinated care; structured clinics in many centres	Heterogeneous pathways; inconsistent coordination with local providers	Consensus on core organisational models; evidence linking structure to outcomes
Documentation and Monitoring	Electronic systems increasingly used; registries support auditing	Fragmentation between systems; inconsistent templates	Standardised templates; interoperable platforms; automatic alerts
Adherence	Use of BAASIS, refill data, drug levels	No gold standard; psychosocial drivers under-recognised	Validated LTx-specific tools; trials of adherence interventions
PROMs and PREMs	Growing use; digital tools feasible	Few validated tools; unclear clinical integration	Broader validation; guidance for real-time use
Site of Follow-Up and Telemedicine	Hybrid specialist–local care; telehealth expanding	No consensus on task division; variable infrastructure	Evidence-based shared-care models; telemonitoring standards
Spirometry	FEV_1 and FEV_1/FVC is cornerstone; widely accessible	% Predicted misclassification; SVC rarely measured	Transplant-specific LLN/z-scores; validation of FEV1/SVC.
Plethysmography	Central for CLAD phenotyping	Limited availability; difficult in severe dyspnoea	Consensus on TLC intervals; alternatives for advanced disease (e.g., imaging-derived lung volumes)
DLCO	Independent prognostic value; complements spirometry and phethysmography	Not in CLAD criteria; limited longitudinal data	Long-term studies; DLCO-informed longitudinal risk models
Imaging	CT with expiratory scans key for CLAD phenotyping; expiratory imaging valuable	No consensus intervals	Evidence-based imaging schedules; externally validated ML-enhanced CT models linked to outcomes
Laboratory Monitoring	TDM, DSA, viral PCR widely used	Assay variability; lack of unified thresholds	Harmonised protocols; integration of advanced biomarkers (e.g., dd-cfDNA) into longitudinal surveillance algorithms
Bronchoscopy Protocols	Widely used; early-phase utility clear	Survival/CLAD benefit unproven; heterogeneity high	Trials defining optimal schedules; personalised bronchoscopy intensity
TBB	Diagnostic standard for rejection	Low sensitivity for CLAD; interobserver variability	Standardisation; clinical validation of cryobiopsy and molecular transcriptomics
BAL and Immunoprofiling	Widely used for infection; consensus technique	Variable diagnostic cut-offs; cytology inconsistent	Prospective validation of BAL biomarkers; molecular signatures
Novel Biomarkers	Emerging biomarkers such as dd-cfDNA, transcriptomic signatures, exosomal markers, and immune profiling show promise for earlier or subclinical injury detection	Limited specificity for injury phenotype; uncertain thresholds; incomplete validation; unclear cost-effectiveness and real-world utility	Prospective validation; definition of actionable thresholds; biomarker-guided surveillance pathways; assessment of cost-benefit and implementation in routine care
ML/Digital Analytics	Increasing availability of multimodal digital data streams from lung function, imaging, laboratory testing, and remote monitoring creates opportunities for ML-supported surveillance	Most models remain retrospective, single-centre, and insufficiently validated; limited interpretability and uncertain clinical utility	External validation, calibration across centres, transparent reporting, and prospective trials assessing whether ML-supported surveillance improves outcomes and standardisation
Overall Strategy	Growing recognition of the need for multimodal, trajectory-based surveillance and increasing availability of digital data streams amenable to AI-based analysis	Absence of unified surveillance guidelines; high inter-centre variability; limited prospective validation and clinical integration of AI-driven tools	International consensus defining minimum surveillance standards, coupled with development and validation of multimodal, trajectory-based risk stratification tools incorporating AI.

Author contributions

Conceptualization, Manuscript Drafting, Critical Review, and Editing: BS-G, JM, and AZ. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

JM reports unrestricted research grant from Boehringer Ingelheim and consulting fees from Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, Takeda Pharma, Vicore Pharma, and Mallinckrodt. These fees are unrelated to this work. BS-G reports grants and consultin fees from Janssen Pharmaceuticals, Chiesi Spain, Sanofi, and Merck. These fees are unrelated to this work.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. During the preparation of this work the authors used ChatGPT (OpenAI) to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

References

1. Brown AW, Tallarico EE, Steen V. Disease beyond the lungs: optimal care of multi-organ disease after lung transplantation. *Chest* (2025) 167(5):1282–4. doi:10.1016/j.chest.2024.09.036

2. Christie JD, Van Raemdonck D, Fisher AJ. Lung transplantation. *N Engl J Med* (2024) 391(19):1822–36. doi:10.1056/NEJMra2401039

3. Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: a systematic literature review. *Eur Respir J* (2015) 46(4):1113–30. doi:10.1183/13993003.02316-2014

4. Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* (2012) 186(2):155–61. doi:10.1164/rccm.201201-0034OC

5. Mesli F, Philippot Q, El Husseini K, Bunel V, Kannengiesser C, Debray MP, et al. Telomere biology disorders in lung transplantation: clinical challenges and management strategies. *JHLT Open* (2025) 9:100333. doi:10.1016/j.jhlto.2025.100333

6. Banaszak LG, Smith-Simmer K, Shoger K, Lovrien L, Malik A, Sandbo N, et al. Implementation of a prospective screening strategy to identify adults with a telomere biology disorder among those undergoing lung transplant evaluation for interstitial lung disease. *Respir Med* (2023) 220:107464. doi:10.1016/j.rmed.2023.107464

7. Alonso-Gonzalez A, Tosco-Herrera E, Molina-Molina M, Flores C. Idiopathic pulmonary fibrosis and the role of genetics in the era of precision medicine. *Front Med (Lausanne)* (2023) 10:1152211. doi:10.3389/fmed.2023.1152211

8. Bush EL, Krishnan A, Chidi AP, Nolley E, Agbor-Enoh S, West NE, et al. The effect of the cystic fibrosis care center on outcomes after lung transplantation for cystic fibrosis. *J Heart Lung Transpl* (2022) 41(3):300–7. doi:10.1016/j.healun.2021.11.013

9. Yang Z, Takahashi T, Terada Y, Meyers BF, Kozower BD, Patterson GA, et al. A comparison of outcomes after lung transplantation between European and North American centers. *J Heart Lung Transpl* (2022) 41(12):1729–35. doi:10.1016/j.healun.2022.07.014

10. Chambers HE, Reinschmidt K, Smith G, Agudelo E, Brodahl K, Herriman E, et al. Examining the critical role of advanced practice providers on a multidisciplinary transplant team. *Am J Transpl* (2021) 21(12):3840–6. doi:10.1111/ajt.16715

11. van Zanten R, van Dijk M, van Rosmalen J, Beck D, Zietse R, Van Hecke A, et al. Nurse-led self-management support after organ transplantation-protocol of a multicentre, stepped-wedge randomized controlled trial. *Trials* (2022) 23(1):14. doi:10.1186/s13063-021-05896-0

12. Wurster F, Fütterer G, Beckmann M, Dittmer K, Jaschke J, Köberlein-Neu J, et al. The analyzation of change in documentation due to the introduction of electronic patient records in Hospitals-A systematic review. *J Med Syst* (2022) 46(8):54. doi:10.1007/s10916-022-01840-0

13. Duettmann W, Naik MG, Zukunft B, Osmonodja B, Bachmann F, Choi M, et al. eHealth in transplantation. *Transpl Int* (2021) 34(1):16–26. doi:10.1111/tri.13778

14. Evald L, Graarup J, Højskov IE. Diary for self-observation: a self-management tool for recipients of lung transplantation-A pilot study. *Nurs Open* (2020) 7(6):1766–73. doi:10.1002/nop2.562

15. Wijbenga N, Hoek RAS, Mathot BJ, Seghers L, van Weezel JJ, den Ouden J, et al. Evaluation of a home monitoring application for follow up after lung Transplantation-A pilot study. *J Pers Med* (2020) 10(4):240. doi:10.3390/jpm10040240

16. Magnusson JM, Zajacová A, Saez-Gimenez B. Risk factors for chronic lung allograft dysfunction and graft surveillance. In: Perch M, Meloni F, Vos R, editors. *Lung transplantation*. Sheffield, UK: European Respiratory Society (2024). p. 210–32. doi:10.1183/2312508X.10002324

17. Shahabeddin Parizi A, Krabbe PFM, Verschuuren EAM, Hoek RAS, Kwakkel-van Erp JM, Erasmus ME, et al. Patient-reported health outcomes in long-term lung transplantation survivors: a prospective cohort study. *Am J Transpl* (2018) 18(3):684–95. doi:10.1111/ajt.14492

18. Bleisch B, Schuurmans MM, Klaghofer R, Benden C, Seiler A, Jenewein J. Health-related quality of life and stress-related post-transplant trajectories of lung transplant recipients: a three-year follow-up of the Swiss transplant cohort study. *Swiss Med Wkly* (2019) 149:w20019. doi:10.57187/smw.2019.20019

19. Rosenberger EM, DeVito Dabbs AJ, DiMartini AF, Landsittel DP, Pilewski JM, Dew MA. Long-term Follow-up of a randomized controlled trial evaluating a Mobile health intervention for self-management in lung transplant recipients. *Am J Transpl* (2017) 17(5):1286–93. doi:10.1111/ajt.14062

20. Denhaerynck K, Burkhalter F, Schäfer-Keller P, Steiger J, Bock A, De Geest S. Clinical consequences of non adherence to immunosuppressive medication in kidney transplant patients. *Transpl Int* (2009) 22(4):441–6. doi:10.1111/j.1432-2277.2008.00820.x

21. Kugler C, Fischer S, Gottlieb J, Tegtbur U, Welte T, Goerler H, et al. Symptom experience after lung transplantation: impact on quality of life and adherence. *Clin Transpl* (2007) 21(5):590–6. doi:10.1111/j.1399-0012.2007.00693.x

22. Singer JP, Soong A, Chen J, Shrestha P, Zhuo H, Gao Y, et al. Development and preliminary validation of the lung transplant quality of life (LT-QOL) survey. *Am J Respir Crit Care Med* (2019) 199(8):1008–19. doi:10.1164/rccm.201806-1198OC

23. Gholamzadeh M, Abtahi H, Safdari R. Telemedicine in lung transplant to improve patient-centered care: a systematic review. *Int J Med Inform* (2022) 167:104861. doi:10.1016/j.ijmedinf.2022.104861

24. Blumenthal JA, Mabe S, Arthur D, Frankel C, McKee DC, Morrison S, et al. Telehealth interventions to improve outcomes in lung transplant recipients: primary results of the INSPIRE-III randomized clinical trial. *J Heart Lung Transpl* (2025) 44(9):1449–59. doi:10.1016/j.healun.2025.03.017

25. Kim J, Villalonga-Olives E, Doumat G, Vesselinov RM, Huapaya JA, Abbas HMN, et al. Patient satisfaction with lung transplant telemedicine: lessons from the COVID-19 pandemic. *Telemed J E Health* (2025) 31(10):1228–35. doi:10.1089/tmj.2025.0090

26. Lesko MB, Rudym D, Kon Z, Snodgrass C, Sureau K, Angel LF, et al. Telehealth and home monitoring in lung transplant. *J Heart Lung Transpl* (2020) 39(4 Suppl. l):S383. doi:10.1016/j.healun.2020.01.492

27. Corr M, Walker A, Maxwell AP, McKay GJ. Non-adherence to immunosuppressive medications in kidney transplant recipients-a systematic scoping review. *Transpl Rev (Orlando)* (2025) 39(1):100900. doi:10.1016/j.trre.2024.100900

28. Korb-Savoldelli V, Sabatier B, Gillaizeau F, Guillemain R, Prognon P, Bégué D, et al. Non-adherence with drug treatment after heart or lung transplantation in adults: a systematic review. *Patient Educ Couns* (2010) 81(2):148–54. doi:10.1016/j.pec.2010.04.013

29. Schäfer-Keller P, Steiger J, Bock A, Denhaerynck K, De Geest S. Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. *Am J Transpl* (2008) 8(3):616–26. doi:10.1111/j.1600-6143.2007.02127.x

30. Denhaerynck K, Dobbels F, Košťálová B, De Geest S, Consortium BAASIS. Psychometric properties of the BAASIS: a meta-analysis of individual participant data. *Transplantation* (2023) 107(8):1795–809. doi:10.1097/TP.0000000000004574

31. Lieb M, Hepp T, Schiffer M, Opgenoorth M, Erim Y. Accuracy and concordance of measurement methods to assess non-adherence after renal transplantation - a prospective study. *BMC Nephrol* (2020) 21(1):114. doi:10.1186/s12882-020-01781-1

32. Cooper BG, Stocks J, Hall GL, Culver B, Steenbruggen I, Carter KW, et al. The global lung function initiative (GLI) network: bringing the world's respiratory reference values together. *Breathe (Sheff).* (2017) 13(3):e56–e64. doi:10.1183/20734735.012717

33. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* (2012) 40(6):1324–43. doi:10.1183/09031936.00080312

34. Miller MR, Quanjer PH, Swanney MP, Ruppel G, Enright PL. Interpreting lung function data using 80% predicted and fixed thresholds misclassifies more than 20% of patients. *Chest* (2011) 139(1):52–9. doi:10.1378/chest.10-0189

35. Sengpiel J, Fuehner T, Kugler C, Avsar M, Bodmann I, Boemke A, et al. Use of telehealth technology for home spirometry after lung transplantation: a randomized controlled trial. *Prog Transpl* (2010) 20(4):310–7. doi:10.1177/152692481002000402

36. Boente RD, Schacht S, Borton R, Vincent J, Golzarri-Arroyo L, Rattray N. Assessing the acceptability and feasibility of remote spirometric monitoring for rural patients with interstitial lung disease: a multimethod approach. *Respir Res* (2024) 25(1):92. doi:10.1186/s12931-024-02735-z

37. Odisho AY, Liu AW, Maiorano AR, Bigazzi MOA, Medina E, Leard LE, et al. Design and implementation of a digital health home spirometry intervention for remote monitoring of lung transplant function. *J Heart Lung Transpl* (2023) 42(6):828–37. doi:10.1016/j.healun.2023.01.010

38. Verleden GM, Glanville AR, Lease ED, Fisher AJ, Calabrese F, Corris PA, et al. Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment-A consensus report from the pulmonary council of the ISHLT. *J Heart Lung Transpl* (2019) 38(5):493–503. doi:10.1016/j.healun.2019.03.009

39. Liu J, Jackson K, Weinkauf J, Kapasi A, Hirji A, Meyer S, et al. Baseline lung allograft dysfunction is associated with impaired survival after double-lung transplantation. *J Heart Lung Transpl* (2018) 37(7):895–902. doi:10.1016/j.healun.2018.02.014

40. Li D, Weinkauf J, Kapasi A, Hirji A, Varughese R, Lien D, et al. Baseline lung allograft dysfunction in primary graft dysfunction survivors after lung transplantation. *Respir Med* (2021) 188:106617. doi:10.1016/j.rmed.2021.106617

41. Keller MB, Sun J, Alnababteh M, Ponor L, D Shah P, Mathew J, et al. Baseline lung allograft dysfunction after bilateral lung transplantation is associated with an increased risk of death: results from a multicenter cohort study. *Transpl Direct* (2024) 10(7):e1669. doi:10.1097/TXD.0000000000001669

42. Tiffeneau R, Pinelli A. Circulating air and captive air in the exploration of the pulmonary ventilator function. *Paris Med* (1947) 37:624–8.

43. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J* (2005) 26(5):948–68. doi:10.1183/09031936.05.00035205

44. Barros AR, Pires MB, Raposo NM. Importance of slow vital capacity in the detection of airway obstruction. *J Bras Pneumol* (2013) 39(3):317–22. doi:10.1590/S1806-37132013000300008

45. Saint-Pierre M, Ladha J, Berton DC, Reimao G, Castelli G, Marillier M, et al. Is the slow vital capacity clinically useful to uncover airflow limitation in subjects with preserved FEV1/FVC ratio? *Chest* (2019) 156(3):497–506. doi:10.1016/j.chest.2019.02.001

46. Fortis S, Comellas AP, Bhatt SP, Hoffman EA, Han MK, Bhakta NR, et al. Ratio of FEV1/Slow vital capacity of < 0.7 is associated with clinical, functional, and radiologic features of obstructive lung disease in smokers with preserved lung function. *Chest* (2021) 160(1):94–103. doi:10.1016/j.chest.2021.01.067

47. Fila L, Zajacova A. Navigating the pitfalls of pulmonary function testing in chronic lung allograft dysfunction and chronic pulmonary graft-versus-host disease. *Eur J Intern Med* (2025) 141:106500. doi:10.1016/j.ejim.2025.106500

48. Kerckhof P, Verstraete K, Beeckmans H, Vos R, Mcdonough J, Vanaudenaerde B, et al. Machine learning of spirometry May predict CLAD onset after lung transplantation. *Presented Eur Respir Soc (Ers) Congress* (2024) OA989. doi:10.1183/13993003.congress-2024.OA989

49. Gottlieb J, Vos R, Jaksch P, Hellemons M, Holm AM, Morlacchi LC, et al. Chronic lung allograft dysfunction after lung transplantation: prevention, diagnosis and treatment in 44 European centres. *ERJ Open Res* (2025) 11(3):00675–2024. doi:10.1183/23120541.00675-2024

50. O'Donnell CR, Bankier AA, Stiebellehner L, Reilly JJ, Brown R, Loring SH. Comparison of plethysmographic and helium dilution lung volumes: which is best for COPD? *Chest* (2010) 137(5):1108–15. doi:10.1378/chest.09-1504

51. Darley DR, Ma J, Huszti E, Ghany R, Hutcheon M, Chow CW, et al. Diffusing capacity of the lung for carbon monoxide: association with long-term outcomes after lung transplantation in a 20-year longitudinal study. *Eur Respir J* (2022) 59(1):2003639. doi:10.1183/13993003.03639-2020

52. Wuyts WA, Wijsenbeek M, Bondue B, Bouros D, Bresser P, Robalo Cordeiro C, et al. Idiopathic pulmonary fibrosis: best practice in monitoring and managing a relentless fibrotic disease. *Respiration* (2020) 99(1):73–82. doi:10.1159/000504763

53. Lee H, Kim SY, Park YS, Choi SM, Lee JH, Park J. Prognostic implication of 1-year decline in diffusing capacity in newly diagnosed idiopathic pulmonary fibrosis. *Sci Rep* (2024) 14(1):8857. doi:10.1038/s41598-024-59649-5

54. Bhakta NR, McGowan A, Ramsey KA, Borg B, Kivastik J, Knight SL, et al. European respiratory society/american thoracic society technical statement: standardisation of the measurement of lung volumes, 2023 update. *Eur Respir J* (2023) 62(4):2201519. doi:10.1183/13993003.01519-2022

55. Cho E, Wu JKY, Birriel DC, Matelski J, Nadj R, DeHaas E, et al. Airway oscillometry detects spirometric-silent episodes of acute cellular rejection. *Am J Respir Crit Care Med* (2020) 201(12):1536–44. doi:10.1164/rccm.201908-1539OC

56. Vasileva A, Hanafi N, Huszti E, Matelski J, Belousova N, Wu JKY, et al. Intra-subject variability in oscillometry correlates with acute rejection and CLAD post-lung transplant. *Front Med (Lausanne)* (2023) 10:1158870. doi:10.3389/fmed.2023.1158870

57. Sim JPY, Nilsen K, Borg BM, Levvey B, Vazirani J, Ennis S, et al. Oscillometry in stable single and double lung allograft recipients transplanted for interstitial lung disease: results of a multi-center Australian study. *Transpl Int* (2023) 36:11758. doi:10.3389/ti.2023.11758

58. Crowhurst TD, Butler JA, Bussell LA, Johnston SD, Yeung D, Hodge G, et al. Impulse oscillometry *versus* spirometry to detect bronchiolitis obliterans syndrome in bilateral lung transplant recipients: a prospective diagnostic study. *Transplantation* (2024) 108(4):1004–14. doi:10.1097/TP.0000000000004868

59. King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellacà RL, et al. Technical standards for respiratory oscillometry. *Eur Respir J* (2020) 55(2):1900753. doi:10.1183/13993003.00753-2019

60. Silkoff PE, Caramori M, Tremblay L, McClean P, Chaparro C, Kesten S, et al. Exhaled nitric oxide in human lung transplantation. A noninvasive marker of acute rejection. *Am J Respir Crit Care Med* (1998) 157(6 Pt 1):1822–8. doi:10.1164/ajrccm.157.6.9707159

61. Gashouta MA, Merlo CA, Pipeling MR, McDyer JF, Hayanga JWA, Orens JB, et al. Serial monitoring of exhaled nitric oxide in lung transplant recipients. *J Heart Lung Transpl* (2015) 34(4):557–62. doi:10.1016/j.healun.2014.09.026

62. Verleden GM, Dupont LJ, Delcroix M, Van Raemdonck D, Vanhaecke J, Lerut T, et al. Exhaled nitric oxide after lung transplantation: impact of the native lung. *Eur Respir J* (2003) 21(3):429–32. doi:10.1183/09031936.03.00023003a

63. Antus B, Csiszer E, Czebe K, Horvath I. Pulmonary infections increase exhaled nitric oxide in lung transplant recipients: a longitudinal study. *Clin Transpl* (2005) 19(3):377–82. doi:10.1111/j.1399-0012.2005.00354.x

64. Stanojevic S, Bowerman C, Robinson P. Multiple breath washout: measuring early manifestations of lung pathology. *Breathe (Sheff).* (2021) 17(3):210016. doi:10.1183/20734735.0016-2021

65. Kao JE, Zirbes JM, Conrad CK, Milla CE. Lung clearance index is sensitive to small airway disease in pediatric lung transplant recipients. *J Heart Lung Transpl* (2017) 36(9):980–4. doi:10.1016/j.healun.2017.05.004

66. Driskel M, Horsley A, Fretwell L, Clayton N, Al-Aloul M. Lung clearance index in detection of post-transplant bronchiolitis obliterans syndrome. *ERJ Open Res* (2019) 5(4):00164–2019. doi:10.1183/23120541.00164-2019

67. Wijbenga N, Mathot BJ, van Pel R, Seghers L, Moor CC, Aerts JGJV, et al. The ability of an electronic nose to distinguish between complications in lung transplant recipients. *Am J Transpl* (2025) 25(4):804–13. doi:10.1016/j.ajt.2024.11.009

68. Wijbenga N, Hoek RAS, Mathot BJ, Seghers L, Moor CC, Aerts JGJV, et al. Diagnostic performance of electronic nose technology in chronic lung allograft dysfunction. *J Heart Lung Transpl* (2023) 42(2):236–45. doi:10.1016/j.healun.2022.09.009

69. Snell GI, Yusen RD, Weill D, Strueber M, Garrity E, Reed A, et al. Report of the ISHLT working group on primary lung graft dysfunction, part I: definition and grading-A 2016 consensus group statement of the international society for heart and lung transplantation. *J Heart Lung Transpl* (2017) 36(10):1097–103. doi:10.1016/j.healun.2017.07.021

70. Calvert AD, Hazelton TR. Role of imaging in lung transplantation evaluation. *J Thorac Dis* (2020) 12(9):5147–58. doi:10.21037/jtd.2019.08.35

71. Sankaran R, Cypro A, Hasenstab K, Steward AM, Afshar K, Golts E, et al. Clinical implementation of inspiratory-expiratory chest CT: defining quality criteria for

diagnostic quality and detection of concurrent FEV1 decline following lung transplantation. *Radiol Cardiothorac Imaging* (2025) 7(5):e240468. doi:10.1148/ryct.240468

72. Konen E, Gutierrez C, Chaparro C, Murray CP, Chung T, Crossin J, et al. Bronchiolitis obliterans syndrome in lung transplant recipients: can thin-section CT findings predict disease before its clinical appearance? *Radiology* (2004) 231(2):467–73. doi:10.1148/radiol.2312030563

73. DeFreitas MR, McAdams HP, Azfar Ali H, Iranmanesh AM, Chalian H. Complications of lung transplantation: update on imaging manifestations and management. *Radiol Cardiothorac Imaging* (2021) 3(4):e190252. doi:10.1148/ryct.2021190252

74. Lee ES, Gotway MB, Reddy GP, Golden JA, Keith FM, Webb WR. Early bronchiolitis obliterans following lung transplantation: accuracy of expiratory thin-section CT for diagnosis. *Radiology* (2000) 216(2):472–7. doi:10.1148/radiology.216.2.r00au21472

75. Habert P, Chetrit E, Coiffard B, Bregeon F, Thomas P, Loundou A, et al. Early chest CT abnormalities to predict the subsequent occurrence of chronic lung allograft dysfunction. *Insights Imaging* (2023) 14(1):154. doi:10.1186/s13244-023-01509-3

76. Solyanik O, Hollmann P, Dettmer S, Kaireit T, Schaefer-Prokop C, Wacker F, et al. Quantification of pathologic air trapping in lung transplant patients using CT density mapping: Comparison with other CT air trapping measures. *PLoS One* (2015) 10(10): e0139102. doi:10.1371/journal.pone.0139102

77. Verleden SE, Vos R, Vandermeulen E, Ruttens D, Bellon H, Heigl T, et al. Parametric response mapping of bronchiolitis obliterans syndrome progression after lung transplantation. *Am J Transpl* (2016) 16(11):3262–9. doi:10.1111/ajt.13945

78. Kim SJ, Azour L, Hutchinson BD, Shirsat H, Zhou F, Narula N, et al. Imaging course of lung transplantation: from patient selection to postoperative complications. *Radiographics* (2021) 41(4):1043–63. doi:10.1148/rg.2021200173

79. Brun AL, Chabi ML, Picard C, Mellot F, Grenier PA. Lung transplantation: CT assessment of chronic lung allograft dysfunction (CLAD). *Diagnostics (Basel)* (2021) 11(5):817. doi:10.3390/diagnostics11050817

80. Barbosa EM, Simpson S, Lee JC, Tustison N, Gee J, Shou H. Multivariate modeling using quantitative CT metrics may improve accuracy of diagnosis of bronchiolitis obliterans syndrome after lung transplantation. *Comput Biol Med* (2017) 89:275–81. doi:10.1016/j.compbiomed.2017.08.016

81. Barbosa EJMJ, Lanclus M, Vos W, Van Holsbeke C, De Backer W, De Backer J, et al. Machine learning algorithms utilizing quantitative CT features May predict eventual onset of Bronchiolitis Obliterans syndrome after lung transplantation. *Acad Radiol* (2018) 25(9):1201–12. doi:10.1016/j.acra.2018.01.013

82. Belloli EA, Gu T, Wang Y, Vummidi D, Lyu DM, Combs MP, et al. Radiographic graft surveillance in lung transplantation: prognostic role of parametric response mapping. *Am J Respir Crit Care Med* (2021) 204(8):967–76. doi:10.1164/rccm.202012-4528OC

83. Koziński M, Oner D, Gwizdała J, Beigelman-Aubry C, Fua P, Koutsokera A, et al. Harnessing deep learning to detect bronchiolitis obliterans syndrome from chest CT. *Commun Med (Lond)* (2025) 5(1):18. doi:10.1038/s43856-025-00732-x

84. Van Herck A, Beeckmans H, Kerckhof P, Sacreas A, Kaes J, Vanstapel A., et al. Prognostic value of chest CT findings at BOS diagnosis in lung transplant recipients. *Transplantation* (2023) 107(11):e292–e304. doi:10.1097/TP.0000000000004726

85. Verleden SE, de Jong PA, Ruttens D, Vandermeulen E, van Raemdonck DE, Verschakelen J, et al. Functional and computed tomographic evolution and survival of restrictive allograft syndrome after lung transplantation. *J Heart Lung Transpl* (2014) 33(3):270–7. doi:10.1016/j.healun.2013.12.011

86. Dettmer S, Shin HO, Vogel-Claussen J, Westphal M, Haverich A, Warnecke G, et al. CT at onset of chronic lung allograft dysfunction in lung transplant patients predicts development of the restrictive phenotype and survival. *Eur J Radiol* (2017) 94:78–84. doi:10.1016/j.ejrad.2017.06.008

87. Weigt SS, Kim GJ, Jones HD, Ramsey AL, Amubieya O, Abtin F, et al. Quantitative image analysis at chronic lung allograft dysfunction onset predicts mortality. *Transplantation* (2022) 106(6):1253–61. doi:10.1097/TP.0000000000003950

88. Dettmer S, Suhling H, Klingenberg I, Otten O, Kaireit T, Fuge J, et al. Lobe-wise assessment of lung volume and density distribution in lung transplant patients and value for early detection of bronchiolitis obliterans syndrome. *Eur J Radiol* (2018) 106:137–44. doi:10.1016/j.ejrad.2018.07.016

89. Horie M, Salazar P, Saito T, Binnie M, Brock K, Yasufuku K, et al. Quantitative chest CT for subtyping chronic lung allograft dysfunction and its association with survival. *Clin Transpl* (2018) 32(5):e13233. doi:10.1111/ctr.13233

90. McInnis MC, Ma J, Karur GR, Houbois C, Levy L, Havlin J, et al. Chronic lung allograft dysfunction phenotype and prognosis by machine learning CT analysis. *Eur Respir J* (2022) 60(1):2101652. doi:10.1183/13993003.01652-2021

91. Fuchs E, Levy L, Huszti E, Renaud-Picard B, Berra G, Kawashima M, et al. Significance of phenotype change after chronic lung allograft dysfunction onset. *Transpl Int* (2021) 34(12):2620–32. doi:10.1111/tri.14157

92. Peräkylä L, Nykänen A, Piilonen A, Kesävuori R, Halme M, Raivio P. Transition from BOS to RAS impairs prognosis after lung transplantation-CLAD subtype analysis by CT volumetry. *PLoS One* (2022) 17(10):e0275563. doi:10.1371/journal.pone.0275563

93. Gast KK, Zaporozhan J, Ley S, Biedermann A, Knitz F, Eberle B, et al. (3)He-MRI in follow-up of lung transplant recipients. *Eur Radiol* (2004) 14(1):78–85. doi:10.1007/s00330-003-2092-4

94. McAdams HP, Palmer SM, Donnelly LF, Charles HC, Tapson VF, MacFall JR. Hyperpolarized 3He-enhanced MR imaging of lung transplant recipients: preliminary results. *AJR Am J Roentgenol* (1999) 173(4):955–9. doi:10.2214/ajr.173.4.10511156

95. Renne J, Lauermann P, Hinrichs JB, Schönfeld C, Sorrentino S, Gutberlet M, et al. Chronic lung allograft dysfunction: oxygen-Enhanced T1-Mapping MR imaging of the lung. *Radiology* (2015) 276(1):266–73. doi:10.1148/radiol.15141486

96. Vogel-Claussen J, Kaireit TF, Voskrebenzev A, Klimeš F, Glandorf J, Behrendt L, et al. Phase-resolved functional lung (PREFUL) MRI-derived ventilation and perfusion parameters predict future lung transplant loss. *Radiology* (2023) 307(4):e221958. doi:10.1148/radiol.221958

97. Moher AT, Voskrebenzev A, Greer M, Becker L, Kaireit TF, Welte T, et al. MRI-derived regional flow-volume loop parameters detect early-stage chronic lung allograft dysfunction. *J Magn Reson Imaging* (2019) 50(6):1873–82. doi:10.1002/jmri.26799

98. Neal MA, Bos S, Holland CW, Hollingsworth KG, Meachery G, Nair A, et al. Dynamic 19F-MRI of pulmonary ventilation in lung transplant recipients with and without chronic lung allograft dysfunction. *JHLT Open* (2024) 7:100167. doi:10.1016/j.jhlto.2024.100167

99. Daniel M, Lang E, Huynh TM, Martin J, Brebion M, Guessous K, et al. Prevalence and time-course of diaphragmatic dysfunction following lung resection: a repeated ultrasonic assessment. *Anaesth Crit Care Pain Med* (2022) 41(2):101024. doi:10.1016/j.accpm.2022.101024

100. Verleden SE, Gheysens O, Goffin KE, Vanaudenaerde BM, Verbeken EK, Weynand B, et al. Role of 18F-FDG PET/CT in restrictive allograft syndrome after lung transplantation. *Transplantation* (2019) 103(4):823–31. doi:10.1097/TP.0000000000002393

101. Pinho DF, Banga A, Torres F, Mathews D. Ventilation perfusion pulmonary scintigraphy in the evaluation of pre-and post-lung transplant patients. *Transpl Rev (Orlando)* (2019) 33(2):107–14. doi:10.1016/j.trre.2018.10.003

102. Ouwens JP, van der Bij W, van der Mark TW, Geertsma A, Piers DA, de Boer WJ, et al. The value of ventilation scintigraphy after single lung transplantation. *J Heart Lung Transpl* (2004) 23(1):115–21. doi:10.1016/s1053-2498(03)00067-6

103. Miyashita Y, Kaiho T, Nagata H, Hiroshima T, Sugiura Y, Zhang K, et al. Exploring fibroblast activation protein as an early biomarker in chronic lung allograft dysfunction. *Eur Respir J* (2025):2501738. doi:10.1183/13993003.01738-2025

104. Martinu T, Koutsokera A, Benden C, Cantu E, Chambers D, Cypel M, et al. International society for heart and lung transplantation consensus statement for the standardization of bronchoalveolar lavage in lung transplantation. *J Heart Lung Transpl* (2020) 39(11):1171–90. doi:10.1016/j.healun.2020.07.006

105. Fricke K, Sievi NA, Schmidt FP, Schuurmans MM, Kohler M. Efficacy of surveillance bronchoscopy *versus* clinically indicated bronchoscopy for detection of acute lung transplant rejection: a systematic review and meta-analysis. *ERJ Open Res* (2024) 10(5):00404–2024. doi:10.1183/23120541.00404-2024

106. Frye BC, Gasplmayr M, Hettich I, Zissel G, Müller-Quernheim J. Surveillance bronchoscopy for the care of lung transplant recipients: a retrospective single center analysis. *Transpl Proc* (2021) 53(1):265–72. doi:10.1016/j.transproceed.2020.08.011

107. McWilliams TJ, Williams TJ, Whitford HM, Snell GI. Surveillance bronchoscopy in lung transplant recipients: risk *versus* benefit. *J Heart Lung Transpl* (2008) 27(11): 1203–9. doi:10.1016/j.healun.2008.08.004

108. Takizawa DB, de Castro CCB, Paiva MA, Campos SV, Carraro RM, Costa AN, et al. Surveillance bronchoscopy in lung transplantation recipients: a single center experience analysis. *Transpl Proc* (2020) 52(5):1380–3. doi:10.1016/j.transproceed.2020.02.029

109. Glanville AR. Bronchoscopic monitoring after lung transplantation. *Semin Respir Crit Care Med* (2010) 31(2):208–21. doi:10.1055/s-0030-1249117

110. Sandrini A, Glanville AR. The controversial role of surveillance bronchoscopy after lung transplantation. *Curr Opin Organ Transpl* (2009) 14(5):494–8. doi:10.1097/MOT.0b013e3283300a3b

111. Rademacher J, Suhling H, Greer M, Haverich A, Welte T, Warnecke G, et al. Safety and efficacy of outpatient bronchoscopy in lung transplant recipients - a single centre analysis of 3,197 procedures. *Transpl Res* (2014) 3:11. doi:10.1186/2047-1440-3-11

112. Glanville AR. The role of bronchoscopic surveillance monitoring in the care of lung transplant recipients. *Semin Respir Crit Care Med* (2006) 27(5):480–91. doi:10.1055/s-2006-954606

113. Scott JP, Fradet G, Smyth RL, Mullins P, Pratt A, Clelland CA, et al. Prospective study of transbronchial biopsies in the management of heart-lung and single lung transplant patients. *J Heart Lung Transpl* (1991) 10(5 Pt 1):626–37.

114. Chan CC, Abi-Saleh WJ, Arroliga AC, Stillwell PC, Kirby TJ, Gordon SM, et al. Diagnostic yield and therapeutic impact of flexible bronchoscopy in lung transplant recipients. *J Heart Lung Transpl* (1996) 15(2):196–205.

115. Chakinala MM, Ritter J, Gage BF, Lynch JP, Aloush A, Patterson GA, et al. Yield of surveillance bronchoscopy for acute rejection and lymphocytic bronchitis/bronchiolitis after lung transplantation. *J Heart Lung Transpl* (2004) 23(12):1396–404. doi:10.1016/j.healun.2003.09.018

116. Stephenson A, Flint J, English J, Vedal S, Fradet G, Chittock D, et al. Interpretation of transbronchial lung biopsies from lung transplant recipients: inter- and intraobserver agreement. *Can Respir J* (2005) 12(2):75–7. doi:10.1155/2005/483172

117. Colombat M, Groussard O, Lautrette A, Thabut G, Marrash-Chahla R, Brugière O, et al. Analysis of the different histologic lesions observed in transbronchial biopsy for the diagnosis of acute rejection. Clinicopathologic correlations during the first 6 months after lung transplantation. *Hum Pathol* (2005) 36(4):387–94. doi:10.1016/j.humpath.2005.01.022

118. Verleden SE, Ruttens D, Vandermeulen E, Vaneylen A, Dupont LJ, Van Raemdonck DE, et al. Bronchiolitis obliterans syndrome and restrictive allograft syndrome: do risk factors differ? *Transplantation* (2013) 95(9):1167–72. doi:10.1097/TP.0b013e318286e076

119. Burton CM, Iversen M, Carlsen J, Andersen CB. Interstitial inflammatory lesions of the pulmonary allograft: a retrospective analysis of 2697 transbronchial biopsies. *Transplantation* (2008) 86(6):811–9. doi:10.1097/TP.0b013e3181852f02

120. Sharples LD, McNeil K, Stewart S, Wallwork J. Risk factors for bronchiolitis obliterans: a systematic review of recent publications. *J Heart Lung Transpl* (2002) 21(2): 271–81. doi:10.1016/s1053-2498(01)00360-6

121. Glanville AR, Aboyoun CL, Havryk A, Plit M, Rainer S, Malouf MA. Severity of lymphocytic bronchiolitis predicts long-term outcome after lung transplantation. *Am J Respir Crit Care Med* (2008) 177(9):1033–40. doi:10.1164/rccm.200706-951OC

122. Valentine VG, Gupta MR, Weill D, Lombard GA, LaPlace SG, Seoane L, et al. Single-institution study evaluating the utility of surveillance bronchoscopy after lung transplantation. *J Heart Lung Transpl* (2009) 28(1):14–20. doi:10.1016/j.healun.2008.10.010

123. Steinack C, Roeder M, Vesenbeckh S, Haberecker M, Rüschoff JH, Hage R, et al. Transbronchial cryobiopsy alone *versus* combined with traditional forceps biopsy for acute cellular rejection in lung transplant recipients. A diagnostic randomized trial. *JHLT Open* (2025) 8:100262. doi:10.1016/j.jhlto.2025.100262

124. Loor K, Culebras M, Sansano I, Álvarez A, Sacanell J, García-de-Acilu M, et al. Lung allograft transbronchial cryobiopsy for critical ventilated patients: a randomised trial. *Eur Respir J* (2023) 61(1):2102354. doi:10.1183/13993003.02354-2021

125. Halloran K, Vos R, Snell G, Greenland JR. The lung transplant endobronchial biopsy: a forgotten specimen comes of age. *J Heart Lung Transpl* (2025) 44(2):293–7. doi:10.1016/j.healun.2024.10.019

126. Mohanty RP, Moghbeli K, Singer JP, Calabrese DR, Hays SR, Iasella C, et al. Small airway brush gene expression predicts chronic lung allograft dysfunction and mortality. *J Heart Lung Transpl* (2024) 43(11):1820–32. doi:10.1016/j.healun.2024.07.010

127. Iasella CJ, Hoji A, Popescu I, Wei J, Snyder ME, Zhang Y, et al. Type-1 immunity and endogenous immune regulators predominate in the airway transcriptome during chronic lung allograft dysfunction. *Am J Transpl* (2021) 21(6):2145–60. doi:10.1111/ajt.16360

128. Vos R, Van Herck A. *Pseudomonas aeruginosa* and chronic lung allograft dysfunction: does evading an iceberg prevent the ship from sinking? *Eur Respir J* (2021) 58(1):2100041. doi:10.1183/13993003.00041-2021

129. Girgis RE, Reichenspurner H, Robbins RC, Reitz BA, Theodore J. The utility of annual surveillance bronchoscopy in heart-lung transplant recipients. *Transplantation* (1995) 60(12):1458–61. doi:10.1097/00007890-199560120-00015

130. Lehto JT, Koskinen PK, Anttila VJ, Lautenschlager I, Lemström K, Sipponen J, et al. Bronchoscopy in the diagnosis and surveillance of respiratory infections in lung and heart-lung transplant recipients. *Transpl Int* (2005) 18(5):562–71. doi:10.1111/j.1432-2277.2005.00089.x

131. Vandermeulen E, Verleden SE, Ruttens D, Moelants E, Mortier A, Somers J, et al. BAL neutrophilia in azithromycin-treated lung transplant recipients: clinical significance. *Transpl Immunol* (2015) 33(1):37–44. doi:10.1016/j.trim.2015.07.001

132. Neurohr C, Huppmann P, Samweber B, Leuschner S, Zimmermann G, Leuchte H, et al. Prognostic value of bronchoalveolar lavage neutrophilia in stable lung transplant recipients. *J Heart Lung Transpl* (2009) 28(5):468–74. doi:10.1016/j.healun.2009.01.014

133. Verleden SE, Ruttens D, Vandermeulen E, Bellon H, Dubbeldam A, De Wever W, et al. Predictors of survival in restrictive chronic lung allograft dysfunction after lung transplantation. *J Heart Lung Transpl* (2016) 35(9):1078–84. doi:10.1016/j.healun.2016.03.022

134. Verleden SE, Ruttens D, Vandermeulen E, van Raemdonck DE, Vanaudenaerde BM, Verleden GM, et al. Elevated bronchoalveolar lavage eosinophilia correlates with poor outcome after lung transplantation. *Transplantation* (2014) 97(1):83–9. doi:10.1097/TP.0b013e3182a6bae2

135. Todd JL, Weber JM, Kelly FL, Neely ML, Mulder H, Frankel CW, et al. BAL fluid eosinophilia associates with chronic lung allograft dysfunction risk: a multicenter study. *Chest* (2023) 164(3):670–81. doi:10.1016/j.chest.2023.03.033

136. Yang JYC, Verleden SE, Zarinsefat A, Vanaudenaerde BM, Vos R, Verleden GM, et al. Cell-free DNA and CXCL10 derived from bronchoalveolar lavage predict lung transplant survival. *J Clin Med* (2019) 8(2):241. doi:10.3390/jcm8020241

137. Shino MY, Weigt SS, Li N, Derhovanessian A, Sayah DM, Saggar R, et al. The prognostic importance of bronchoalveolar lavage fluid CXCL9 during minimal acute rejection on the risk of chronic lung allograft dysfunction. *Am J Transpl* (2018) 18(1): 136–44. doi:10.1111/ajt.14397

138. Gregson AL, Hoji A, Injean P, Poynter ST, Briones C, Palchevskiy V, et al. Altered exosomal RNA profiles in bronchoalveolar lavage from lung transplants with acute rejection. *Am J Respir Crit Care Med* (2015) 192(12):1490–503. doi:10.1164/rccm.201503-0558OC

139. Crossland RE, Bolton SJ, Fisher AJ. The role of extracellular vesicles in chronic lung allograft dysfunction and response to extracorporeal photopheresis. *JHLT Open* (2025) 9:100322. doi:10.1016/j.jhlto.2025.100322

140. Halloran K, Mackova M, Parkes MD, Hirji A, Weinkauf J, Timofte IL, et al. The molecular features of chronic lung allograft dysfunction in lung transplant airway mucosa. *J Heart Lung Transpl* (2022) 41(12):1689–99. doi:10.1016/j.healun.2022.08.014

141. Halloran K, Parkes MD, Timofte I, Snell G, Westall G, Havlin J, et al. Molecular T-cell–mediated rejection in transbronchial and mucosal lung transplant biopsies is associated with future risk of graft loss. *J Heart Lung Transpl* (2020) 39(12):1327–37. doi:10.1016/j.healun.2020.08.013

142. Gauthier PT, Mackova M, Hirji A, Weinkauf J, Timofte IL, Snell GI, et al. Defining a natural killer cell-enriched molecular rejection-like state in lung transplant transbronchial biopsies. *Am J Transpl* (2023) 23(12):1922–38. doi:10.1016/j.ajt.2023.06.003

143. Zajacova A, Mackova M, Halloran K, Gauthier P, Balko J, Guney M, et al. Treatment responses in histologic *versus* molecular diagnoses of lung rejection. *Transpl Int* (2024) 37:12847. doi:10.3389/ti.2024.12847

144. Mehlman Y, Valledor AF, Moeller C, Rubinstein G, Lotan D, Rahman S, et al. The utilization of molecular microscope in management of heart transplant recipients in the era of noninvasive monitoring. *Clin Transpl* (2023) 37(12):e15131. doi:10.1111/ctr.15131

145. Naesens M, Roufosse C, Haas M, Lefaucheur C, Mannon RB, Adam BA, et al. The banff 2022 kidney meeting report: reappraisal of microvascular inflammation and the role of biopsy-based transcript diagnostics. *Am J Transpl* (2024) 24(3):338–49. doi:10.1016/j.ajt.2023.10.016

146. Weigt SS, Wang X, Palchevskiy V, Li X, Patel N, Ross DJ, et al. Usefulness of gene expression profiling of bronchoalveolar lavage cells in acute lung allograft rejection. *J Heart Lung Transpl* (2019) 38(8):845–55. doi:10.1016/j.healun.2019.05.001

147. Nelson J, Alvey N, Bowman L, Schulte J, Segovia MC, McDermott J, et al. Consensus recommendations for use of maintenance immunosuppression in solid organ transplantation: endorsed by the American college of clinical pharmacy, American society of transplantation, and international society for heart and lung transplantation: an executive summary. *Pharmacotherapy* (2022) 42(8):594–8. doi:10.1002/phar.2718

148. Katada Y, Nakagawa S, Itohara K, Suzuki T, Kato R, Endo H, et al. Association between time in therapeutic range of tacrolimus blood concentration and acute rejection within the first three months after lung transplantation. *J Pharm Health Care Sci* (2022) 8(1):25. doi:10.1186/s40780-022-00256-9

149. Mabasa VH, Ensom MH. The role of therapeutic monitoring of everolimus in solid organ transplantation. *Ther Drug Monit* (2005) 27(5):666–76. doi:10.1097/01.ftd.0000175911.70172.2e

150. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. *Clin Pharmacokinet* (2007) 46(1):13–58. doi:10.2165/00003088-200746010-00002

151. Gregoor PJ, de Sévaux RG, Hené RJ, Hesse CJ, Hilbrands LB, Vos P, et al. Effect of cyclosporine on mycophenolic acid trough levels in kidney transplant recipients. *Transplantation* (1999) 68(10):1603–6. doi:10.1097/00007890-199911270-00028

152. Mathew BS, Mathew SK, Aruldhas BW, Prabha R, Gangadharan N, David VG, et al. Analytical and clinical validation of dried blood spot and volumetric absorptive microsampling for measurement of tacrolimus and creatinine after renal transplantation. *Clin Biochem* (2022) 105-106:25–34. doi:10.1016/j.clinbiochem.2022.04.014

153. Zwart TC, Gokoel SRM, van der Boog PJM, de Fijter JW, Kweekel DM, Swen JJ, et al. Therapeutic drug monitoring of tacrolimus and mycophenolic acid in outpatient renal transplant recipients using a volumetric dried blood spot sampling device. *Br J Clin Pharmacol* (2018) 84(12):2889–902. doi:10.1111/bcp.13755

154. Forier B, Schaevers V, Spriet I, Quintens C, Desmet S, Bos S, et al. Outpatient parenteral antibiotic therapy in non-cystic fibrosis lung transplant recipients: characteristics, efficacy and safety. *Eur J Clin Microbiol Infect Dis* (2025) 44(6): 1481–90. doi:10.1007/s10096-024-04921-9

155. Dvořáčková E, Michaličková D, Petrus J, Klapková E, Dutková A, Kotowski T, et al. Population pharmacokinetics and dose optimization of valganciclovir and ganciclovir in lung transplant recipients. *Med Princ Pract* (2025) 35:169–80. doi:10.1159/000548942

156. Dvorackova E, Sima M, Vyskocilova K, Kotowski T, Dunovská K, Klapkova E, et al. Population pharmacokinetics and covariate-based dosing individualization of voriconazole in lung transplant recipients. *J Chemother* (2024) 36(1):35–44. doi:10.1080/1120009X.2023.2219590

157. Dvořáčková E, Šíma M, Zajacová A, Vyskočilová K, Kotowski T, Dunovská K, et al. Dosing optimization of posaconazole in lung-transplant recipients based on population pharmacokinetic model. *Antibiotics (Basel)* (2023) 12(9):1399. doi:10.3390/antibiotics12091399

158. Levine DJ, Glanville AR, Aboyoun C, Belperio J, Benden C, Berry GJ, et al. Antibody-mediated rejection of the lung: a consensus report of the international society for heart and lung transplantation. *J Heart Lung Transpl* (2016) 35(4):397–406. doi:10.1016/j.healun.2016.01.1223

159. European Federation for Immunogenetics. *Standards for histocompatibility and immunogenetics testing*. Strasbourg: European Federation for Immunogenetics (EFI) (2024).

160. Lefaucheur C, Louis K, Morris AB, Taupin JL, Nickerson P, Tambur AR, et al. Clinical recommendations for posttransplant assessment of anti-HLA (human leukocyte antigen) donor-specific antibodies: a sensitization in transplantation: assessment of risk consensus document. *Am J Transpl* (2023) 23(1):115–32. doi:10.1016/j.ajt.2022.11.013

161. Courtwright AM, Cao S, Wood I, Mallidi HR, Kawasawa J, Moniodis A, et al. Clinical outcomes of lung transplantation in the presence of donor-specific antibodies. *Ann Am Thorac Soc* (2019) 16(9):1131–7. doi:10.1513/AnnalsATS.201812-869OC

162. Ius F, Müller C, Sommer W, Verboom M, Hallensleben M, Salman J, et al. Six-year experience with treatment of early donor-specific anti-HLA antibodies in pediatric lung transplantation using a human immunoglobulin-based protocol. *Pediatr Pulmonol* (2020) 55(3):754–64. doi:10.1002/ppul.24639

163. Senev A, Emonds MP, Van Sandt V, Lerut E, Coemans M, Sprangers B, et al. Clinical importance of extended second field high-resolution HLA genotyping for kidney transplantation. *Am J Transpl* (2020) 20(12):3367–78. doi:10.1111/ajt.15938

164. Xu Q, Elrefaei M, Taupin JL, Hitchman KMK, Hiho S, Gareau AJ, et al. Chronic lung allograft dysfunction is associated with an increased number of non-HLA antibodies. *J Heart Lung Transpl* (2024) 43(4):663–72. doi:10.1016/j.healun.2023.12.007

165. Philogene MC, Tchoukina I, Gimferrer I. Challenges and opportunities in bringing non-HLA antibody testing for post-transplant monitoring. *Front Transpl* (2025) 4: 1594241. doi:10.3389/frtra.2025.1594241

166. Tague LK, Scozzi D, Wallendorf M, Gage BF, Krupnick AS, Kreisel D, et al. Lung transplant outcomes are influenced by severity of neutropenia and granulocyte colony-stimulating factor treatment. *Am J Transpl* (2020) 20(1):250–61. doi:10.1111/ajt.15581

167. Wey E, Kibbler C. Infections associated with neutropenia and transplantation. *Antibiot Chemother* (2010) 21.

168. He X, Luo Z, Han Y, Yu J, Fang S, Guo L. Correlation analysis of the peripheral blood lymphocyte count and occurrence of pneumonia after lung transplantation. *Transpl Immunol* (2023) 78:101822. doi:10.1016/j.trim.2023.101822

169. Coiffard B, Pelardy M, Loundou AD, Nicolino-Brunet C, Thomas PA, Papazian L, et al. Effect of immunosuppression on target blood immune cells within 1 year after lung transplantation: influence of age on T lymphocytes. *Ann Transpl* (2018) 23:11–24. doi:10.12659/aot.906372

170. Kaes J, Van der Borght E, Vanstapel A, Van Herck A, Sacreas A, Heigl T, et al. Peripheral blood eosinophilia is associated with poor outcome post-lung transplantation. *Cells* (2020) 9(11):2516. doi:10.3390/cells9112516

171. Barry M, Chandra S, Hymes KB. Cytopenias in transplant patients. In: Safdar A, editor. *Principles and practice of transplant infectious diseases*. New York, NY: Springer (2019). p. 199–207.

172. Phillips-Houlbracq M, Mal H, Cottin V, Gauvain C, Beier F, Sicre de Fontbrune F, et al. Determinants of survival after lung transplantation in telomerase-related gene mutation carriers: a retrospective cohort. *Am J Transpl* (2022) 22(4):1236–44. doi:10.1111/ajt.16893

173. Borie R, Kannengiesser C, Hirschi S, Le Pavec J, Mal H, Bergot E, et al. Severe hematologic complications after lung transplantation in patients with telomerase complex mutations. *J Heart Lung Transpl* (2015) 34(4):538–46. doi:10.1016/j.healun.2014.11.010

174. Rosseels W, Godinas L, Jallah P, Vos R, Dupont L, Kuypers D, et al. Thrombotic microangiopathy: a devastating complication after lung transplantation. *Transpl Direct* (2025) 11(4):e1758. doi:10.1097/TXD.0000000000001758

175. Zajacova A, Alkhouri M, Ferrao G, Guney M, Rezac D, Vyskocilova K, et al. Early post-lung transplant cell-free DNA levels are associated with baseline lung allograft dysfunction. *Transpl Immunol* (2025) 92:102245. doi:10.1016/j.trim.2025.102245

176. Sorbini M, Togliatto G, Mioli F, Simonato E, Marro M, Cappuccio M, et al. Validation of a simple, rapid, and cost-effective method for acute rejection monitoring in lung transplant recipients. *Transpl Int* (2022) 35:10546. doi:10.3389/ti.2022.10546

177. Nogueiras-Álvarez R, Mora-Cuesta VM, Cifrián-Martínez JM, de Cos-Cossío MÁ, García-Sáiz MDM. Calcineurin inhibitors' impact on cardiovascular and renal function, a descriptive study in lung transplant recipients from the north of Spain. *Sci Rep* (2022) 12(1):21207. doi:10.1038/s41598-022-25445-2

178. Farrell CL, Miano TA, Griffiths S, Christie JD, Diamond JM, Shashaty MGS. Early post-lung transplant calcineurin inhibitor management varies widely: an international survey. *Clin Transpl* (2022) 36(2):e14510. doi:10.1111/ctr.14510

179. Hyzny EJ, Chan EG, Morrell M, Harano T, Sanchez PG. A review of liver dysfunction in the lung transplant patient. *Clin Transpl* (2021) 35(8):e14344. doi:10.1111/ctr.14344

180. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. *Bethesda (MD): National institute of diabetes and digestive and kidney diseases* (2012).

181. Sharif A, Chakkera H, de Vries APJ, Eller K, Guthoff M, Haller MC, et al. International consensus on post-transplantation diabetes mellitus. *Nephrol Dial Transpl* (2024) 39(3):531–49. doi:10.1093/ndt/gfad258

182. Agarwal A, Prasad GV. Post-transplant dyslipidemia: mechanisms, diagnosis and management. *World J Transpl* (2016) 6(1):125–34. doi:10.5500/wjt.v6.i1.125

183. Wenger U, Cottini SR, Noll G, Arndt S, Stehberger PA, Klinzing S, et al. Pretransplant dyslipidaemia determines outcome in lung transplant recipients. *Lipids Health Dis* (2013) 12:53. doi:10.1186/1476-511X-12-53

184. Ki MS, Kim NE, Woo A, Kim SY, Kim YS, Kim HE, et al. Post-transplant vitamin D deficiency in lung transplant recipients: impact on outcomes and prognosis. *Transpl Int* (2024) 37:13313. doi:10.3389/ti.2024.13313

185. Rakusa M, Vrtovec B, Poglajen G, Janez A, Jensterle M. Endocrine disorders after heart transplantation: national cohort study. *BMC Endocr Disord* (2020) 20(1):54. doi:10.1186/s12902-020-0533-6

186. Jelić Pranjić I, Orlić L, Carević A, Vrdoljak Margeta T, Šimić J, Bubić I. Exploring thyroid function after kidney transplantation: the complex interplay unacknowledged in post-transplant care. *J Clin Med* (2024) 13(12):3559. doi:10.3390/jcm13123559

187. Mawhorter S, Yamani MH. Hypogammaglobulinemia and infection risk in solid organ transplant recipients. *Curr Opin Organ Transpl* (2008) 13(6):581–5. doi:10.1097/MOT.0b013e3283186bbc

188. Fernández-Ruiz M, Kumar D, Humar A. Clinical immune-monitoring strategies for predicting infection risk in solid organ transplantation. *Clin Transl Immunol* (2014) 3(2):e12. doi:10.1038/cti.2014.3

189. Calarota SA, Chiesa A, De Silvestri A, Morosini M, Oggionni T, Marone P, et al. T-lymphocyte subsets in lung transplant recipients: association between nadir CD4 T-cell count and viral infections after transplantation. *J Clin Virol* (2015) 69: 110–6. doi:10.1016/j.jcv.2015.06.078

190. Westall GP, Brooks AG, Kotsimbos T. CD8+ T-cell maturation following lung transplantation: the differential impact of CMV and acute rejection. *Transpl Immunol* (2007) 18(2):186–92. doi:10.1016/j.trim.2007.07.002

191. Kotton CN, Kumar D, Manuel O, Chou S, Hayden RT, Danziger-Isakov L, et al. The fourth international consensus guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation* (2025) 109(7):1066–110. doi:10.1097/TP.0000000000005374

192. Piloni D, Gabanti E, Morosini M, Cassinelli G, Frangipane V, Zavaglio F, et al. Fifteen-year surveillance of LTR receiving pre-emptive therapy for CMV infection: prevention of CMV disease and incidence of CLAD. *Microorganisms* (2022) 10(12): 2339. doi:10.3390/microorganisms10122339

193. Aris RM, Maia DM, Neuringer IP, Gott K, Kiley S, Gertis K, et al. Post-transplantation lymphoproliferative disorder in the epstein-barr virus-naïve lung transplant recipient. *Am J Respir Crit Care Med* (1996) 154(6 Pt 1):1712–7. doi:10.1164/ajrccm.154.6.8970360

194. San-Juan R, De Dios B, Navarro D, García-Reyne A, Lumbreras C, Bravo D, et al. Epstein-barr virus DNAemia is an early surrogate marker of the net state of immunosuppresion in solid organ transplant recipients. *Transplantation* (2013) 95(5):688–93. doi:10.1097/TP.0b013e31827a4bd6

195. Barten MJ, Zuckermann A. BK virus: a cause for concern in thoracic transplantation? *Ann Transpl* (2018) 23:310–21. doi:10.12659/AOT.908429

196. Crowhurst T, Nolan J, Faull R, Holmes M, Holmes-Liew CL. BK virus-associated nephropathy in a lung transplant patient: case report and literature review. *BMC Infect Dis* (2020) 20(1):600. doi:10.1186/s12879-020-05292-0

197. Nikolova A, Agbor-Enoh S, Bos S, Crespo-Leiro M, Ensminger S, Jimenez-Blanco M, et al. European society for organ transplantation (ESOT) consensus statement on the use of non-invasive biomarkers for cardiothoracic transplant rejection surveillance. *Transpl Int* (2024) 37:12445. doi:10.3389/ti.2024.12445

198. Keller M, Sun J, Mutebi C, Shah P, Levine D, Aryal S, et al. Donor-derived cell-free DNA as a composite marker of acute lung allograft dysfunction in clinical care. *J Heart Lung Transpl* (2022) 41(4):458–66. doi:10.1016/j.healun.2021.12.009

199. Keller M, Ross D, Bhorade S, Agbor S. Study design for a randomized control trial of lung allograft monitoring with blood donor-derived cell-free DNA assessments (LAMBDA 001). *J Heart Lung Transpl* (2023) 42(4):S509. doi:10.1016/j.healun.2023.02.1398

200. Gottlieb J, Reuss A, Mayer K, Weide K, Schade-Brittinger C, Hoyer S, et al. Viral load-guided immunosuppression after lung transplantation (VIGILung)-study protocol for a randomized controlled trial. *Trials* (2021) 22(1):48. doi:10.1186/s13063-020-04985-w

201. Jaksch P, Görzer I, Puchhammer-Stöckl E, Bond G. Integrated immunologic monitoring in solid organ transplantation: the road toward torque teno virus-guided immunosuppression. *Transplantation* (2022) 106(10):1940–51. doi:10.1097/TP.0000000000004153

202. Nord M, Schubert K, Cassel TN, Andersson O, Riise GC. Decreased serum and bronchoalveolar lavage levels of clara cell secretory protein (CC16) is associated with bronchiolitis Obliterans syndrome and airway neutrophilia in lung transplant recipients. *Transplantation* (2002) 73(8):1264–9. doi:10.1097/00007890-200204270-00013

203. Bansal S, Itabashi Y, Perincheri S, Poulson C, Bharat A, Smith MA, et al. The role of miRNA-155 in the immunopathogenesis of obliterative airway disease in mice induced by circulating exosomes from human lung transplant recipients with chronic lung allograft dysfunction. *Cell Immunol* (2020) 355:104172. doi:10.1016/j.cellimm.2020.104172

204. Nordén R, Magnusson J, Lundin A, Tang KW, Nilsson S, Lindh M, et al. Quantification of torque teno virus and epstein-barr virus is of limited value for predicting the net state of immunosuppression after lung transplantation. *Open Forum Infect Dis* (2018) 5(4):ofy050. doi:10.1093/ofid/ofy050

ESOT | Transplant International

TYPE Review
PUBLISHED 11 May 2026
DOI 10.3389/ti.2026.16006

Check for updates

OPEN ACCESS

*CORRESPONDENCE
A. Della Penna,
andrea.della-penna@med.uni-tuebingen.de
M. Quante,
quante.markus@mh-hannover.de

RECEIVED 04 December 2025
REVISED 19 April 2026
ACCEPTED 27 April 2026
PUBLISHED 11 May 2026

CITATION
Della Penna A, Beer-Hammer S, Nadalin S, Capobianco I, Felgendreff P, Schmelzle M and Quante M (2026) The obese transplant organ recipient: experimental and clinical evidence for tailored immunosuppression. *Transpl. Int.* 39:16006. doi: 10.3389/ti.2026.16006

COPYRIGHT
© 2026 Della Penna, Beer-Hammer, Nadalin, Capobianco, Felgendreff, Schmelzle and Quante. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

The obese transplant organ recipient: experimental and clinical evidence for tailored immunosuppression

A. Della Penna[1]*, S. Beer-Hammer[2], S. Nadalin[1], I. Capobianco[1], P. Felgendreff[3], M. Schmelzle[3] and M. Quante[3]*

[1]Department of General, Visceral and Transplantation Surgery, University Hospital Tübingen, Tübingen, Germany, [2]Department of Pharmacology, Experimental Therapy and Toxicology, Institute of Experimental and Clinical Pharmacology and Pharmacogenomics, University Hospital Tübingen, Tübingen, Germany, [3]Hannover Medical School, Department of General, Visceral and Transplant Surgery, Hannover, Germany

Obesity has become a major determinant of outcomes across solid organ transplantation. Beyond its well-recognized metabolic and cardiovascular burden, obesity profoundly affects both immune regulation and the pharmacology of immunosuppressive therapy. Experimental evidence has established adipose tissue as an active immune organ that promotes low-grade inflammation through leptin, TNF-α, and IL-6, thereby altering alloimmune responses and impairing graft tolerance. Clinically, obesity is associated with increased surgical complications, delayed graft function, and reduced survival after kidney, liver, and thoracic organ transplantation. In parallel, obesity modifies drug disposition at every pharmacokinetic step, expanding the distribution volume for lipophilic agents such as calcineurin and mTOR inhibitors, altering CYP3A metabolism, and increasing interindividual variability in exposure. Consequently, both underexposure and toxicity remain frequent, underscoring the need for individualized therapeutic strategies. Current evidence supports the integration of therapeutic drug monitoring, pharmacogenomics, and biomarker-based approaches to refine immunosuppression intensity. This review summarizes experimental and clinical data linking obesity-induced inflammation with altered immunosuppressive pharmacology and proposes a framework for precision immunosuppression that balances efficacy, nephroprotection, and metabolic safety. Tailoring therapy to the specific immunometabolic profile of obese recipients may thus transform a major clinical challenge into an opportunity for precision transplant medicine.

KEYWORDS
immunosuppression, obesity, pharmacokinetic, precision medicine, solid organ transplant (SOT)

Introduction

The prevalence of obesity among solid organ transplant recipients has risen steadily over recent decades in parallel to global population trends [1, 2]. Registry analyses indicate higher mean BMI at the time of listing and transplantation nowadays when compared with historical cohorts [3–5]. This epidemiological shift has major clinical implications, as obesity is associated with increased perioperative risk, altered pharmacokinetics of immunosuppressive agents, and long-term metabolic complications that can compromise graft function [6–8]. Obesity has therefore transitioned from a secondary

comorbidity to a primary determinant of transplant outcomes, underscoring the need for risk-adapted recipient selection, perioperative management, and individualized immunosuppressive strategies [9, 10]. This narrative review aims to provide an integrated overview of obesity-related immunological and pharmacokinetic alterations in transplantation, and to define a framework for individualized immunosuppressive strategies in obese recipients.

Clinical graft outcome in obese recipients

Kidney

Kidney transplantation is consistently associated with poorer outcomes in obese recipients. Large registry analyses demonstrate that severe obesity independently impairs graft and patient survival [4, 11]. Meta-analyses confirm that obesity increases the incidence of delayed graft function, surgical complications, and even mortality [7, 12]. Recent multicenter data suggest that these risks persist despite advances in immunosuppressive protocols and perioperative care [13, 14]. Histopathological evidence links obesity with renal microvascular injury and chronic inflammatory graft infiltration, as described in obesity-related glomerulopathy with glomerulomegaly, mesangial expansion, focal segmental glomerulosclerosis, interstitial fibrosis and immune cell infiltration [15, 16].

Liver

Obesity may have negative implications on both candidacy and post-transplant outcomes in liver transplantation. Here, obese candidates often face higher surgical risk and comorbidity burdens, consecutively impacting listing eligibility [8, 17]. After transplantation, obesity is associated with increased rates of wound complications, prolonged hospital stays, and most importantly diminished survival [8, 18, 19]. Here, meta-analytic data confirm higher perioperative morbidity and long-term mortality in obese liver recipients [8, 19]. Of note, emerging evidence reveals sex-specific patterns in obesity-related liver transplant outcomes. For instance, female recipients with elevated BMI undergoing DCD liver transplantation are carrying a higher risk of early graft rejection [20], while among NASH-related hepatocellular carcinoma cases, women had significantly lower post-transplant mortality than men [21]. Hormonal milieu and metabolic derangements—especially in post-menopausal women—add further complexity to this dynamic processes [22].

Thoracic organs

Beyond liver and kidney transplantation, obesity is also impacting outcomes in the clinical context of thoracic organ transplantation. For heart transplantation, excess body weight has been associated with increased perioperative risk and inferior long-term survival, particularly due to the higher prevalence of cardiovascular and metabolic comorbidities in obese recipients [23]. Moreover, in a large cohort study, obese heart transplant recipients demonstrated a significantly higher risk of death, primary graft dysfunction, and any treated rejection [24].

In lung transplantation, accumulating evidence indicates that obesity is an independent predictor of adverse outcomes. Gries et al. demonstrated that obese recipients with idiopathic pulmonary fibrosis have a significantly increased 90-day mortality risk following bilateral lung transplantation [25]. Along the same lines, BMI has been shown to be a strong predictor of early mortality within the first 90 days post lung-transplant [26], while long-term follow-up revealed lower overall survival among overweight and obese recipients compared to their normal-weight counterparts [27].

Taken together, these observations highlight that the deleterious effects of obesity extend beyond abdominal organ transplantation and are particularly relevant in thoracic organs, where perioperative complications, impaired wound healing, and cardiopulmonary stress further aggravate the pre-existing risk profile of obese transplant recipients [2].

Perioperative considerations

Beyond organ-specific outcomes, obesity is also linked to relevant surgical and perioperative challenges that may influence early graft outcomes and, consequently, immunosuppressive management. Increased adipose tissue and altered anatomy are associated with increasing operative complexity, including prolonged procedure and ischemia times, as well as technical difficulties during vascular anastomosis [28]. From an anesthesiological perspective, obese recipients are at higher risk of perioperative respiratory complications and hemodynamic instability, further contributing to early postoperative vulnerability [29].

Wound-related complications still represent one of the most consistent findings across organ types, with obesity being strongly associated with higher rates of surgical site infections, wound dehiscence, and prolonged hospitalization [30]. In kidney transplantation, obesity is also an independent risk factor for delayed graft function, likely reflecting a combination of technical factors, ischemia–reperfusion injury, and underlying inflammatory alterations [7].

These perioperative factors have direct implications for early immunosuppressive management. On the one hand, increased rates of wound complications and infection may favor more cautious immunosuppressive exposure in the immediate postoperative phase. On the other hand, the higher risk of delayed graft function and obesity-related immune activation may require adequate immunosuppressive intensity to prevent early rejection. This clinical tension underscores the need for careful balancing of efficacy and safety, further calling for an individualized approach to immunosuppression in obese transplant recipients.

Obesity promoting inflammation

Experimental evidence

Seminal studies defined adipose tissue as an active immune organ rather than a passive energy reservoir [31, 32]. Here, tumor necrosis factor-α production from adipose tissue was first identified

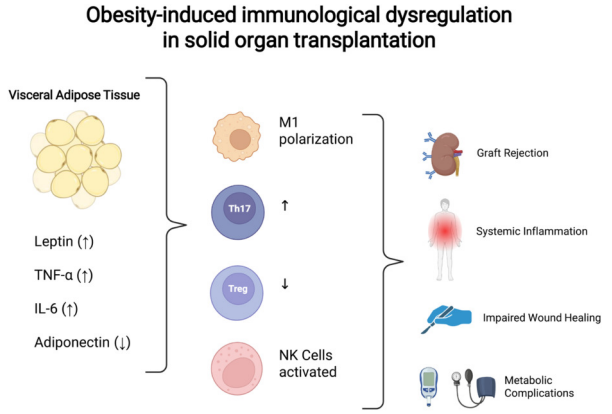


FIGURE 1
Obesity-associated immunological dysregulation relevant to solid organ transplantation. Schematic representation of the pro-inflammatory milieu induced by visceral adiposity, characterized by increased leptin, TNF-α, and IL-6 levels, reduced adiponectin, and macrophage M1 polarization. Obesity promotes natural killer cell activation, systemic inflammation, impaired wound healing, and metabolic complications. These alterations converge to amplify alloreactivity and increase the risk of graft rejection, thereby linking adipose-driven immune dysregulation with inferior transplant outcomes.

as a link between adiposity and systemic inflammation [33]. Furthermore, leptin, an adipocyte-derived hormone, was shown to regulate both metabolic and immune processes [34, 35]. Adipose tissue was subsequently recognized as a major source of interleukin-6, while adiponectin—an anti-inflammatory adipokine—was found to be reduced in obesity [36, 37]. Macrophage infiltration into adipose depots is a further key driver of the chronic low-grade inflammatory state characteristic of obesity [38, 39]. Recent reviews reinforce these findings, detailing the regulation of immunometabolism within adipose tissue [40] and highlighting macrophage recruitment dynamics in obesity-related adipose tissue inflammation [41].

Clinical evidence

Clinical studies confirm that obesity-induced inflammation is both measurable and clinically significant in the context of solid organ transplantation. Visceral adiposity is associated with increased immune activation and elevated systemic inflammatory markers compared to subcutaneous depots [42, 43]. In transplant recipients, obesity is accompanied by a pro-inflammatory state that directly contributes to poorer graft outcomes [9, 44]. Evidence from clinical kidney and liver transplantation confirms that the systemic inflammation characteristic of obesity is a major determinant of reduced graft survival [44]. These observations establish obesity-related inflammation as a key regulator linking obesity to inferior transplant outcomes [10, 32] (see Figure 1).

Immunosuppression and obesity

Obesity has profound impact on the pharmacokinetics and pharmacodynamics of immunosuppressive drugs. Here, alterations may occur at virtually every step of drug disposition: absorption, distribution, metabolism, and clearance [45, 46]. Increased adipose mass and lean body mass expand the volume of distribution for lipophilic agents, while hepatic steatosis and comorbid metabolic syndrome may impair drug metabolism [47]. Moreover, renal hyperfiltration in obesity alters the clearance of renally excreted metabolites [48]. These metabolic-driven changes translate into significant variability in drug exposure, complicating therapeutic drug monitoring and raising the risk of both rejection and toxicity [49, 50] (see Figure 2).

Calcineurin inhibitors (tacrolimus and cyclosporine)

Calcineurin inhibitors remain the cornerstone of most immunosuppressive regimens. Both tacrolimus and cyclosporine are highly lipophilic, extensively protein-bound, and metabolized by CYP3A enzymes, thus making them highly susceptible to obesity-related alterations [45, 46]. Obesity increases the apparent volume of distribution, while trough concentrations do not reliably reflect systemic exposure [51]. Tacrolimus in particular shows reduced predictability of trough levels in obese recipients, therefore complicating standard monitoring approaches [49, 52]. Cyclosporine clearance and distribution were already shown decades ago to be significantly altered by obesity [53]. Clinically, these pharmacokinetic changes translate into an increased risk of overexposure and nephrotoxicity. When using conventional weight-based dosing, whereas fixed or capped dosing strategies may reduce toxicity, but require close monitoring to avoid underexposure in fast metabolizers [54]. Further data suggest that full-dose CNI regimens in obese recipients are disproportionately nephrotoxic [51]. Consequently, minimization strategies and individualized monitoring are highly recommended [55]. Current practice increasingly favors fixed dosing with careful monitoring, rather than strict weight-based dosing, to avoid systematic overdosing in obese patients [49].

Mechanistic target of rapamycin (mTOR) inhibitors (sirolimus and everolimus)

Inhibitors of mTOR are also highly lipophilic and demonstrate significantly altered pharmacokinetics in obesity [56, 57]. In detail, sirolimus has a prolonged half-life and greater distribution in obese recipients, increasing the risk of cumulative toxicity [58]. Everolimus, though shorter-acting, has been associated with increased metabolic complications in obese recipients, particularly dyslipidemia and post-transplant diabetes [59, 60]. These metabolic toxicities align with the pro-inflammatory and insulin-resistant milieu of obesity, thus finally compounding the cardiovascular risk [59].

While mTOR inhibitors facilitate CNI minimization, advantageous for nephrotoxicity-prone obese patients, their potential to worsen dyslipidemia and insulin resistance may offset these benefits, particularly in metabolically fragile individuals [55]. Recent registry analyses further support this concept: in an SRTR cohort, regimens combining mTOR inhibitors with tacrolimus were associated with reduced acute rejection rates in obese kidney transplant recipients, suggesting

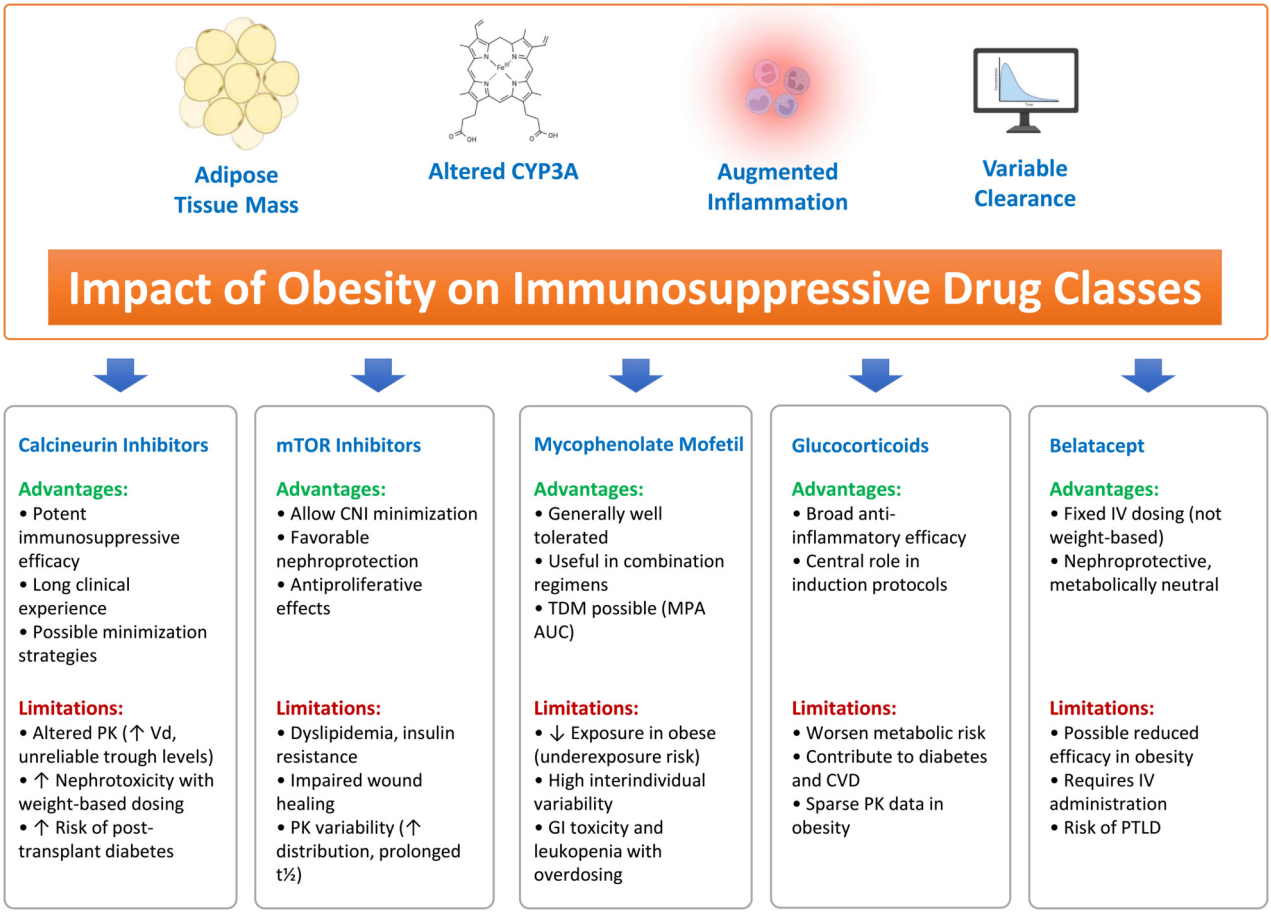


FIGURE 2
Impact of obesity on pharmacokinetics and clinical performance of major immunosuppressive drug classes. Overview of how increased adipose mass, altered CYP3A activity, and inflammation modulate drug disposition in obese recipients. Calcineurin inhibitors exhibit expanded volume of distribution, unreliable trough levels, and enhanced nephrotoxicity with weight-based dosing. mTOR inhibitors demonstrate variable exposure, prolonged half-life, and increased metabolic toxicity. Mycophenolate mofetil shows reduced MPA exposure in heavier patients, while glucocorticoids exacerbate metabolic risk with limited obesity-specific PK data. Belatacept, administered as fixed dosing, may display altered clearance and reduced efficacy in obesity. Together, these obesity-driven changes underscore the need for individualized dosing and careful therapeutic monitoring.

tailored benefits in this subgroup [61]. In contrast, combinations of mTOR inhibitors with mycophenolate mofetil have consistently been associated with inferior efficacy and increased toxicity, and are therefore neither recommended in obese recipients nor in the general transplant population [61]. Clinical application therefore requires judicious patient selection and close metabolic monitoring [62]. Fixed dosing strategies with trough-level adjustment remain standard, but variability in obese recipients suggests that more refined AUC-based or model-informed precision dosing could improve safety [63].

Mycophenolate mofetil (MMF)

As a hydrophilic prodrug converted to mycophenolic acid (MPA), MMF demonstrates high interindividual variability in exposure [64]. Body weight has been identified as a major determinant of exposure variability: data from the OPTICEPT trial showed that heavier kidney transplant recipients had significantly lower MPA area under the curve (AUC) per mg dose compared with lighter patients, despite identical dosing regimen [65]. A systematic evaluation of clinical practice confirmed that individualized dosing based on therapeutic drug monitoring (TDM) can optimize exposure in patients with high pharmacokinetic variability, including those with obesity [50]. Clinically, suboptimal MMF exposure in obese recipients can contribute to breakthrough rejection, while overdosing increases the risk of leukopenia and gastrointestinal toxicity [66]. Because MMF is typically applied with fixed dosing, obesity poses challenges in predicting systemic exposure. This makes TDM of MMF particularly valuable in obese transplant recipients [67]. Unfortunately, routine AUC monitoring is rarely implemented outside specialized centers, representing an unmet need in current practice. A prospective multicenter study confirmed that individualized AUC-based MMF dosing significantly improves clinical outcomes after renal transplantation [68].

Glucocorticoids

Steroids still remain a backbone of induction and maintenance therapy, though their utilization has declined due to their well-known metabolic side effects [69, 70]. Obesity modifies

glucocorticoid metabolism, leading to altered efficacy and increased risk of complications such as weight gain, diabetes, and cardiovascular disease [71, 72]. Evidence for steroid minimization or withdrawal in obese recipients suggests potential benefits in reducing metabolic complications, but these strategies carry an increased risk of graft rejection [69, 70]. While steroid minimization or withdrawal strategies are often pursued to mitigate the well-documented metabolic adverse effects of glucocorticoids, increasing evidence suggests that obesity and post-transplant weight gain may still occur independently of steroid exposure. For example, in a cohort of kidney transplant recipients managed with steroid avoidance, Elster et al. reported significant weight gain despite the absence of maintenance glucocorticoids [73]. These findings indicate that although glucocorticoids are a major driver of post-transplant metabolic complications, additional mechanisms—including pre-existing obesity, immunosuppressive drug classes such as CNIs or mTOR inhibitors, and lifestyle factors—may substantially contribute to post-transplant adiposity. Pharmacokinetic data on steroids in obese transplant recipients are sparse, thus reflecting a critical gap of knowledge [69]. Unlike for CNIs and mTOR inhibitors, systematic obesity-stratified pharmacological studies of glucocorticoids are virtually absent, leaving dosing largely empirical [74]. Given their profound impact on the individual patients' metabolic risk, more focused studies are needed to optimize steroid use in obesity [71].

Belatacept (CTLA4-Ig)

Belatacept, a fusion protein targeting the costimulatory ligands CD80/86, is offering an appealing alternative to CNIs [75]. Unlike small molecules, it is administered at fixed intravenous doses, largely independent of body weight [76]. Importantly, efficacy of belatacept has been demonstrated in kidney transplant recipients, including those with obesity, with a significant lower risk of nephrotoxicity compared to CNIs [77]. However, recent pharmacokinetic data indicate altered clearance in obese patients, thus raising the possibility of under- or overexposure with fixed dosing [78].

In addition, emerging evidence has raised concerns regarding the efficacy of belatacept specifically in obese recipients. A pooled analysis of the BENEFIT and BENEFIT-EXT trials demonstrated that obesity was independently associated with a higher incidence of acute rejection in belatacept-treated patients [79]. This observation suggests that obesity-related factors—potentially including altered pharmacokinetics, increased clearance, or distinct immune mechanisms—may attenuate the protective effect of belatacept. Consequently, while belatacept remains a valuable option for selected obese recipients due to its favorable metabolic and renal profile, its utilization must be carefully balanced against the risk of post-transplant lymphoproliferative disorder, the need for intravenous administration, and foremost the possibility of reduced efficacy in obese patients.

Therapeutic drug monitoring and tailoring strategies

As already discussed for the individual immunosuppressive agents, therapeutic drug monitoring (TDM) is indispensable in obese transplant recipients, but conventional trough-level monitoring may be unreliable due to obesity-related changes and disturbances. In detail, trough concentrations of tacrolimus do not consistently predict overall exposure [51, 54], and similar limitations have been reported for cyclosporine [46]. This mismatch thus raises the risk of relevant therapeutic misclassification in patients with obesity. Here, limited-sampling approaches and Bayesian AUC estimation may pave the way towards more accurate dosing strategies by providing better correlation with exposure. However, these techniques remain underutilized in current routine care [80]. Along the same lines, AUC-based monitoring correlates more closely with outcomes than fixed dosing for MMF, as shown in a multicenter trial where individualized exposure significantly improved patient outcomes [68]. Another important aspect of tailoring is the choice between weight-based and fixed-dose regimens. Weight-based dosing often leads to overexposure in obese patients, particularly for CNIs and mTOR inhibitors [49, 51]. Therefore, fixed dosing with close monitoring appears safer but is still associated with the potential risk of impaired efficacy. Although desperately needed, no consensus guidelines currently exist [45]. When striving out for concepts beyond pharmacokinetics, biomarker-based strategies may further help to refine immunosuppression intensity. Here, donor-specific antibody monitoring, immune cell functional assays (such as IFN-γ ELISPOT), and transcriptomic signatures have demonstrated additional prognostic value [81]. Therefore, integration of TDM with biomarker-based tools might represent the next level in precision transplant pharmacology [82].

Cross-class comparison

When comparing drug classes, the individual profile of each immunosuppressive agent reveals both obesity-specific strengths and limitations. While still representing the gold standard of immunosuppression in the global population, CNIs remain highly effective in obese transplant recipients, but their use in this particular patient subgroup is complicated by pharmacokinetic variability, nephrotoxicity, and the limited reliability of trough levels; moreover, tacrolimus in particular confers a substantially increased risk of post-transplant diabetes, a complication of major concern in this population [45, 46]. Here, mTOR inhibitors provide an alternative to CNIs and allow for minimization strategies but frequently exacerbate dyslipidemia and insulin resistance, thereby worsening metabolic syndrome in obese recipients [60, 61, 83]. Mycophenolate mofetil is generally well tolerated but may exhibit exposure variability that may be even altered by obesity [50, 64]. Glucocorticoids remain the most problematic class, as their adverse metabolic effects directly overlap with the obesity phenotype, although systematic obesity-specific pharmacokinetic data are lacking [70, 71]. Of note, belatacept has emerged as an attractive therapeutic option because of its nephroprotective properties, fixed intravenous dosing, and absence of metabolic toxicity [77, 78, 84]. However, recent evidence indicates that obese recipients treated with belatacept may experience a higher incidence of acute rejection, highlighting the need for careful patient selection and close immunological monitoring [79].

Taken together, these cross-class comparisons underscore that none of the presented immunosuppressive agents provides an ideal

single solution for obese graft recipients. Yet, a rational, tailored combination—balancing efficacy, nephroprotection, and metabolic safety—may offer the opportunity to optimize clinical outcomes. Framing immunosuppression within an individualized, obesity-aware therapeutic strategy may thus transform the apparent challenge into an opportunity for precision medicine in transplantation.

Precision medicine in obese transplant recipients

Since no single immunosuppressive agent provides an ideal solution for obese transplant recipients, this obvious limitation should rather serve as the starting point for future precision approaches.

In detail, pharmacogenomic testing, most notably CYP3A5 genotyping for tacrolimus, may represent another tangible strategy for individualized dosing. Growing evidence supports its value in optimizing initial dosing, although robust outcome data in obese patient cohorts remain scarce [85–87]. In addition, advances in biomarker-based monitoring—including donor-derived cell-free DNA, microRNAs, chemokine panels, and gene expression profiling—offer further noninvasive tools for dynamic immunological risk assessment [88, 89]. The Barcelona Consensus already recommended integrating biomarkers into clinical immunosuppressive drug management, while acknowledging that most assays still remain under evaluation and are not yet ready for broad implementation [90].

Beyond pharmacogenomic profiling and pharmacokinetic monitoring, biomarker-based approaches are increasingly being explored to refine immunological risk assessment. Here, donor-derived cell-free DNA (dd-cfDNA) is currently the most advanced tool in this context and has already shown good performance for the detection of allograft injury, particularly antibody-mediated rejection, although its specificity remains limited, as elevated levels may also occur in the setting of infection or non-immune injury [89, 91].

Other platforms, including circulating microRNAs, chemokine panels, and gene expression profiling, provide complementary insights into immune activation and graft injury. Among these approaches, dd-cfDNA is currently the most clinically advanced and widely implemented one, whereas transcriptomic platforms are gaining increasing traction in selected settings. In contrast, microRNAs and chemokine-based assays remain largely investigational, with limited availability in routine clinical practice. While these approaches have shown promising diagnostic accuracy in selected settings, their clinical implementation is still limited by the lack of standardized assays and consistent validation across centers [88, 89]. Transcriptomic strategies, in particular, are increasingly incorporated into clinical algorithms, especially in heart and kidney transplantation, but their broader applicability remains under evaluation [82, 89].

Despite these advances, several barriers continue to limit the routine use of biomarker-based monitoring, including costs, limited availability outside specialized centers, and inter-variability between platforms with respect to thresholds and analytical performance [89]. Of critical relevance, prospective data demonstrating a clear impact on clinical outcomes are still scarce.

Importantly, data on biomarker performance in obese transplant recipients are largely lacking. Given that obesity is associated with chronic low-grade inflammation, altered immune cell function, and a high burden of metabolic comorbidities, biomarker readouts may be more difficult to interpret in this population [92]. This represents a relevant knowledge gap and highlights the need for further studies specifically addressing biomarker-guided immunosuppression across different metabolic phenotypes. In this context, obesity may represent a clinically relevant stress model to test and refine biomarker-driven precision immunosuppression strategies.

Of note, real-world analyses have already begun to address obese populations specifically: a propensity-matched study in kidney transplantation demonstrated that immunosuppressive protocol choice significantly influences outcomes in obese recipients, supporting the concept of tailored immunsuppressive approaches [61].

From this perspective, obesity should not only be regarded as a potentially deleterious patient´s variable but rather as an ideal clinical scenario for the implementation of precision medicine in clinical transplantation. Here, integrating TDM, pharmacogenomics, and validated biomarkers with detailed phenotyping and computational modeling may truly enable individualized immunosuppressive regimens although further prospective validation will be crucial (see Figure 3).

Building on these concepts, a pragmatic framework for individualized immunosuppressive management in obese transplant recipients can be proposed. While high-quality prospective data are lacking, several principles emerge from available pharmacokinetic and clinical evidence. A concise overview of key drug-specific considerations is summarized in Table 1. In general, fixed or capped dosing strategies may be preferable to total body weight-based approaches for lipophilic agents such as calcineurin inhibitors, in order to reduce the risk of overexposure and toxicity. Early and repeated therapeutic drug monitoring, ideally incorporating AUC-based approaches where feasible, appears particularly important in this population, especially for agents such as tacrolimus and mycophenolate.

Drug class selection should be primarily considered based on the metabolic and clinical profile of the individual patient. In detail, calcineurin inhibitor minimization strategies may be considered in individuals at high risk of nephrotoxicity, whereas mTOR inhibitors require caution in patients with pre-existing dyslipidemia or impaired wound healing. Mycophenolate exposure may be reduced in obese recipients, supporting the use of exposure-guided dosing strategies. In selected cases, belatacept-based regimens may offer a metabolically favorable alternative, although data in obese populations remain limited.

Importantly, these considerations should not be interpreted as prescriptive recommendations but rather as a conceptual framework to support individualized decision-making. Integration of pharmacokinetic monitoring, emerging biomarkers, and clinical phenotyping is likely essential to optimize the balance between rejection and toxicity in this complex patient population.

In addition to immunosuppressive tailoring, adjunctive management of obesity-related metabolic risk is becoming

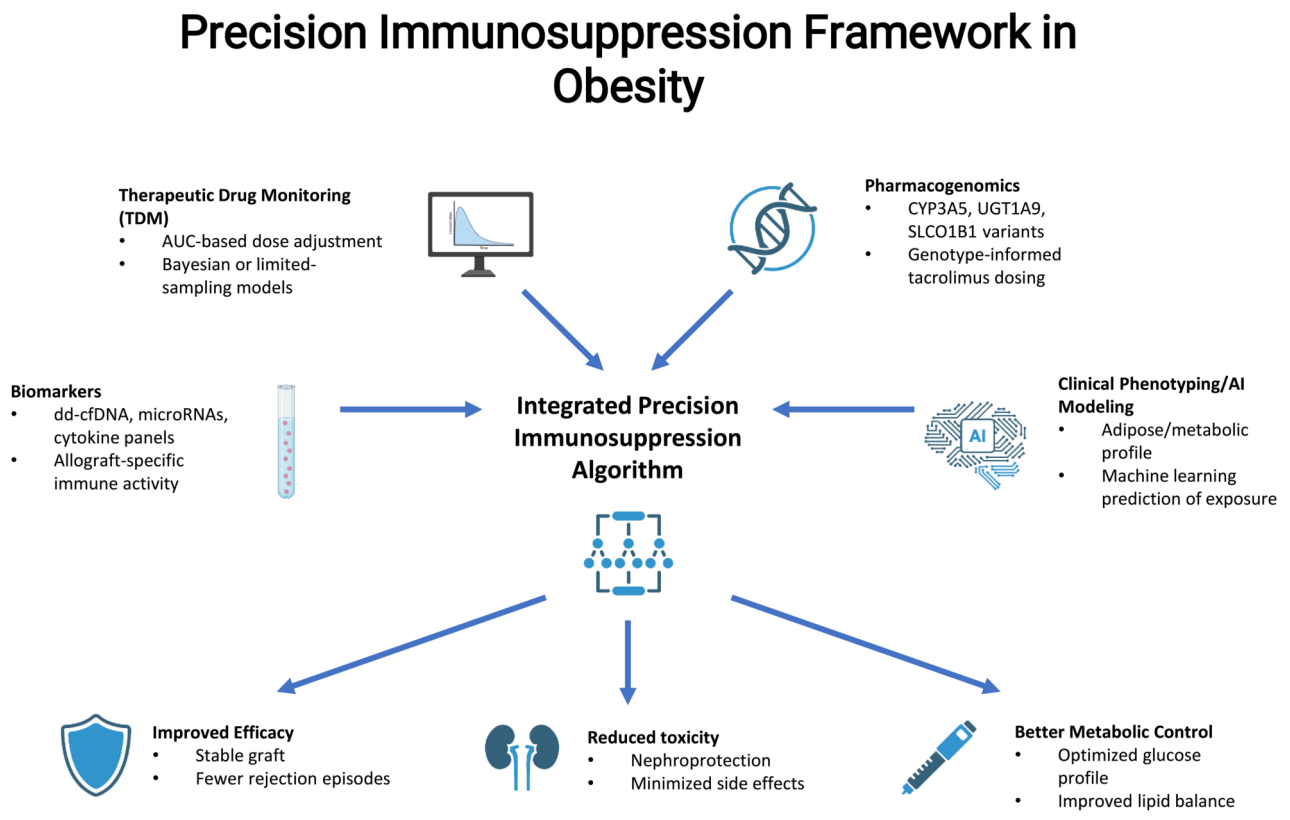


FIGURE 3
Precision immunosuppression framework for obese transplant recipients. Integrated model combining clinical phenotyping, metabolic and adipose-tissue profiling, pharmacogenomics (e.g., CYP3A5 variants), biomarker-based immunomonitoring (dd-cfDNA, microRNAs, cytokine panels), and therapeutic drug monitoring using AUC-based or Bayesian approaches. This multidimensional algorithm aims to optimize immunosuppressive exposure, reduce toxicity, stabilize graft function, and improve metabolic outcomes, outlining a precision-medicine strategy tailored to the obese transplant population.

TABLE 1 Immunosuppressive drug class considerations in obese transplant recipients.

Drug class	Key considerations in obesity	Practical approach
Calcineurin inhibitors	Variable pharmacokinetics; risk of overexposure with weight-based dosing; nephrotoxicity	Prefer fixed or capped dosing; early and repeated therapeutic drug monitoring
mTOR inhibitors	Dyslipidemia, insulin resistance; impaired wound healing	Careful patient selection; close metabolic monitoring
Mycophenolate mofetil	Reduced exposure in higher body weight	Consider AUC-guided dosing where feasible
Glucocorticoids	Enhanced metabolic impairment	Early minimization depending on the immunological risk profile
Belatacept	Favorable metabolic profile; limited data in obesity	Consider in selected patients at high risk of calcineurin inhibitor toxicity

increasingly relevant in transplant recipients. Emerging evidence suggests that glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter-2 inhibitors (SGLT2 inhibitors) may improve body weight, glycemic control, and cardiovascular risk profiles in selected transplant populations, particularly after kidney transplantation [93, 94]. Available studies further indicate an overall favorable safety profile, with no consistent evidence for clinically relevant interactions with standard immunosuppressive agents, although gastrointestinal intolerance with GLP-1RAs and genitourinary infections with SGLT2 inhibitors remain important considerations [93, 94].

Yet, the underlying evidence is still largely observational, and transplant-specific prospective data remain limited [93–95]. These agents should therefore be viewed as promising adjuncts within a multidisciplinary metabolic strategy rather than as established components of immunosuppressive management.

Knowledge gaps, future directions and conclusion

Despite a growing body of evidence, important gaps of knowledge continue to limit the development of evidence-based strategies for obese transplant recipients. Most pharmacokinetic studies remain small and retrospective [47, 49, 51], and only few trials prespecify obesity as a stratification variable, thus leaving uncertainty about optimal dosing [5, 11]. Especially steroids are understudied in this vulnerable population [69, 70], and current data rarely integrate obesity-driven inflammation, pharmacokinetic variability, and clinical outcomes within the same cohorts [82]. Large datasets seldom include detailed body composition or metabolic phenotyping [43], and mechanistic insights such as histopathological correlates are only rarely linked with pharmacological and clinical data [15].

A major limitation in current practice is the reliance on body mass index as the primary measure of obesity. Additional metrics such as waist-to-hip ratio, visceral fat quantification, and CT-based skeletal muscle index provide a more refined assessment of metabolic and immunological risk and may better identify high-risk phenotypes such as sarcopenic obesity. BMI does not reflect body composition or fat distribution and therefore provides only a limited estimate of metabolic risk. In this context, visceral adiposity and ectopic fat appear to be more closely linked to metabolic and inflammatory complications than overall body weight. Similarly, sarcopenic obesity—defined by the coexistence of excess adiposity and reduced muscle mass—has been associated with frailty and poorer post-transplant outcomes [96].

Imaging-based approaches, particularly computed tomography-based assessment of skeletal muscle mass, as well as functional measures of body composition, may allow for a more accurate characterization of metabolic risk. Integrating these parameters into clinical studies and transplant registries could improve risk stratification and help refining immunosuppressive strategies according to individual metabolic risk profiles [96].

Nevertheless, these challenges outline a clear roadmap for future research. Obesity-stratified randomized controlled trials, adequately powered pharmacokinetic/pharmacodynamic studies, and systematic evaluation of AUC-based monitoring will be essential [68, 80]. Advances in model-informed precision dosing, pharmacogenomics, and biomarker-guided immunomonitoring offer unprecedented opportunities towards individualized immunosuppressive therapy [82, 97]. Integrating these tools with detailed phenotyping and computational prediction models may help to transform the current limitations into actionable strategies [97].

In summary, obesity consistently emerges as a risk factor for inferior graft outcomes, higher perioperative morbidity, and increased metabolic complications across solid organ transplantation [7, 8]. By understanding the complex interplay of obesity-induced inflammation, pharmacokinetic variability, and immunological risk [33, 38], clinicians will have to move beyond "one-size-fits-all" approaches. Here, tailoring immunosuppression through therapeutic drug monitoring, biomarker-guided adjustments, and precision dosing algorithms holds the promise of improving long-term graft survival and patient wellbeing in this high-risk population [66, 68, 82, 97]. From this perspective, obesity should not only be regarded as a clinical challenge but as an ideal context for precision medicine, where individualized strategies can turn risk into opportunity.

Author contributions

AD and MQ conceived the review concept and designed the overall structure of the manuscript. AD conducted the primary literature search, synthesized the experimental and clinical evidence, and drafted the initial manuscript. MQ provided critical revisions to the clinical sections and contributed to the refinement of the conceptual framework on tailored immunosuppression. SB-H contributed to the interpretation of pharmacokinetic and pharmacodynamic evidence and provided substantial editorial input to enhance clarity and coherence across the manuscript. IC, MS, SN, and PF reviewed the manuscript and provided additional critical feedback. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The authors(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. During the preparation of this manuscript, the authors used ChatGPT (OpenAI, GPT-5.1, 2025) to assist with literature summarization and text structuring. All AI-assisted content was thoroughly reviewed and edited by the authors, who take full responsibility for the accuracy and integrity of the manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

References

1. Beckmann S, Drent G, Ruppar T, Nikolić N, De Geest S. Body weight parameters are related to morbidity and mortality after liver transplantation: a systematic review and meta-analysis. *Transplantation* (2019) 103:2287–303. doi:10.1097/tp.0000000000002811

2. Bhat M, Usmani SE, Azhie A, Woo M. Metabolic consequences of solid organ transplantation. *Endocr Rev* (2021) 42:171–97. doi:10.1210/endrev/bnaa030

3. Orci LA, Majno PE, Berney T, Morel P, Mentha G, Toso C. The impact of wait list body mass index changes on the outcome after liver transplantation. *Transpl Int* (2013) 26:170–6. doi:10.1111/tri.12017

4. Liese J, Bottner N, Büttner S, Reinisch A, Woeste G, Wortmann M, et al. Influence of the recipient body mass index on the outcomes after kidney transplantation. *Langenbecks Arch Surg* (2018) 403:73–82. doi:10.1007/s00423-017-1584-7

5. Yin S, Wu L, Huang Z, Fan Y, Lin T, Song T. Nonlinear relationship between body mass index and clinical outcomes after kidney transplantation: a dose-response meta-analysis of 50 observational studies. *Surgery* (2022) 171:1396–405. doi:10.1016/j.surg.2021.10.024

6. Queruel V, Kabore R, Guillaume A, Moreau K, Leffondre K, Merville P, et al. Is recipient's body mass index a determinant of short term complications in early renal transplantation? *Prog Urol* (2020) 30:663–74. doi:10.1016/j.purol.2020.07.003

7. Hill CJ, Courtney AE, Cardwell CR, Maxwell AP, Lucarelli G, Veroux M, et al. Recipient obesity and outcomes after kidney transplantation: a systematic review and meta-analysis. *Nephrol Dial Transpl* (2015) 30:1403–11. doi:10.1093/ndt/gfv214

8. Hakeem AR, Cockbain AJ, Raza SS, Pollard SG, Toogood GJ, Attia MA, et al. Increased morbidity in overweight and obese liver transplant recipients: a single-center experience of 1325 patients from the United Kingdom. *Liver Transpl* (2013) 19:551–62. doi:10.1002/lt.23618

9. Veroux M, Mattone E, Cavallo M, Gioco R, Corona D, Volpicelli A, et al. Obesity and bariatric surgery in kidney transplantation: a clinical review. *World J Diabetes* (2021) 12:1563–75. doi:10.4239/wjd.v12.i9.1563

10. Hegyi PJ, Soós A, Hegyi P, Szakács Z, Hanák L, Váncsa S, et al. Pre-transplant sarcopenic obesity worsens the survival after liver transplantation: a meta-analysis and a systematic review. *Front Med (Lausanne)* (2020) 7:599434. doi:10.3389/fmed.2020.599434

11. Schold JD, Augustine JJ, Huml AM, Fatica R, Nurko S, Wee A, et al. Effects of body mass index on kidney transplant outcomes are significantly modified by patient characteristics. *Am J Transpl* (2021) 21:751–65. doi:10.1111/ajt.16196

12. Lafranca JA, Jn IJ, Betjes MG, Dor FJ. Body mass index and outcome in renal transplant recipients: a systematic review and meta-analysis. *BMC Med* (2015) 13:111. doi:10.1186/s12916-015-0340-5

13. Caamiña L, Pietropaolo A, Basile G, Dönmez MI, Uleri A, Territo A, et al. Does obesity really affect renal transplantation outcomes? *Actas Urol Esp Engl Ed* (2024) 48(48):125–33. doi:10.1016/j.acuroe.2023.08.007

14. Foroutan F, Friesen EL, Clark KE, Motaghi S, Zyla R, Lee Y, et al. Risk factors for 1-Year graft loss after kidney transplantation: systematic review and meta-analysis. *Clin J Am Soc Nephrol* (2019) 14:1642–50. doi:10.2215/CJN.05560519

15. Tsuboi N, Okabayashi Y, Shimizu A, Yokoo T. The renal pathology of obesity. *Kidney Int Rep* (2017) 2:251–60. doi:10.1016/j.ekir.2017.01.007

16. Wang Y, Chen X, Song Y, Caballero B, Cheskin LJ. Association between obesity and kidney disease: a systematic review and meta-analysis. *Kidney Int* (2008) 73:19–33. doi:10.1038/sj.ki.5002586

17. LaMattina JC, Foley DP, Fernandez LA, Pirsch JD, Musat AI, D'Alessandro AM, et al. Complications associated with liver transplantation in the obese recipient. *Clin Transpl* (2012) 26:910–8. doi:10.1111/j.1399-0012.2012.01669.x

18. Nair S, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. *Hepatology* (2002) 35:105–9. doi:10.1053/jhep.2002.30318

19. Saab S, Lalezari D, Pruthi P, Alper T, Tong MJ. The impact of obesity on patient survival in liver transplant recipients: a meta-analysis. *Liver Int* (2015) 35:164–70. doi:10.1111/liv.12431

20. Wei Q, Wang K, Yang M, Chen J, Shen T, Song P, et al. Recipient gender and body mass index are associated with early acute rejection in donation after cardiac death liver transplantation. *Clin Res Hepatol Gastroenterol* (2020) 44S:100004. doi:10.1016/j.clirex.2020.100004

21. Koh JH, Chee D, Ng CH, Wijarnpreecha K, Muthiah M, Tan DJH, et al. Sex-based disparities in liver transplantation for hepatocellular carcinoma and the impact of the growing burden of NASH. *Transpl Direct* (2024) 10:e1642. doi:10.1097/TXD.0000000000001642

22. Rodriguez-Castro KI, De Martin E, Gambato M, Lazzaro S, Villa E, Burra P. Female gender in the setting of liver transplantation. *World J Transpl* (2014) 4:229–42. doi:10.5500/wjt.v4.i4.229

23. Chouairi F, Milner A, Sen S, Guha A, Stewart J, Jastreboff AM, et al. Impact of obesity on heart transplantation outcomes. *J Am Heart Assoc* (2021) 10:e021346. doi:10.1161/JAHA.121.021346

24. Kim D, Kim IC, Youn JC, Chang WS, Kim JJ, Jung MH, et al. Impact of obesity on long term post heart transplantation outcomes. *J Heart Lung Transpl* (2025) 44:1396–404. doi:10.1016/j.healun.2025.04.021

25. Gries CJ, Bhadriraju S, Edelman JD, Goss CH, Raghu G, Mulligan MS. Obese patients with idiopathic pulmonary fibrosis have a higher 90-day mortality risk with bilateral lung transplantation. *J Heart Lung Transpl* (2015) 34:241–6. doi:10.1016/j.healun.2014.09.031

26. Madill J, Gutierrez C, Grossman J, Allard J, Chan C, Hutcheon M, et al. Nutritional assessment of the lung transplant patient: body mass index as a predictor of 90-day mortality following transplantation. *J Heart Lung Transpl* (2001) 20:288–96. doi:10.1016/s1053-2498(00)00315-6

27. Kanasky WF, Jr., Anton SD, Rodrigue JR, Perri MG, Szwed T, Baz MA. Impact of body weight on long-term survival after lung transplantation. *Chest* (2002) 121:401–6. doi:10.1378/chest.121.2.401

28. Dobrzycka M, Bzoma B, Bieniaszewski K, Debska-Slizien A, Kobiela J. Pretransplant BMI significantly affects perioperative course and graft survival after kidney transplantation: a retrospective analysis. *J Clin Med* (2022) 11:11. doi:10.3390/jcm11154393

29. De Jong A, Rolle A, Souche FR, Yengui O, Verzilli D, Chanques G, et al. How can I manage anaesthesia in obese patients? *Anaesth Crit Care Pain Med* (2020) 39:229–38. doi:10.1016/j.accpm.2019.12.009

30. El-Mahrouk M, Sorgnitt R, Schwantzer G, Karitinig R, Jaradat D, Mathe Z, et al. Body mass index: a key factor in surgical site infections after kidney transplantation? *Int Wound J* (2026) 23:e70901. doi:10.1111/iwj.70901

31. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* (1993) 259:87–91. doi:10.1126/science.7678183

32. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* (2011) 11:85–97. doi:10.1038/nri2921

33. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest* (1995) 95:2409–15. doi:10.1172/JCI117936

34. Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature* (1998) 394:897–901. doi:10.1038/29795

35. Procaccini C, Jirillo E, Matarese G. Leptin as an immunomodulator. *Mol Aspects Med* (2012) 33:35–45. doi:10.1016/j.mam.2011.10.012

36. Matsuzawa Y. Adiponectin: a key player in obesity related disorders. *Curr Pharm Des* (2010) 16:1896–901. doi:10.2174/138161210791208893

37. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, *in vivo*. *J Clin Endocrinol Metab* (1997) 82:4196–200. doi:10.1210/jcem.82.12.4450

38. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW, Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* (2003) 112:1796–808. doi:10.1172/JCI19246

39. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *J Clin Invest* (2007) 117:175–84. doi:10.1172/JCI29881

40. Kumari M, Heeren J, Scheja L. Regulation of immunometabolism in adipose tissue. *Semin Immunopathol* (2018) 40:189–202. doi:10.1007/s00281-017-0668-3

41. Bai Y, Sun Q. Macrophage recruitment in obese adipose tissue. *Obes Rev* (2015) 16:127–36. doi:10.1111/obr.12242

42. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes* (2007) 56:1010–3. doi:10.2337/db06-1656

43. Neeland IJ, Ross R, Despres JP, Matsuzawa Y, Yamashita S, Shai I, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *Lancet Diabetes Endocrinol* (2019) 7:715–25. doi:10.1016/S2213-8587(19)30084-1

44. Nicoletto BB, Fonseca NK, Manfro RC, Gonçalves LF, Leitão CB, Souza GC. Effects of obesity on kidney transplantation outcomes: a systematic review and meta-analysis. *Transplantation* (2014) 98:167–76. doi:10.1097/tp.0000000000000028

45. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol* (2009) 4:481–508. doi:10.2215/CJN.04800908

46. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet* (2004) 43:623–53. doi:10.2165/00003088-200443100-00001

47. Campara M, Lourenco LM, Melaragno JI, Kaiser TE. Implications for body weight extremes in solid organ transplantation. *Pharmacotherapy* (2021) 41:44–58. doi:10.1002/phar.2493

48. Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE. Functional and structural changes in the kidney in the early stages of obesity. *J Am Soc Nephrol* (2001) 12:1211–7. doi:10.1681/ASN.V1261211

49. Vanhove T, Annaert P, Kuypers DR. Clinical determinants of calcineurin inhibitor disposition: a mechanistic review. *Drug Metab Rev* (2016) 48:88–112. doi:10.3109/03602532.2016.1151037

50. Saint-Marcoux F, Vandierdonck S, Premaud A, Debord J, Rousseau A, Marquet P. Large scale analysis of routine dose adjustments of mycophenolate mofetil based on global exposure in renal transplant patients. *Ther Drug Monit* (2011) 33:285–94. doi:10.1097/FTD.0b013e31821633a6

51. Shuker N, van Gelder T, Hesselink DA. Intra-patient variability in tacrolimus exposure: causes, consequences for clinical management. *Transpl Rev (Orlando)* (2015) 29:78–84. doi:10.1016/j.trre.2015.01.002

52. Andrews LM, de Winter BC, Tang JT, Shuker N, Bouamar R, van Schaik RH, et al. Overweight kidney transplant recipients are at risk of being overdosed following standard bodyweight-based tacrolimus starting dose. *Transpl Direct* (2017) 3:e129. doi:10.1097/TXD.0000000000000644

53. Flechner SM, Kolbeinsson ME, Tam J, Lum B. The impact of body weight on cyclosporine pharmacokinetics in renal transplant recipients. *Transplantation* (1989) 47:806–10. doi:10.1097/00007890-198905000-00012

54. Borobia AM, Romero I, Jimenez C, Gil F, Ramirez E, De GR, et al. Trough tacrolimus concentrations in the first week after kidney transplantation are related to acute rejection. *Ther Drug Monit* (2009) 31:436–42. doi:10.1097/FTD.0b013e3181a8f02a

55. Ekberg H, Tedesco-Silva H, Demirbas A, Vitko S, Nashan B, Gurkan A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* (2007) 357:2562–75. doi:10.1056/NEJMoa067411

56. Kirchner GI, Meier-Wiedenbach I, Manns MP. Clinical pharmacokinetics of everolimus. *Clin Pharmacokinet* (2004) 43:83–95. doi:10.2165/00003088-200443020-00002

57. Tedesco-Silva H, Saliba F, Barten MJ, De Simone P, Potena L, Gottlieb J, et al. An overview of the efficacy and safety of everolimus in adult solid organ transplant recipients. *Transpl Rev (Orlando)* (2022) 36:100655. doi:10.1016/j.trre.2021.100655

58. Kahan BD. Sirolimus: a new agent for clinical renal transplantation. *Transpl Proc* (1997) 29:48–50. doi:10.1016/s0041-1345(96)00008-5

59. Morath C, Arns W, Schwenger V, Mehrabi A, Fonouni H, Schmidt J, et al. Sirolimus in renal transplantation. *Nephrol Dial Transpl* (2007) 22:viii61–viii65. doi:10.1093/ndt/gfm652

60. Lebranchu Y, Thierry A, Toupance O, Westeel PF, Etienne I, Thervet E, et al. Efficacy on renal function of early conversion from cyclosporine to sirolimus 3 months after renal transplantation: concept study. *Am J Transpl* (2009) 9:1115–23. doi:10.1111/j.1600-6143.2009.02615.x

61. Serna-Higuita LM, Della Penna A, Guthoff M, Heyne N, Beer-Hammer S, Nadalin S, et al. Impact of different immunosuppressive protocols on clinical outcomes in obese kidney transplant recipients: a propensity score-matched analysis. *Nephrol Dial Transpl* (2023) 38:2052–66. doi:10.1093/ndt/gfad014

62. Kuppahally S, Al-Khaldi A, Weisshaar D, Valantine HA, Oyer P, Robbins RC, et al. Wound healing complications with *de novo* sirolimus *versus* mycophenolate mofetil-based regimen in cardiac transplant recipients. *Am J Transpl* (2006) 6:986–92. doi:10.1111/j.1600-6143.2006.01282.x

63. Hartinger JM, Rysanek P, Slanar O, Sima M. Pharmacokinetic principles of dose adjustment of mTOR inhibitors in solid organ transplanted patients. *J Clin Pharm Ther* (2022) 47:1362–7. doi:10.1111/jcpt.13753

64. Bullingham RE, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. *Clin Pharmacokinet* (1998) 34:429–55. doi:10.2165/00003088-199834060-00002

65. Kaplan B, Gaston RS, Meier-Kriesche HU, Bloom RD, Shaw LM. Mycophenolic acid exposure in high- and low-weight renal transplant patients after dosing with mycophenolate mofetil in the opticept trial. *Ther Drug Monit* (2010) 32:224–7. doi:10.1097/FTD.0b013e3181d18baa

66. van Gelder T, Le Meur Y, Shaw LM, Oellerich M, DeNofrio D, Holt C, et al. Therapeutic drug monitoring of mycophenolate mofetil in transplantation. *Ther Drug Monit* (2006) 28:145–54. doi:10.1097/01.ftd.0000199358.80013.bd

67. Shaw LM, Holt DW, Oellerich M, Meiser B, van Gelder T. Current issues in therapeutic drug monitoring of mycophenolic acid: report of a roundtable discussion. *Ther Drug Monit* (2001) 23:305–15. doi:10.1097/00007691-200108000-00001

68. Le Meur Y, Buchler M, Thierry A, Caillard S, Villemain F, Lavaud S, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. *Am J Transpl* (2007) 7:2496–503. doi:10.1111/j.1600-6143.2007.01983.x

69. Pascual J, Zamora J, Galeano C, Royuela A, Quereda C. Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev* (2009) (1):CD005632. doi:10.1002/14651858.CD005632.pub2

70. Vincenti F, Schena FP, Paraskevas S, Hauser IA, Walker RG, Grinyo J, et al. A randomized, multicenter study of steroid avoidance, early steroid withdrawal or standard steroid therapy in kidney transplant recipients. *Am J Transpl* (2008) 8:307–16. doi:10.1111/j.1600-6143.2007.02057.x

71. Walker BR. Glucocorticoids and cardiovascular disease. *Eur J Endocrinol* (2007) 157:545–59. doi:10.1530/EJE-07-0455

72. Tomlinson JW, Walker EA, Bujalska IJ, Draper N, Lavery GG, Cooper MS, et al. 11beta-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. *Endocr Rev* (2004) 25:831–66. doi:10.1210/er.2003-0031

73. Elster EA, Leeser DB, Morrissette C, Pepek JM, Quiko A, Hale DA, et al. Obesity following kidney transplantation and steroid avoidance immunosuppression. *Clin Transpl* (2008) 22:354–9. doi:10.1111/j.1399-0012.2008.00792.x

74. van Raalte DH, Ouwens DM, Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? *Eur J Clin Invest* (2009) 39:81–93. doi:10.1111/j.1365-2362.2008.02067.x

75. Vincenti F, Larsen C, Durrbach A, Wekerle T, Nashan B, Blancho G, et al. Costimulation blockade with belatacept in renal transplantation. *N Engl J Med* (2005) 353:770–81. doi:10.1056/NEJMoa050085

76. Rostaing L, Massari P, Garcia VD, Mancilla-Urrea E, Nainan G, del Carmen Rial M, et al. Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: a randomized phase II study. *Clin J Am Soc Nephrol* (2011) 6:430–9. doi:10.2215/CJN.05840710

77. Vincenti F, Rostaing L, Grinyo J, Rice K, Steinberg S, Gaite L, et al. Belatacept and long-term outcomes in kidney transplantation. *N Engl J Med* (2016) 374:333–43. doi:10.1056/NEJMoa1506027

78. Shen J, Townsend R, You X, Shen Y, Zhan P, Zhou Z, et al. Pharmacokinetics, pharmacodynamics, and immunogenicity of belatacept in adult kidney transplant recipients. *Clin Drug Investig* (2014) 34:117–26. doi:10.1007/s40261-013-0153-2

79. Lange NW, King K, Husain SA, Salerno DM, Tsapepas DS, Hedvat J, et al. Obesity is associated with a higher incidence of rejection in patients on belatacept: a pooled analysis from the BENEFIT/BENEFIT-EXT clinical trials. *Am J Transpl* (2024) 24:1027–34. doi:10.1016/j.ajt.2024.02.015

80. Musuamba FT, Rousseau A, Bosmans JL, Senessael JJ, Cumps J, Marquet P, et al. Limited sampling models and Bayesian estimation for mycophenolic acid area under the curve prediction in stable renal transplant patients co-medicated with ciclosporin or sirolimus. *Clin Pharmacokinet* (2009) 48:745–58. doi:10.2165/11318060-000000000-00000

81. Lefaucheur C, Loupy A, Vernerey D, Duong-Van-Huyen JP, Suberbielle C, Anglicheau D, et al. Antibody-mediated vascular rejection of kidney allografts: a population-based study. *Lancet* (2013) 381:313–9. doi:10.1016/S0140-6736(12)61265-3

82. Naesens M, Anglicheau D. Precision transplant medicine: biomarkers to the rescue. *J Am Soc Nephrol* (2018) 29:24–34. doi:10.1681/ASN.2017010004

83. Kuypers DR. Benefit-risk assessment of sirolimus in renal transplantation. *Drug Saf* (2005) 28:153–81. doi:10.2165/00002018-200528020-00006

84. Durrbach A, Pestana JM, Pearson T, Vincenti F, Garcia VD, Campistol J, et al. A phase III study of belatacept *versus* cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). *Am J Transpl* (2010) 10:547–57. doi:10.1111/j.1600-6143.2010.03016.x

85. Cheung CY, Tang SCW. Personalized immunosuppression after kidney transplantation. *Nephrology (Carlton)* (2022) 27:475–83. doi:10.1111/nep.14035

86. Turolo S, Edefonti A, Syren ML, Montini G. Pharmacogenomics of old and new immunosuppressive drugs for precision medicine in kidney transplantation. *J Clin Med* (2023) 12:12. doi:10.3390/jcm12134454

87. Belardi R, Pacifici F, Baldetti M, Velocci S, Minieri M, Pieri M, et al. Trends in precision medicine and pharmacogenetics as an adjuvant in establishing a correct immunosuppressive therapy for kidney transplant: an up-to-date historical overview. *Int J Mol Sci* (2025) 26:26. doi:10.3390/ijms26051960

88. Millan O, Julian J, Brunet M. miRNAs, dd-cf-DNA, and chemokines as potential noninvasive biomarkers for the assessment of clinical graft evolution and personalized immunosuppression requirement in solid organ transplantation. *Ther Drug Monit* (2025) 47:77–97. doi:10.1097/FTD.0000000000001276

89. Loupy A, Sablik M, Khush K, Reese PP. Advancing patient monitoring, diagnostics, and treatment strategies for transplant precision medicine. *Lancet* (2025) 406:389–402. doi:10.1016/S0140-6736(25)00195-3

90. Brunet M, Shipkova M, van Gelder T, Wieland E, Sommerer C, Budde K, et al. Barcelona consensus on biomarker-based immunosuppressive drugs management in solid organ transplantation. *Ther Drug Monit* (2016) 38(Suppl. 1):S1–20. doi:10.1097/FTD.0000000000000287

91. Filippone EJ, Farber JL. The monitoring of donor-derived cell-free DNA in kidney transplantation. *Transplantation* (2021) 105:509–16. doi:10.1097/TP.0000000000003393

92. Zhou H, Gizlenci M, Xiao Y, Martin F, Nakamori K, Zicari EM, et al. Obesity-associated inflammation and alloimmunity. *Transplantation* (2025) 109:588–96. doi:10.1097/TP.0000000000005183

93. Lee SA, Verhoeff R, Hullekes F, Hansrivijit P, de Bruin RWF, Porte RJ, et al. SGLT2 inhibitors and GLP-1 receptor agonists in kidney transplantation: a systematic review and meta-analysis. *Transplantation* (2026) 110:e217–e28. doi:10.1097/TP.0000000000005496

94. Ertuglu LA, Porrini E, Hornum M, Demiray A, Afsar B, Ortiz A, et al. Glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors for diabetes after solid organ transplantation. *Transpl Int* (2021) 34:1341–59. doi:10.1111/tri.13883

95. Dotan I, Rudman Y, Turjeman A, Akirov A, Steinmetz T, Calvarysky B, et al. Glucagon-like peptide 1 receptor agonists and cardiovascular outcomes in solid organ transplant recipients with diabetes mellitus. *Transplantation* (2024) 108:e121–e8. doi:10.1097/TP.0000000000004945

96. Carey EJ, Lai JC, Sonnenday C, Tapper EB, Tandon P, Duarte-Rojo A, et al. A north American expert opinion statement on sarcopenia in liver transplantation. *Hepatology* (2019) 70:1816–29. doi:10.1002/hep.30828

97. Minichmayr IK, Dreesen E, Centanni M, Wang Z, Hoffert Y, Friberg LE, et al. Model-informed precision dosing: state of the art and future perspectives. *Adv Drug Deliv Rev* (2024) 215:115421. doi:10.1016/j.addr.2024.115421

ESOT | Transplant International

TYPE Mini Review
PUBLISHED 04 May 2026
DOI 10.3389/ti.2026.16305

Check for updates

OPEN ACCESS

*CORRESPONDENCE
Sophie Caillard,
sophie.caillard@chru-strasbourg.fr

RECEIVED 26 January 2026
REVISED 15 April 2026
ACCEPTED 21 April 2026
PUBLISHED 04 May 2026

CITATION
Caillard S, Solis M, Benotmane I, Gallais F and Fafi Kremer S (2026) Predictive biomarkers and preventive strategies for PTLD: a turning point in viro-immunologic precision medicine?
Transpl. Int. 39:16305.
doi: 10.3389/ti.2026.16305

COPYRIGHT
© 2026 Caillard, Solis, Benotmane, Gallais and Fafi Kremer. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Predictive biomarkers and preventive strategies for PTLD: a turning point in viro-immunologic precision medicine?

Sophie Caillard[1,2]*, Morgane Solis[2,3], Ilies Benotmane[1,2], Floriane Gallais[2,3] and Samira Fafi Kremer[2,3]

[1]Department of Nephrology Dialysis and Transplantation, Strasbourg University Hospital, Strasbourg, France, [2]Molecular ImmunoRhumatology, INSERM UMR_S1109, Strasbourg University, Strasbourg, France, [3]Department of Virology, Strasbourg University Hospital, Strasbourg, France

Post-transplant lymphoproliferative disorders (PTLD) represent a heterogeneous group of complications with rising complexity, particularly as EBV-negative forms are increasingly recognized in adult recipients. While early EBV-driven PTLD was historically monitored by viral load, this approach fails to detect EBV-negative disease and lacks specificity even in EBV-positive cases. Recent advances in tumor immunology, virology, and liquid biopsy technologies have led to the emergence of novel biomarkers that offer improved diagnostic precision. These include plasma soluble ZEBRA antigen, reflecting lytic EBV activation; EBV DNA methylation status, which may distinguish latent from benign viral replication; and LMP1 sequence variants that influence immune evasion through the NKG2A/HLA-E axis. For EBV-negative PTLD, circulating tumor DNA profiling has shown promise for early, non-invasive detection. These innovations are complemented by preventive strategies such as anti-CD20 therapy in high-risk EBV-seronegative transplant recipients and ongoing trials of EBV-targeted vaccines. However, such approaches remain limited to EBV-naïve patients. Moving forward, integrating viral, immune, and tumor-derived markers—alongside host genetic factors—may enable more personalized surveillance and preemptive interventions. This review outlines the evolving paradigm of PTLD monitoring and highlights key areas where viro-immunologic precision medicine may reshape clinical practice.

KEYWORDS
biomarker, EBV, HSCT, PTLD, SOT (solid organ transplant)

Introduction

Post-transplant lymphoproliferative disorders (PTLD) occupy a unique space in transplantation medicine: relatively rare, with an incidence reaching two percent after 10 years in solid organ recipients [1], but disproportionately feared because of their unpredictability, severity, and the inadequate precision of available monitoring tools. For decades, PTLD was predominantly an Epstein–Barr virus (EBV)-driven complication occurring early after transplantation [2, 3], detectable in some cases by rising EBV viral loads [4], especially in paediatric population [5]. This paradigm has been replaced by a much more complex picture, shaped by the rise of EBV-negative PTLD occurring later after transplantation and by deeper insights into the immune dysfunctions underlying both EBV- and non–EBV-driven lymphoproliferations. Moreover, improved understanding of the pathophysiology of this malignant process may support the

development of a new generation of biomarkers that are more specific than those currently used, which are often unreliable.

Epidemiological shift towards EBV-negative PTLD

The first notable shift to highlight is epidemiological. In a recent Canadian registry study, the authors reported that adult solid organ transplant recipients now face a sustained risk of late-onset PTLD, whereas the risk of early PTLD appears to have declined in recent years [6]. Multiple cohorts, including the French K-VIROGREF registry, now report that EBV-negative PTLD represents nearly half of all cases of PTLD in adults. This is a profound transformation, because EBV-negative disease is biologically distinct from EBV-positive forms.

Divergent pathways in EBV-negative versus EBV-positive PTLD

This observation implies that viral monitoring may fail to detect a substantial proportion of lymphoproliferative disorders. In other words, half of PTLD may be virologically silent and immunologically invisible unless new classes of biomarkers are developed. Instead of uncontrolled expansion of EBV-infected B cells due to defective immune surveillance, EBV-negative PTLD exhibits genomic instability and molecular hallmarks close to *de novo* diffuse large B-cell lymphoma, including recurrent TP53 pathway alterations, overexpression of DNA interaction-related genes and a heavy burden of chromosomal copy-number changes [7, 8]. Pathology studies in tumors retrieved from solid organ transplant recipients have further shown that the immune microenvironment of EBV-negative PTLD is characterized by CD4-positive T cells expression of exhaustion markers such as TIM-3 [9]. Moreover, NK cells demonstrate also dysfunctional phenotypes, and tumor infiltration by effector lymphocytes is sparse [9].

Simultaneously, advances in the understanding of EBV-positive PTLD have shed new light on its complex pathogenesis. Far from a simple failure of CD8-mediated control, EBV-positive PTLD now appears to emerge from a confluence of factors. Dysfunctional NK cells, despite phenotypic activation, lack cytotoxic competency; CD8-positive T cells demonstrate impaired effector programs; and the microenvironment is enriched in PD-L1 expression, offering an immune-escape niche [9]. These insights have inspired the search for biomarkers that look beyond viral quantity to viral behavior, viral genetics, and the host's capacity to respond Figure 1.

Innovative biomarkers and PTLD risk assessment

Soluble ZEBRA: a marker of lytic EBV activation

One promising development is soluble ZEBRA (Z Epstein-Barr virus replication activator, a protein encoded by the EBV *BZLF1* gene), a marker of lytic viral activation that appears more specific than the classical EBV viral load for EBV-driven PTLD [10, 11]. The presence of ZEBRA in plasma likely reflects a biologically meaningful transition from viral latency to lytic activation—an early event associated with oncogenic reprogramming. Moreover, studies have shown that proteins expressed during the lytic cycle contribute not only to cellular transformation but also to subsequent tumor development in animal models and human EBV induced tumors [12]. Indeed, modulation of host gene expression by ZEBRA can also deregulate the immune surveillance, allow immune escape, and favor tumor progression [13]. In a recent multicentric cohort of solid organ and hematopoietic stem cells transplant recipients, soluble ZEBRA achieved specificity over ninety percent and sensitivity above eighty percent for EBV-positive PTLD, outperforming EBV viral load and, surprisingly, identifying four cases of EBER (Epstein-Barr virus-encoded small RNA) negative tumor with negative blood EBV PCR assays [10]. The performance of this test was lower in an external validation cohort of solid organ and hematopoietic stem cells transplant recipients [11], but the accuracy of this biomarker still needs to be refined and assessed in additional cohorts of solid organ transplant recipients.

EBV DNA methylation as diagnostic tools

A parallel innovation comes from epigenetic analyses, particularly DNA methylation assays. DNA methylation plays a central role in the regulation of gene expression, and both host genomic DNA and EBV DNA methylation are emerging as potential biomarkers. Two patients with the same EBV viral load may have different viral infections. A highly methylated EBV signal would suggest latent EBV within tumor cells, whereas unmethylated DNA could indicate a benign lytic infection. Recently, plasma EBV DNA methylation profiles were shown to discriminate three distinct EBV-associated conditions—infectious mononucleosis, EBV-associated lymphoma, and nasopharyngeal carcinoma [14]. In a small study conducted in patients who had undergone hematopoietic stem cell transplantation, one patient with predominantly unmethylated EBV DNA failed to respond to rituximab, whereas those with highly methylated EBV patterns were consistent with PTLD and responded to anti-CD20 therapy [15]. Beyond EBV DNA, host genomic DNA methylation status is also of major interest in oncology. Malignant tumors are characterized by aberrant DNA methylation. Panels of methylated host genes in circulating cell-free DNA (cfDNA) have also shown potential as diagnostic and prognostic biomarkers in EBV-associated lymphomas in non-transplant patients [16].

Genomic characterization and immune evasion pathways

Another breakthrough lies in the genomic characterization of EBV itself. The risk of EBV-associated PTLD has recently been linked to the NKG2A/LMP1/HLA-E axis, involving specific viral and host variations [17]. More specifically, recent sequencing analyses have identified two variants of the EBV LMP1 gene—GGDPHLPTL and GGDPPLPTL—that are markedly enriched in solid organ and hematopoietic stem cells transplant recipients who develop EBV-positive PTLD. Moreover, patients with PTLD more frequently carry the HLA-E*0103/

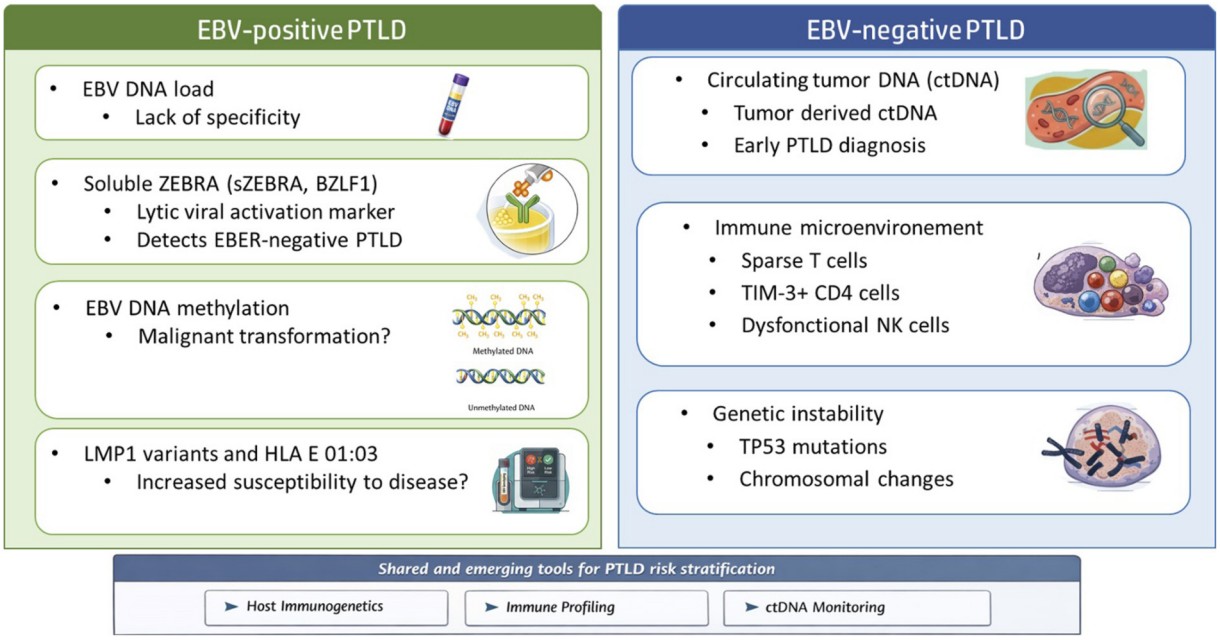


FIGURE 1
Predictive biomarkers for EBV-positive and EBV-negative PTLD.

0103 allele, indicating an increased susceptibility to disease when EBV peptides are presented in this context. Lastly, the GGDPHLPTL and GGDPPLPTL LMP1 peptides strongly inhibit NKG2A$^+$ NK cells and CD8$^+$ T cells, thereby promoting immune evasion by these EBV strains. In the same manner, in a cohort of pediatric solid organ transplant recipients, the presence of two specific mutations in the EBV LMP1 gene (G212S and S366T) was associated with a nearly 12-fold increased risk of developing PTLD. Nevertheless, it is important to note that these mutations were also found at a high frequency in patients without PTLD; however, the absence of these mutations was associated with a high negative predictive value for PTLD occurrence [18]. Although these findings have been described mainly in young patients, they raise the possibility that EBV sequencing could become part of transplant risk assessment, with EBV lineage analysis helping to predict which patients are most vulnerable to malignant transformation following primary EBV infection.

Liquid biopsy strategies

While EBV-focused biomarkers continue to advance, the detection of EBV-negative PTLD may benefit most from technologies adapted from oncology, particularly by detection of circulating tumor DNA. CfDNA sequencing studies have demonstrated that tumor-derived DNA fragments—harboring lymphoma-associated mutations and characteristic copy-number changes in specific genes—can be detected in plasma months before clinical diagnosis. In one landmark study, cfDNA levels were increased not only in solid organ transplant recipients with EBV-positive PTLD but also in those with EBV-negative PTLD, with the observed range of cfDNA levels being consistent with that reported in other malignancies [19]. Moreover, cfDNA levels correlated with tumor burden. Beyond genomic cfDNA profiling, cfDNA methylation provides an additional biomarker. To date, cfDNA methylation has not yet been evaluated in PTLD. However, similar to EBV-positive lymphomas, aberrant methylation patterns in cfDNA can be used as diagnostic biomarkers and may enable earlier cancer detection -including lymphoma-than mutation-based cfDNA assays [20]. In addition to their diagnostic value, these methylation patterns have also shown prognostic significance, being associated with clinical outcomes [21]. The implications are substantial: EBV-negative PTLD, once thought to be “invisible” until symptoms arise, may in fact shed detectable genetic material long before overt disease. For clinicians, this could offer a reliable tool for pre-symptomatic detection, enabling diagnosis at an early stage when treatment is more effective and potentially improving patient outcomes. However, despite these promising results, data correlating EBV DNA methylation patterns with EBV load dynamics or response to rituximab remain limited, and validation in larger cohorts is still required.

Torque teno virus load as a surrogate marker of global overimmunosuppression

Torque teno virus (TTV) load has emerged as a marker reflecting the net state of immunosuppression in solid organ and hematopoietic stem cell transplant recipients. Although high TTV titers have been associated with infectious complications, current evidence does not establish a clear relationship between TTV replication and PTLD risk. Only a small exploratory study have suggested a possible association between high TTV viral load and the

development of PTLD in hematopoiectic stem cell transplant patients [22], and no validated thresholds exist to date to guide PTLD prediction.

Emerging preventive strategies for PTLD

In parallel, preventive strategies for PTLD are advancing. The REPLY randomized trial evaluating preventive rituximab in EBV D+/R–kidney transplant recipients has completed enrolment and may soon clarify whether early B-cell depletion can prevent primary EBV infection and subsequent PTLD in treated patients (NCT04989491). Another promising development is the emergence of EBV vaccines, including mRNA- and nanoparticle-based platforms, which are currently being evaluated in healthy young adults with the aim of reducing the incidence of infectious mononucleosis (NCT05164094, NCT05831111, NCT06908096). If effective, these vaccines could substantially lower the burden of EBV-driven PTLD in EBV-seronegative transplant recipients and potentially reshape clinical practice. However, both strategies—anti-CD20 therapy and EBV mRNA vaccination—would primarily benefit patients who are EBV seronegative, and therefore would not apply to the majority of adult transplant recipients, who are mostly EBV seropositive. Conversely, these approaches may prove particularly valuable in paediatric transplantation, where a large proportion of candidates are EBV-naïve and at high risk for primary infection and early PTLD development.

Conclusion

In conclusion, significant hope has emerged from preventive strategies—either vaccination or therapies aimed at depleting the EBV reservoir—but these approaches apply primarily to EBV seronegative organ recipients. In parallel, there is a clear need to refine biomarkers that can identify patients at highest risk of developing PTLD, whether during primary EBV infection or later, at the time of viral reactivation. In addition, specific biomarkers for EBV negative lymphomas—which are becoming increasingly frequent due to the aging transplant population—must also be developed. A combination of genetic data, associated with virological, immunological, and tumor-derived markers could enable a more effective and personalized approach to PTLD screening, whether EBV-driven or not. Among these emerging candidates, HLA-E genotyping, plasma ZEBRA protein measurement, viral DNA methylation, sequencing of the viral LMP1 protein, and circulating tumor DNA quantification represent particularly promising opportunities.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. This manuscript contains content edited with the assistance of generative AI (ChatGPT, OpenAI). The tool was used to improve consistency of style, and linguistic accuracy during the drafting process. All scientific content, interpretations, and references were developed, reviewed, and validated entirely by the authors, who take full responsibility for the final version of the manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

References

1. Caillard S, Porcher R, Provot F, Dantal J, Choquet S, Durrbach A, et al. Post-transplantation lymphoproliferative disorder after kidney transplantation: report of a nationwide French registry and the development of a new prognostic score. *J Clin Oncol* (2013) 31(10):1302–9. doi:10.1200/JCO.2012.43.2344

2. Dierickx D, Habermann TM. Post-transplantation lymphoproliferative disorders in adults. *N Engl J Med* (2018) 378:549–62. doi:10.1056/NEJMra1702693

3. Caillard S, Lamy FX, Quelen C, Dantal J, Lebranchu Y, Lang P, et al. Epidemiology of posttransplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: report of the French registry and analysis of subgroups of lymphomas. *Am J Transpl* (2012) 12(3):682–93. doi:10.1111/j.1600-6143.2011.03896

4. Holman CJ, Karger AB, Mullan BD, Brundage RC, Balfour HH, Jr. Quantitative epstein-barr virus shedding and its correlation with the risk of post-transplant lymphoproliferative disorder. *Clin Transpl* (2012) 26(5):741–7. doi:10.1111/j.1399-0012.2012.01608

5. Gridelli B, Spada M, Riva S, Colledan M, Segalin A, Lucianetti A, et al. Circulating epstein-barr virus DNA to monitor lymphoproliferative disease following pediatric liver transplantation. *Transpl Int* (2000) 13(Suppl. 1):S399–401. doi:10.1007/s001470050370

6. Peters AC, Akinwumi MS, Cervera C, Mabilangan C, Ghosh S, Lai R, et al. The changing epidemiology of posttransplant lymphoproliferative disorder in adult solid organ transplant recipients over 30 years: a single-center experience. *Transplantation* (2018) 102(9):1553–62. doi:10.1097/TP.0000000000002146

7. Ferreiro JF, Morscio J, Dierickx D, Vandenberghe P, Gheysens O, Verhoef G, et al. EBV-positive and EBV-Negative posttransplant diffuse large B cell Lymphomas have distinct genomic and transcriptomic features. *Am J Transpl* (2016) 16(2):414–25. doi:10.1111/ajt.13558

8. Toh J, Reitsma AJ, Tajima T, Younes SF, Ezeiruaku C, Jenkins KC, et al. Tumor and immune features distinguishing EBV-positive and EBV-negative PTLD. *Cell Rep Med* (2024) 5:101851. doi:10.1016/j.xcrm.2024.101851

9. Nakid-Cordero C, Arzouk N, Gauthier N, Tarantino N, Larsen M, Choquet S, et al. Distinct immunopathological mechanisms of EBV-positive and EBV-negative PTLD. *Am J Transpl* (2021) 21:2846–63. doi:10.1111/ajt.16547

10. Lupo J, Wielandts AS, Buisson M, Consortium C, Habib M, Hamoudi M, et al. High predictive value of the soluble ZEBRA antigen (Epstein-Barr virus trans-activator Zta) in transplant patients with PTLD. *Pathogens* (2022) 11(8):928. doi:10.3390/pathogens11080928

11. Wareham NE, Kjærgaard VS, Habib M, Reekie J, Rossing K, Sengeløv H, et al. The diagnostic value of soluble epstein-barr virus BZLF1 protein in posttransplant lymphoproliferative disease among solid organ and hematopoietic cell transplant recipients. *J Infect Dis* (2026) 233(3):521–7. doi:10.1093/infdis/jiaf477

12. Germini D, Sall FB, Shmakova A, Wiels J, Dokudovskaya S, Drouet E, et al. Oncogenic properties of the EBV ZEBRA protein. *Cancers (Basel)* (2020) 12(6):1479. doi:10.3390/cancers12061479

13. Rosemarie Q, Sugden B. Epstein–barr virus: how its lytic phase contributes to oncogenesis. *Microorganisms* (2020) 8:1824. doi:10.3390/microorganisms8111824

14. Lam WKJ, Jiang P, Chan KCA, Peng W, Shang H, Heung MMS, et al. Methylation analysis of plasma DNA informs etiologies of epstein-barr virus-associated diseases. *Nat Commun* (2019) 10(1):3256. doi:10.1038/s41467-019-11226-5

15. Borde C, Quignon F, Amiel C, Gozlan J, Marechal V, Brissot E. Methyl-qPCR to investigate EBV infection in post-transplant lymphoproliferative diseases. *Clin Epigenetics* (2022) 14:33. doi:10.1186/s13148-022-01255-1

16. Tian XP, Zhang YC, Lin NJ, Wang L, Li ZH, Guo HG, et al. Diagnostic performance and prognostic value of circulating tumor DNA methylation marker in extranodal natural killer/T cell lymphoma. *Cell Rep Med* (2023) 4(2):100859. doi:10.1016/j.xcrm.2022.100859

17. Vietzen H, Furlano PL, Cornelissen JJ, Böhmig GA, Jaksch P, Puchhammer-Stöckl E. HLA-E-restricted immune responses are crucial for the control of EBV infections and the prevention of PTLD. *Blood* (2023) 141(13):1560–73. doi:10.1182/blood.2022017650

18. Martinez OM, Krams SM, Robien MA, Lapasaran MG, Arvedson MP, Reitsma A, et al. Mutations in latent membrane protein 1 of epstein-barr virus are associated with increased risk of posttransplant lymphoproliferative disorder in children. *Am J Transpl* (2023) 23(5):611–8. doi:10.1016/j.ajt.2023.02.014

19. Veltmaat N, Zhong Y, de Jesus FM, Tan GW, Bult JAA, Terpstra MM, et al. Genomic profiling of PTLD using cell-free DNA. *J Hematol Oncol* (2023) 16:104. doi:10.1186/s13045-023-01500-x

20. Witzig TE, Taylor WR, Mahoney DW, Bamlet WR, Foote PH, Burger KN, et al. Blood plasma methylated DNA markers in the detection of lymphoma: discovery, validation, and clinical pilot. *Am J Hematol* (2025) 100(2):218–28. doi:10.1002/ajh.27533

21. Wedge E, Hansen JW, Garde C, Asmar F, Tholstrup D, Kristensen SS, et al. Global hypomethylation is an independent prognostic factor in diffuse large B cell lymphoma. *Am J Hematol* (2017) 92(7):689–94. doi:10.1002/ajh.24751

22. Pociupany M, Tarabella C, Snoeck R, Dierickx D, Andrei G. Viral infections in HSCT recipients with post-transplant lymphoproliferative disorder: the role of torque teno virus as a marker of immune functions. *Microorganisms* (2025) 13(2):326. doi:10.3390/microorganisms13020326

ESOT | Transplant International

ORIGINAL RESEARCH
published: 07 May 2026
doi: 10.3389/ti.2026.15711

The Sex of Donor and Recipients in Solid Organ Transplantation: An in Depth Analysis Across the Council of Europe Member States

Emanuele Cozzi[1,2], Claudia Carella[1], Francesca Puoti[1], Lucia Masiero[1], John Forsythe[3], Derek Manas[3], Naomi Nathan[4], Artur Kaminski[5], Marina Álvarez[6], Mar Carmona[6], Beatriz Mahíllo[6], Corinne Antoine[7], Marta López-Fraga[8], Giuseppe Feltrin[1] and Beatriz Domínguez-Gil[6] on behalf of the European Committee on Organ Transplantation of the Council of Europe (CD-P-TO)*

[1]Centro Nazionale Trapianti-Istituto Superiore di Sanità (CNT-ISS), Rome, Italy, [2]Department of Cardiac, Thoracic and Vascular Sciences, Transplant Immunology Unit, Padua University Hospital, University of Padua, Padua, Italy, [3]NHS Blood and Transplant (NHSBT), Bristol, United Kingdom, [4]Nederlandse Transplantatie Stichting, Leiden, Netherlands, [5]Department of Transplantology and Central Tissue Bank, Medical University of Warsaw, Polish Transplant Coordinating Centre POLTRANSPLANT, Warsaw, Poland, [6]Organización Nacional de Trasplantes (ONT), Madrid, Spain, [7]Agence de la Biomédecine, Saint-Denis de la Plaine, France, [8]European Directorate for the Quality of Medicines and Healthcare (EDQM), Council of Europe, Strasbourg, France

Sex equity in organ donation and access to transplantation represents a key priority of the European Committee on Organ Transplantation of the Council of Europe (CD-P-TO). To increase our knowledge on sex-related differences in transplantation in the Council of Europe Member States, a specifically designed questionnaire was distributed to the CD-P-TO countries. Results confirm that, irrespective of the organ, males represent the majority of patients on the transplant waiting list. For all organs except for heart the time spent on the waiting list was shorter for men compared to women. Women represent the majority of living kidney donors (58%), whilst males are the major source of livers from living donation (54%). Across all organ types, men received 64% of deceased donor organs and 58% of living donor organs. We have found sex-related differences in transplantation activities conducted in the Council of Europe Member States. However, these may be the consequence of the higher incidence of some diseases in men, organ size mismatch, or the greater difficulty in finding immunologically compatible donors in women. At this stage, the CD-P-TO will continue its monitoring activity on this highly relevant topic and possibly extend its commitment beyond sex to include gender related aspects.

Keywords: council of europe, equity, organ donation, sex, transplantation

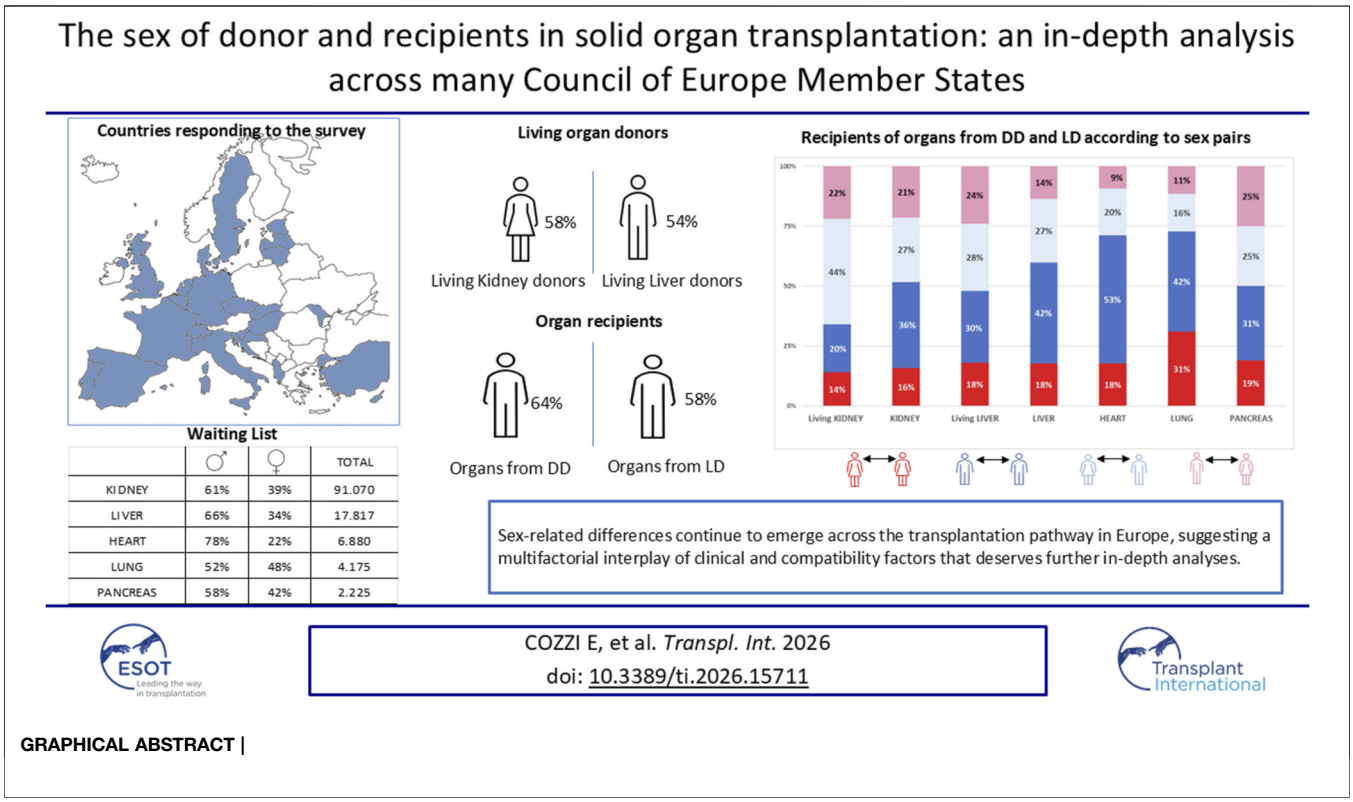
OPEN ACCESS

***Correspondence**
Emanuele Cozzi,
emanuele.cozzi@unipd.it

Received: *08 October 2025*
Revised: *14 February 2026*
Accepted: *15 April 2026*
Published: *07 May 2026*

Citation:
Cozzi E, Carella C, Puoti F, Masiero L, Forsythe J, Manas D, Nathan N, Kaminski A, Álvarez M, Carmona M, Mahíllo B, Antoine C, López-Fraga M, Feltrin G and Domínguez-Gil B (2026) The Sex of Donor and Recipients in Solid Organ Transplantation: An in Depth Analysis Across the Council of Europe Member States. Transpl. Int. 39:15711. doi: 10.3389/ti.2026.15711

Abbreviations: European Committee on Organ Transplantation of the Council of Europe; DBD, donor/donation after brain death; DD, deceased donor; DCDD, donor/donation after circulatory determination of death; LD, living donor; LKD, living kidney donation; LLD, living liver donation; ONT, Organización Nacional de Trasplantes; PMP, per million population.



GRAPHICAL ABSTRACT |

INTRODUCTION

Gender and sex equity in organ donation and access to transplantation represent a key priority of the European Committee on Organ Transplantation of the Council of Europe (CD-P-TO). To date, the sex of donors and recipients involved in donation and transplantation activities across the Council of Europe Member States has been preliminarily investigated through the data collection undertaken by the Newsletter Transplant of the Council of Europe and a preliminary analysis on the *European landscape of donors and recipients sex in solid organ transplantation* was published in late 2022 [1].

According to our earlier international investigation involving 69 countries from four continents, globally men are the more frequent deceased donors, while women are the main source of kidneys and livers from living donors [1]. Furthermore, men have a greater access to transplantation compared to women. At present there is no reason to believe that, as far as the Council of Europe Member States, such differences between sex in organ donation and transplantation may be the ultimate outcome of an unfair process. However, some have previously reported that some of the differences could be the result of social roles or pressures on women [2]. Other studies involving men and women who served as living kidney donors did not demonstrate differences in psychosocial profiles or greater vulnerability to family pressure between sex [3]. In any case, men receive the majority of transplanted organs [4] in part because of a higher incidence of chronic diseases [5, 6] and because immunological factors may disadvantage women [7]. In addition, cultural and social factors, physician biases in the perception of patient frailty, as well as potential sex-based inequities of formulas used for organ allocation and transplant criteria may limit transplant opportunities for women [2, 8–12]. At this stage, the CD-P-TO felt that a more in depth collection and analysis of data disaggregated by sex would enable a better comprehension of the possible impact of sex and gender on transplant opportunities. To this end, the CD-P-TO prepared a specifically designed questionnaire aimed at supplementing the information already available through the Newsletter Transplant [13]. Such a questionnaire was applied to all CD-P-TO Member States and a detailed analysis of the new set of data collected is here provided.

MATERIALS AND METHODS

The aim of the survey was to collect comprehensive data on organ donors and recipients in the CD-P-TO Member States, with a particular focus on sex. The key components of the study were composition of waiting lists, donor and recipient baseline information, sex combinations of donor-recipient pairs for various organ transplants, and the 5-years graft survival rates based on these combinations. The collated dataset refers to the year 2019, which is the latest year that was not affected by the SARS-CoV-2 pandemic.

The CD-P-TO established an *ad hoc* working group lead by the Italian National Transplant Centre (CNT), who prepared a questionnaire whose final version was agreed by the CD-P-TO on 7 April 2022, and formally approved in its plenary meeting held in Warsaw on 7 October 2022. The approved version of the questionnaire is appended (**Supplementary Material**). The questionnaire was circulated to the 39 CD-P-TO Member States and 5 Observers Countries, and was completed by national focal points already designated by the Ministries of Health at each country for the routine data collection performed for the Newsletter Transplant. CNT then compiled the information collected by the questionnaires, assessed the accuracy and level of completeness of the data provided and performed the data analysis. In cases of inconsistencies, the CNT contacted the designated focal point in each country for a final data check.

A total number of 33 countries filled in questionnaires were received. Four member states were removed from the analysis due to incomplete data (notwithstanding the extensive efforts put in place to clarify some inaccuracies or incomplete answers). Answers to questionnaires included in the analysis were provided by 6 Ministries of Health and 23 National Competent Authorities [**Supplementary Table S1**]. The 5-year organ survival calculation was derived from data supplied from countries with 10 transplants or more per organ type (from either living or deceased donor).

Waiting Lists

In the first instance we collected data on the number of male (M) and female (F) patients that were ever active on waiting lists (WL) in the year 2019. Additionally, each organ type respondents were asked to provide, when available, the median waiting time and the min-max range for all the patients on the WL, as well as the data disaggregated per male and female, respectively. The waiting time for kidney patients on the WL was calculated from the first day on dialysis. All the countries were also asked to provide both the median waiting time of any patient on the WL in 2019 irrespective as to whether the patient got transplanted or not, and the waiting time of only those who were actually transplanted in 2019.

Donors' Information

The questions relating to deceased organ donors focused on both donation after brain death (DBD) and donation after the circulatory determination of death (DCD), including uncontrolled and controlled DCD, namely type II, III and IV DCD Maastricht categories. For each of these, mean age and min-man range of M and F donors was collected. The same set of data was collected for living donors (LD), namely living kidney donors (LKD) and living liver donors (LLD), respectively.

Recipients' Information

In the section relating to recipients of solid organ transplants, countries provided the total number of M and F recipients of kidney, liver, heart, lung and pancreas from both DBD and DCD donors. The information regarding the recipients of organs from living donors in each respondent country was obtained from Newsletter Transplant.

Transplantation and Sex Pairs

Sex pairs in organ transplantation from deceased and living donors were also investigated. For each solid organ, countries were asked to provide the total number of transplants performed according to the following sex pairs: male to male (M-M), male to female (M-F), female to female (F-F) and female to male (F-M). Additionally, for each organ, countries were asked to provide the 5 year non-censored for death graft survival according to sex pair combinations.

Relationship Between Living Donors and Recipients

The survey addressed also the relationship between LKD and LLD and their recipients. In case of LKD and LLD between parent and child, the possible combinations were the following: mother-to-son, mother-to-daughter, father-to-son, father-to-daughter, son-to-mother, son-to-father, daughter-to-mother and daughter-to-father. In case of siblings, the possible combinations were the following: brother-to-brother, brother-to-sister, sister-to-brother and sister-to-sister. In the case of living organ donation between spouses, the combinations were husband-to-wife and wife-to-husband. Additional combinations namely husband-to-husband and wife-to-wife were provided by the respondent countries, when available.

Statistical Analysis

When examining the sex differences, all the analyses were conducted by organ and according to participating country, and the results were compared with the mean values obtained when combining all the countries: i) number and percentages of men and women were presented in the following analyses: (a) patients enrolled in the organ WL, (b) stratified by living and deceased transplanted patients and (c) DBD and DCD donors; ii) median age of patients on the WL and of transplanted patients; iii) 5-year non-censored for death Kaplan-Meier survival probability estimates. Specific comparisons of sexes were presented according to different Living Donor-Transplanted pairs. For all statistical analyses, we used Stata version 17.0 (StataCorp, College Station, TX, USA).

RESULTS

A total of 29 countries accurately completed the questionnaire and were included in the analysis. These consisted of 26 CD-P-TO Member States (Albania, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Moldova, the Netherlands, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom) and 3 observer countries (Armenia, Georgia and Israel). The two main CD-P-TO observer countries, namely United States and Canada, could not take part to the analysis. Furthermore, the amount of data required and the degree of details requested did not allow several Member States to participate in this analysis.

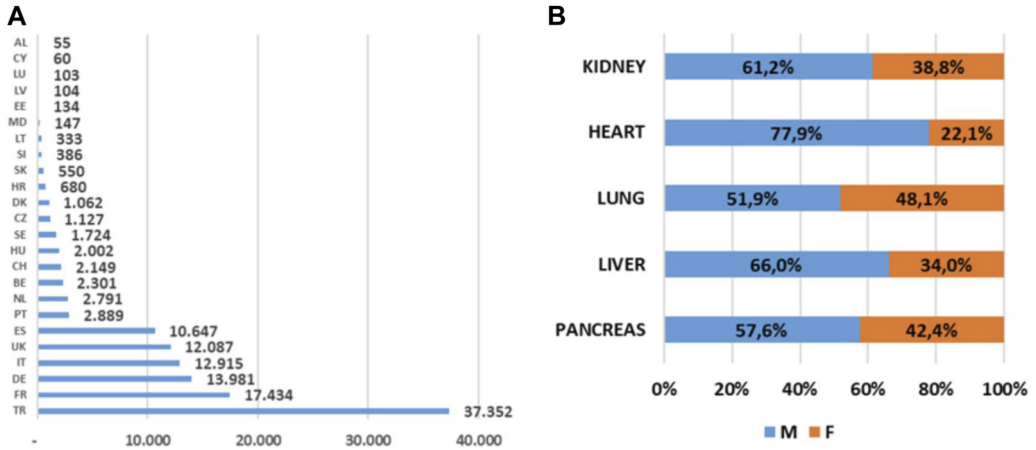


FIGURE 1 | Patients on the waiting list in the CD-P-TO MS. **(A)** Total number of patients on the waiting list (any organ) at any time in 2019; **(B)** Sex distribution of patients on the waiting list in 2019 divided by organs.

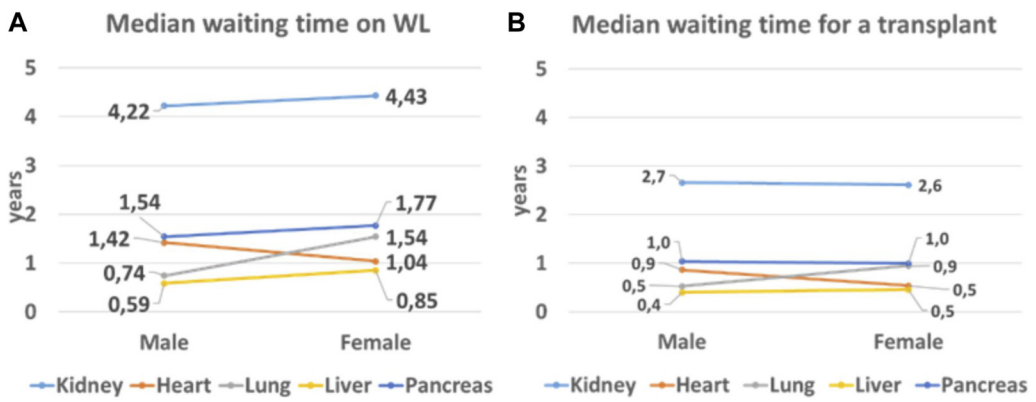


FIGURE 2 | Median waiting time of patients on the WL in the CD-P-TO MS. **(A)** Waiting time of any patient on the WL in 2019 irrespective as to whether the patient got transplanted or not; **(B)** waiting time of patients who were transplanted in 2019.

Waiting Lists

For the year 2019, a total number of 122.197 patients were ever active on the WL in Member States that took part to the survey [**Figure 1**]. The patient distribution per organ was 91,070 for kidney (61% M; 39% F); 17,817 liver (66% M; 34% F); 6,880 heart (78% M; 22,1% F); 4,175 lung (52% M; 48% F); and 2,255 pancreas (58% M; 42% F). For each organ, the median time spent on the WL is shown in **Figure 2**.

Donor Information

Transplantation after DBD donation was performed in 26 of the responding countries. Overall, 8,891 actual DBD donors were reported, of which 8,495 resulted in at least one organ transplant. The mean age of DBD donors was 54.4 years for males and 50.3 years for females. Male donors accounted for 56% of both actual and utilized DBD donors.

Only a limited number of countries performed DCD donation activities. Among the countries participating in this analysis, DCD was performed in Austria, Belgium, France, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden, Switzerland, the United Kingdom and Israel. In this context, category III DCD was the most prevalent form, being performed in 12 of the respondent countries. Overall there were 1,995 actual DCD donors of which 1,745 were utilised. The mean age of category III DCD donors was 56.6 years for males and 53 years for females. Male donors accounted for 67% of actual DCD donors and 66% of utilized DCD donors.

LD transplantation was reported by 26 respondent countries [**Figure 3**]. In particular, there were 6,950 LKD and 1,383 LLD. As far as LKD, living donors accounted for only 30% of the transplanted kidneys, reaching the highest rate in Turkey (79% kidney transplants). Females were the most common donors, accounting for 58% of the donors, but received only 36% of the organs from LKD [**Supplementary Figure S1**]. As far as LLD, living donor lobe donation accounted for 17% of the liver

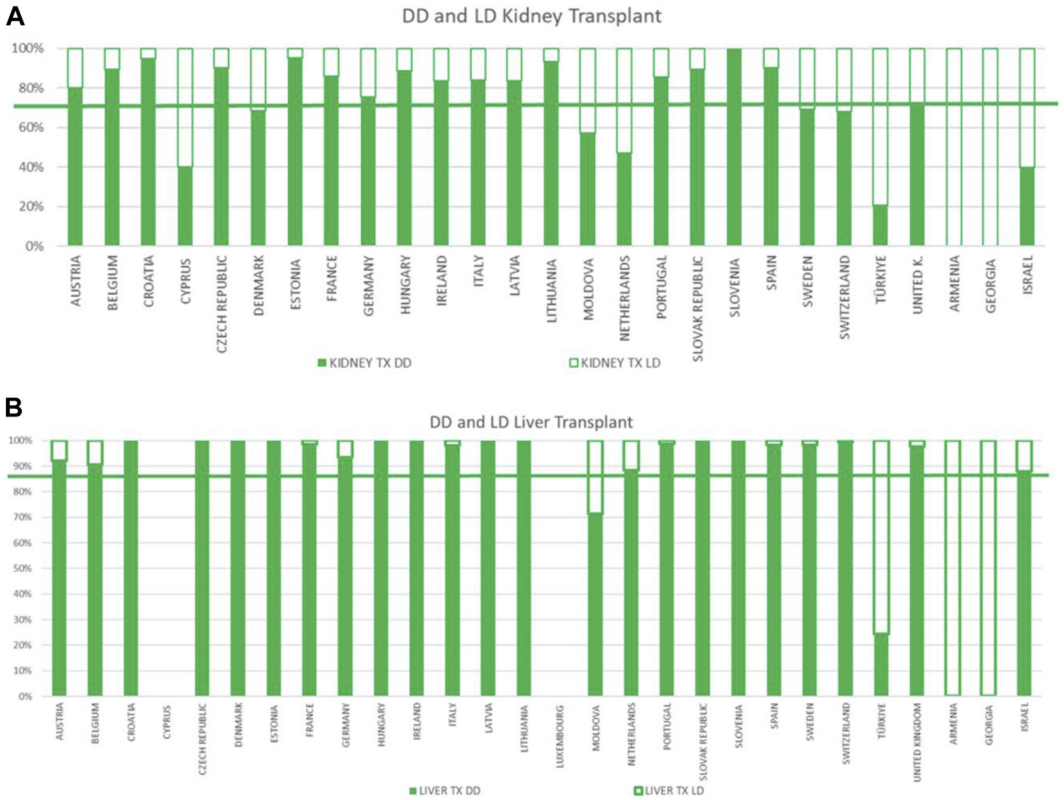


FIGURE 3 | Kidney and liver deceased or living donors in CD-P-TO MS and OC. **(A)** Information regarding the kidney deceased and living donors; **(B)** information regarding the liver deceased and living donors.

transplants performed in Europe; it was performed in only 12 of the respondent countries and represented 76% of living liver transplants performed in Turkey. Females represented only 46% of LLD and received 42% of organs from LLD [**Supplementary Figure S1**]. The mean age of living donors according to sex and organ type was 49.3 years for males and 50 years for females LKD; and 47.1 years and 50 years respectively, for LLD.

Recipient Information

The sex pairs in the case of living or deceased donors are reported in **Figure 4**. Our data confirm that men received the majority of the organs from deceased donors. In particular, males received 63% of kidneys, 69% of livers, 73% of hearts, 58% of lungs, and 56% of pancreases.

Similarly, as far as organs from living donors, males received the majority of the kidneys (64%) and livers (58%) available.

Sex Pairs and Post-Transplant Outcomes

Five-year graft survival according to sex pairs is reported in **Figure 5**. As expected, for each of the sex pairs organs from living donors had a better 5-year survival compared to the deceased counterpart. On the other hand, in our study 5-year graft survival (for organs either from deceased or living donors) did not differ when considering the different sex pair combinations.

Relationship Between Living Donors and Recipients

Out of a total number of 6,950 LKD, 2,339 (34%) organs were transplanted between parent and child; 1,412 (20%) between siblings; 1,774 (26%) between spouses; and 1,425 (20%) between other relatives or friends [**Figure 6**]. The relationship between LKDs and recipients in the responding countries is reported in **Supplementary Figure S2**. Kidneys from male living donors (42% of the kidneys from LKD) were transplanted into 49% of male recipients; in contrast, kidneys from female living donors (58% of the kidneys from LKD) were primarily transplanted into males (75%) [**Supplementary Figure S3**]. The relationship between LKD and recipients distributed according to sex pairs is reported in **Supplementary Figure S4**.

Out of a total number of 1,383 LLD, 902 (65%) organs were transplanted between parent and child; 217 (16%) between siblings; 83 (6%) between spouses and 181 (13%) between other relatives or friends [**Figure 6**]. The relationship between LLD and recipients in the responding countries is reported in **Supplementary Figure S2**. Livers donated from male donors (54% of the overall number of livers from LLD) were transplanted in 55% of cases into male

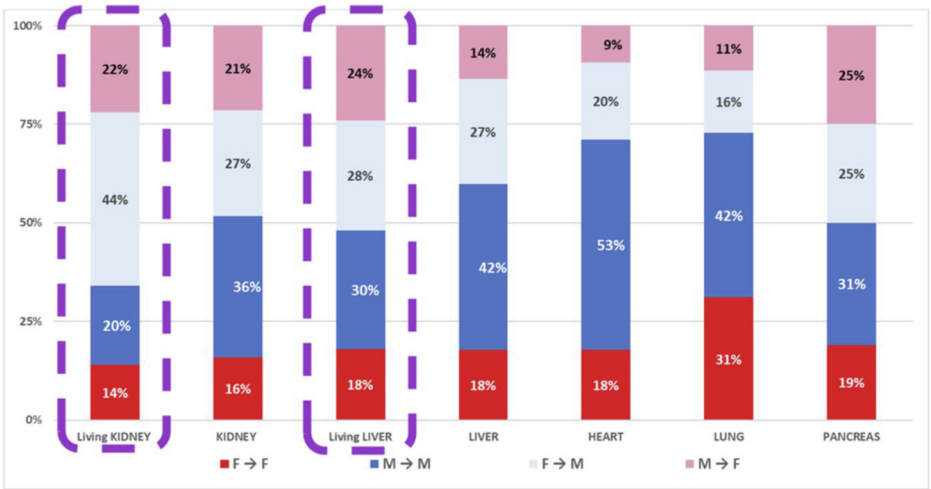


FIGURE 4 | Recipients of organs from DD and LD according to sex pairs.

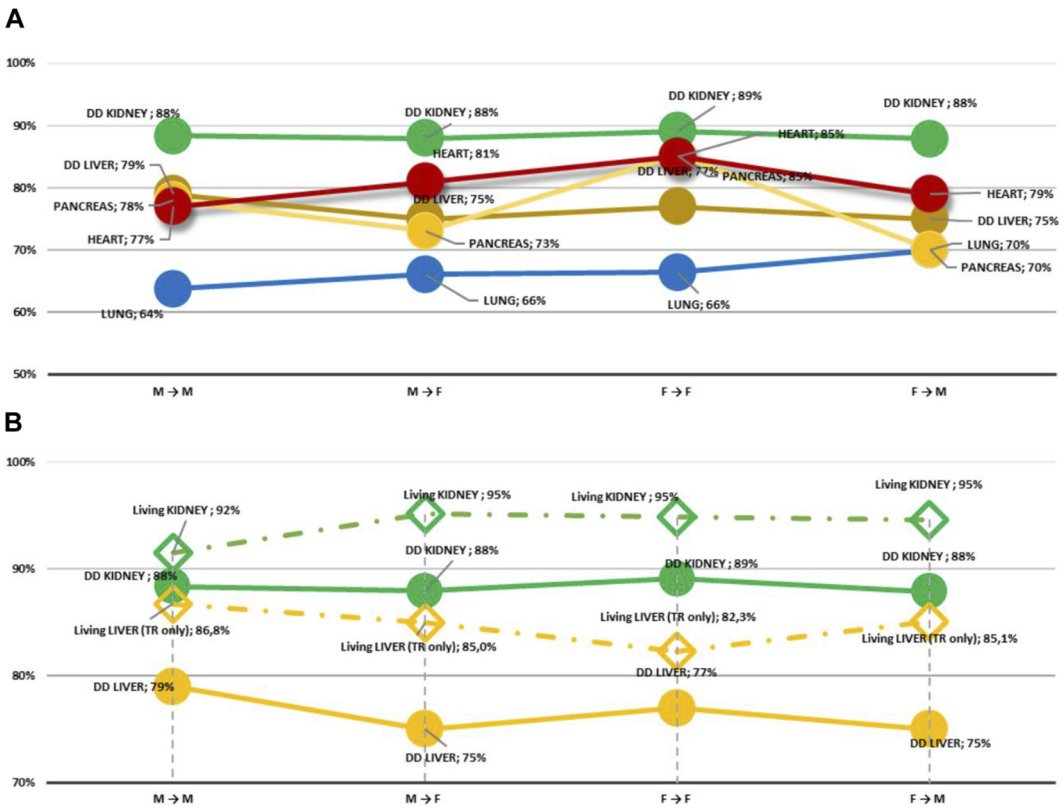


FIGURE 5 | 5-Year graft survival. **(A)** Recipients from DD according to sex pairs (all organs); **(B)** Kidney and liver recipients from DD and LD according to sex pairs.

recipients; in contrast, livers from female donors (46% of the overall number of livers from LLD) were primarily transplanted into male recipients (63% cases) [**Supplementary Figure S3B**]. The relationship between donors and recipients distributed according to sex pairs are reported in **Supplementary Figure S4B**.

DISCUSSION

Transplantation is the most effective therapeutic option for eligible patients diagnosed with advanced or end stage organ failure. Even though countries performing organ transplantation,

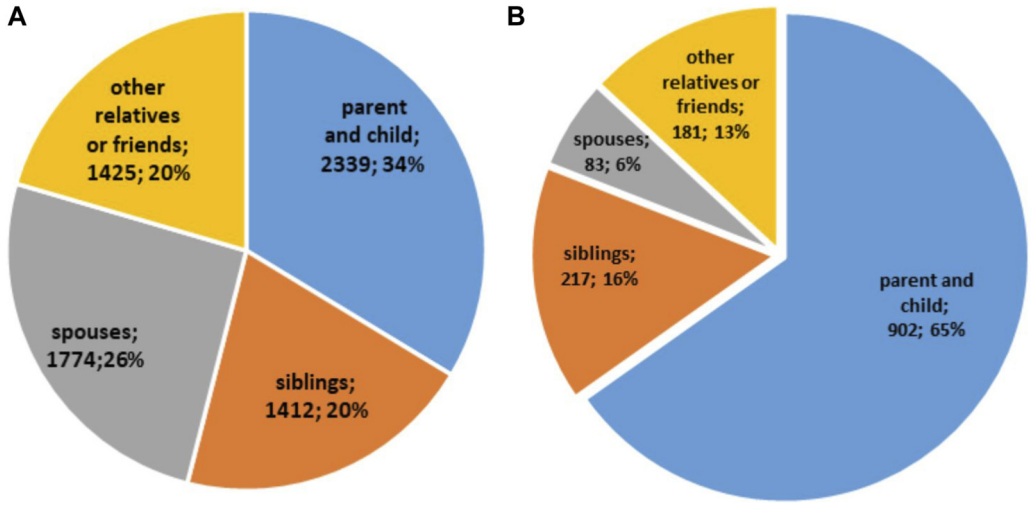


FIGURE 6 | Relationship between living donors and recipients. **(A)** Relationship between LK donors and recipients; **(B)** Relationship between LL donors and recipients.

make the treatment accessible to all eligible patients, irrespective of sex, age and race, it has been previously reported that, compared to men, women are disadvantaged with regards to both access to active transplant waiting lists and access to transplantation after waitlisting [13–17].

Indeed, women have lower access to transplantation. In many cases, this is the ultimate outcome of unbiased circumstances that include a higher burden of diseases treatable with transplantation among men [5, 6], organ size mismatch [18] or greater difficulties in finding an immunologically compatible donor in women due to prior immunizing events [4, 7].

Nonetheless, in the context of kidney transplantation, the choice of glomerular filtration rate (GFR) estimation methods for determining access to waiting lists remains a subject of debate. Indeed, both the MDRD and CKD-EPI equations, which are commonly used to estimate GFR, are creatinine-based and thus dependent on muscle mass; consequently, they tend to underestimate GFR in women, despite adjustments also in late chronic kidney disease (CKD) stages [19, 20]. In clinical practice, awareness of the systematic underestimation of GFR in women may create diagnostic uncertainty. This is particularly evident when evaluating borderline GFR values for transplant eligibility, where such bias can delay the initiation of the evaluation process, its completion, or final access to the waiting list—steps that are less frequent in female patients [21].

With regard to access to liver transplantation, the MELD score adopted in the United States two decades ago heavily weighted creatinine, ultimately generating a negative bias for women access to transplantation. In 2008, the MELD score was modified to incorporate serum sodium (MELD-Na). However, this update failed to mitigate—and may have even exacerbated—gender disparities, with women remaining 20% less likely to receive a transplant than men [22–24]. Furthermore, women experienced higher rates of waitlist mortality or delisting due to clinical deterioration [25]. This higher attrition rate may result, at least in part, from prolonged waiting times secondary to lower calculated MELD-Na scores.

Some reports suggest that socioeconomic or cultural factors may underlie the variation in access to transplantation between sex [3, 21, 26, 27]. Furthermore, even medical biases have been described as a possible explanation for the sex-related differences in access to this treatment [4, 28–30]. Sex-related imbalances in terms of both donation and access to transplantation have also been reported when transplantation takes place using organs from living donors [15].

To study whether sex-related aspects may contribute to a potential disparity in the transplantation activity in Europe, the CD-P-TO commissioned a further in depth analysis of organ donation and transplantation across the Council of Europe member states previously conducted in 2019 [1]. Our survey eventually enabled us to have access to data from 26 of the 39 Council of Europe Member States, ultimately covering an overall population of 527.4 million European citizens (UNFPA report [31]).

The data collected confirm that, irrespective of the organ considered, men still account for the majority of the patients awaiting transplantation.

To establish whether women on the WL wait longer than men, in this study we determined the median waiting time on the WL. Our data indicate that in the Council of Europe Member States, for all the organs except for hearts, women have a longer waiting time on the WL compared to men.

As far as organ donation is concerned, our data confirm that, as previously reported, male donors make up the majority of deceased donors (DBD or DCD) in Europe and females provide the majority of kidneys from LD. Interestingly, males make up the majority of living liver donors in the Council of Europe countries.

In light of earlier reports suggesting that sex pairs may affect graft survival [21, 32], the impact of sex combinations on 5-year graft survival was analysed for organs from both deceased and

living donors. As expected, 5-year graft survival of organs from living donors had a better outcome than that of the deceased counterpart. However, in our study 5-year graft survival (for organs either from deceased or living donors) did not differ when considering the different sex pair combinations. While our data confirm recent findings suggesting that, *per se*, the patient sex may not represent a key determinant affecting transplant outcomes [33], we cannot rule out that the impact of the limited number of cases and the duration of the observation period in our study may explain the different findings compared to earlier reports [21, 32].

We also analysed the relationship between living donors and recipients. In Council of Europe countries, the parent-to-child pair represents the most frequent combination for both LKD and LLD. The greater involvement of parents in this case is not unexpected as having a child recipient and helping a family member are amongst the most motivating factors for considering living organ donation [34].

We acknowledge that our study presents several limitations. First, the analyses were conducted on data provided by only 26 of the 39 Council of Europe CD-P-TO Member States. Second, the data provided refer to an observation period of 1 year, a condition that may not accurately reflect the routine activities of some of the countries involved. Third, the use of the median waiting time on the WL as a means to establish whether women on the WL wait longer than men does not differentiate whether patients removal from the WL is due to access to transplantation, death on the waiting list or delisting due worsening condition. Fourth, because the data were collected in aggregate form, it was not possible to perform statistical inference analyses; therefore, only a descriptive analysis could be conducted, and differences could be evaluated solely in these terms. Nevertheless, the available data allowed us to gain an overall view of the situation. In this light, a follow up study in countries able to establish the cumulative incidence of access to transplantation for patients on the active waiting list will represent an important tool to increase our knowledge on the impact of sex on the access to transplantation for women on the active WL. Eventually, the data analysed refer to the year 2019, the last year that was not impacted by the COVID-19 pandemic. Still, this is the only set of data available that explore in detail the impact of sex on transplantation activities across the CD-P-TO Member States.

In summary, altogether the data collected from 26 Council of Europe Member States and 3 observer countries suggest that, whilst men represent the majority of patients on the organ transplant waiting lists and receive the largest number of organs from deceased or living donors, at this stage there is no evidence of unfair sex-related inequities in the transplantation activities conducted in Europe. Women provide the majority of kidneys from living donors whilst men are the major source of livers from living donors. Currently, however, we are still missing the sex-associated data regarding transplantation activities taking place in many of the Council of Europe Member States. In this light, the Newsletter Transplant has now broadened its annual data collection on organ transplantation activity to include data disaggregated by sex. In any case, this analysis provides a foundation for future in-depth studies aimed at understanding biological sex disparities in organ donation and transplantation. In this regard, the CD-P-TO will continue its monitoring activity on this highly relevant topic, possibly extending its commitment beyond sex to include gender related aspects. This should allow the CD-P-TO to uncover possibly unexpected imbalances and, where relevant, release recommendations that could act as a trigger for the adoption of new national policies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

EC, CC, FP, LM, JF, NN, AK, MÁ, MC, BM, ML-F, and BD-G participated in the conception and design of the study, interpretation of the data, and critical revision of the manuscript; EC, CC, FP, LM, JF, MÁ, MC, BM, and BD-G Designed and prepared the questionnaire; CC, DM, NN, and AK Coordinated the distribution and collection of the questionnaire among the States; EC, CC, FP, LM, MÁ, MC, BM, and BD-G performed the data analysis and prepared the figures of the manuscript; CC, DM, NN, AK, MÁ, CA, and GF contributed to the interpretation of national data and provided country-specific information; EC, CC, FP, and LM drafted the first version of the manuscript; All authors supervised the project, contributed to data interpretation, and finalized the manuscript for submission. All authors contributed to the article and approved the submitted version.

GROUP MEMBERS OF THE EUROPEAN COMMITTEE ON ORGAN TRANSPLANTATION OF THE COUNCIL OF EUROPE (CD-P-TO)

The CD-P-TO is the steering committee in charge of organ, tissue and cell donation and transplantation activities at the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe. It actively promotes the non-commercialization of organ, tissue and cell donation, the fight against organ trafficking and the development of ethical, quality and safety standards in the field of organ, tissue and cell transplantation. Its activities include the collection of international data and monitoring of practices in Europe, the transfer of knowledge and expertise between organisations and experts through training and networking and the elaboration of reports, surveys, and recommendations. As of September 2025, the CD-P-TO was composed of 39 members (Albania, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany,

Greece, Hungary, Iceland, Ireland, Italy, Lithuania, Latvia, Luxembourg, Malta, Montenegro, Netherlands, Republic of North Macedonia, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Republic of Moldova, Turkey, Ukraine, and United Kingdom) and 20 observers (Armenia, Canada, Georgia, Israel, United States, Council of Europe Committee on Bioethics, DTI Foundation, European Association of Tissue and Cell Banks, European Commission, European Eye Bank Association, European Society for Blood and Marrow Transplantation, European Society for Organ Transplantation, European Society of Human Reproduction and Embryology, Eurotransplant, Scandiatransplant, South-Europe Alliance for Transplants (SAT), The Transplantation Society, United Network for Organ Sharing (UNOS), World Health Organization (WHO), and World Marrow Donors Association).

FUNDING

The author(s) declared that financial support was not received for this work and/or its publication.

CONFLICT OF INTEREST

The authors(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

GENERATIVE AI STATEMENT

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

ACKNOWLEDGEMENTS

Authors would like to thank the colleagues of the CD-P-TO Member States and Observer Countries who provided and supplemented the requested data contribution for this analysis: Flutra Beqo, Alma Idrizi, Martina Brix-Zuleger, Luc Colembie, Martina Anušić Juričić, Andreas Soloukides, Michaela Vrbova, Ilse Duus Weinreich, Virge Pall, Emilie Savoye, Josephine Wadewitz, Sandor Mihaly, Brenda Poole, Ilaria Lombardi, Kotryna Caikauskaite, Julien Darmina, Alexandre Mzabi, Vladimir Bolocan, Martin Heemskerk, Jarosław Czerwiński, Pedro Venturini, Daniel Kuba, Danica Avsec, Alicia Perez Blanco, Ilse Duus Weinreich, Alexandra Volz, Omar Bal, Lisa Mumford, Milena Voskanyan, Gia Tomadze and Tamar Ashkenazi. Also, we would like to thank Dr. Marta Vadori for her editorial support and Dr. Luigi Biancone for his substantial contribution to the discussion section.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2026.15711/full#supplementary-material

SUPPLEMENTARY TABLE 1 | List of CDPTO Member States and Observer countries involved in the analysis.

SUPPLEMENTARY FIGURE S1 | Sex combination of living donors and transplant recipients. **(A)** LKD and kidney transplant recipients; **(B)** LLD and liver transplant recipients.

SUPPLEMENTARY FIGURE S2 | Relationship between living donors and recipients distributed per CD-P-TO MS and Observers Countries. **(A)** Relationship between living kidney donors and recipients distributed per country; **(B)** Relationship between living liver donors and recipients distributed per country.

SUPPLEMENTARY FIGURE S3 | Destination of organs donated by M and F donors in CD-P-TO MS. **(A)** Living donor kidney transplantation (n=6.950); **(B)** Living donor liver transplantation (n = 1.383).

SUPPLEMENTARY FIGURE S4 | Relationship between living kidney and liver donors and recipients according to sex pairs in CD-P-TO MS. **(A)** Relationship between living kidney donors and recipients according to sex pairs (%); **(B)** Relationship between living liver donors and recipients according to sex pairs (%).

SUPPLEMENTARY FILE S1 | Gender aspects in transplantation: expanded disaggregated activity data collection and analysis (TO115).

REFERENCES

1. Cozzi E, Álvarez M, Carmona M, Mahíllo B, Forsythe J, Lomero M, et al. An Analysis by the European Committee on Organ Transplantation of the Council of Europe Outlining the International Landscape of Donors and Recipients Sex in Solid Organ Transplantation. *Transpl Int* (2022) 35:10322. doi:10.3389/ti.2022.10322
2. Csete M. Gender Issues in Transplantation. *Anesth and Analgesia* (2008) 107(1):232–8. doi:10.1213/ane.0b013e318163feaf
3. Achille M, Soos J, Fortin M-C, Pâquet M, Hébert M-J. Differences in Psychosocial Profiles Between Men and Women Living Kidney Donors. *Clin Transpl* (2007) 21:314–20. doi:10.1111/j.1399-0012.2007.00641.x
4. Sawinski D, Lai JC, Pinney S, Gray AL, Jackson AM, Stewart D, et al. Addressing Sex-Based Disparities in Solid Organ Transplantation in the United States - A Conference Report. *Am J Transpl* (2023) 23(3):316–25. doi:10.1016/j.ajt.2022.11.008
5. Reyes D, Lew SQ, Kimmel PL. Gender Differences in Hypertension and Kidney Disease. *Med Clin North Am* (2005) 89:613–30. doi:10.1016/j.mcna.2004.11.010
6. Halbesma N, Brantsma AH, Bakker SJL, Jansen DF, Stolk RP, De Zeeuw D, et al. Gender Differences in Predictors of the Decline of Renal Function in the General Population. *Kidney Int* (2008) 74:505–12. doi:10.1038/ki.2008.200
7. Bromberger B, Spragan D, Hashmi S, Morrison A, Thomasson A, Nazarian S, et al. Pregnancy-Induced Sensitization Promotes Sex Disparity in Living Donor Kidney Transplantation. *J Am Soc Nephrol* (2017) 28(10):3025–33. doi:10.1681/ASN.2016101059
8. Ebong IA, DeFilippis EM, Hamad EA, Hsich EM, Randhawa VK, Billia F, et al. Special Considerations in the Care of Women with Advanced Heart Failure. *Front Cardiovasc Med* (2022) 9:890108. doi:10.3389/fcvm.2022.890108
9. Bellini MI, Balleste C, Martins PN, Ulasi I, Valantine H, Potena L. Diversity, Equity, and Inclusion in Transplantation. *Transpl Int* (2024) 37:13832. doi:10.3389/ti.2024.13832

10. Nonterah CW. Systems Connected to Inequities in Access to Kidney Transplantation and the Value of Intersectionality. *Transpl Int* (2024) 37: 11658. doi:10.3389/ti.2024.11658
11. Lai JC, Pomfret EA, Verna EC. Implicit Bias and the Gender Inequity in Liver Transplantation. *Am J Transpl* (2022) 22(6):1515–8. doi:10.1111/ajt.16986
12. Wiering L, Aigner A, van Rosmalen M, Globke B, Dziodzio T, Raschzok N, et al. Systematic Sex-Based Inequity in the MELD Score-Based Allocation System for Liver Transplantation in Germany. *Transpl Int* (2025) 38:13844. doi:10.3389/ti.2025.13844
13. Council of Europe and Organización Nacional de Trasplantes. *Newsletter Transplant*, 30. EDQM (2020). 30:20205. Available online at: www.edqm.eu/freepub.
14. Couchoud C, Bayat S, Villar E, Jacquelinet C, Ecochard RREINR, REIN registry. A New Approach for Measuring Gender Disparity in Access to Renal Transplantation Waiting Lists. *Transplantation* (2019) 103:1094–519. doi:10.1097/TP.0b013e31825d156a
15. Harding JL, Hu C, Pastan SO, Rossi A, Patzer RE. Trends in Sex Disparities in Access to Kidney Transplantation: A Nationwide US Cohort Study. *Am J Kidney Dis* (2025) 86(1):18–31.e1. doi:10.1053/j.ajkd.2024.12.008
16. Sheikh SS, Locke JE. Gender Disparities in Transplantation. *Curr Opin Organ Transpl* (2021) 26(5):513–20. doi:10.1097/MOT.0000000000000909
17. Adoli LK, Couchoud C, Chatelet V, Lobbedez T, Bayer F, Vabret E, et al. Lower Access to Kidney Transplantation for Women in France Is Not Explained by Comorbidities and Social Deprivation. *Nephrol Dial Transpl* (2024) 39(10): 1613–23. doi:10.1093/ndt/gfae047
18. Nephew LD, Goldberg DS, Lewis JD, Abt P, Bryan M, Forde KA. Exception Points and Body Size Contribute to Gender Disparity in Liver Transplantation. *Clin Gastroenterol Hepatol* (2017) 15:1286–93. doi:10.1016/j.cgh.2017.02.033
19. Carrero JJ, Hecking M, Chesnaye NC, Jager KJ. Sex and Gender Disparities in the Epidemiology and Outcomes of Chronic Kidney Disease. *Nat Rev Nephrol* (2018) 14(3):151–64. doi:10.1038/nrneph.2017.181
20. Lewandowski MJ, Krenn S, Kurnikowski A, Bretschneider P, Sattler M, Schwaiger E, et al. Chronic Kidney Disease Is More Prevalent Among Women but More Men than Women Are Under Nephrological Care: Analysis from Six Outpatient Clinics in Austria 2019. *Wien Klin Wochenschr* (2023) 135(3-4):89–96. doi:10.1007/s00508-022-02074-3
21. Melk A, Babitsch B, Borchert-Mörlins B, Claas F, Dipchand AI, Eifert S, et al. Equally Interchangeable? How Sex and Gender Affect Transplantation. *Transplantation* (2019) 103(6):1094–110. doi:10.1097/TP.0000000000002655
22. Allen AM, Heimbach JK, Larson JJ, Mara KC, Kim WR, Kamath PS, et al. Reduced Access to Liver Transplantation in Women: Role of Height, MELD Exception Scores, and Renal Function Underestimation. *Transplantation* (2018) 102(10):1710–6. doi:10.1097/TP.0000000000002196
23. Tejedor M, Neria F, De La Rosa G, Almohalla Álvarez C, Padilla M, Boscà Robledo A, et al. Women Are Also Disadvantaged in Accessing Transplant Outside the United States: Analysis of the Spanish Liver Transplantation Registry. *Transpl Int* (2024) 37:12732. doi:10.3389/ti.2024.12732
24. Giorgakis E, Estrada MM, Wells A, Garcia Saenz de Sicilia M, Deneke M, Patel R, et al. Women Referred for Liver Transplant Are Less Likely to Be Transplanted Irrespective of Socioeconomic Status. *Transpl Int* (2023) 36: 11667. doi:10.3389/ti.2023.11667
25. Cullaro G, Sarkar M, Lai JC. Sex-Based Disparities in Delisting for Being "Too Sick" for Liver Transplantation. *Am J Transpl* (2018) 18(5):1214–9. doi:10.1111/ajt.14608
26. Kim S, van Zwieten A, Wyld M, Ladhani M, Guha C, Dominello A, et al. Sociodemographic Drivers of Donor and Recipient Gender Disparities in Living Kidney Donation in Australia. *Kidney Int Rep* (2023) 8(8):1553–61. doi:10.1016/j.ekir.2023.05.016
27. Taylor DM, Bradley JA, Bradley C, Draper H, Dudley C, Fogarty D, et al. Limited Health Literacy Is Associated with Reduced Access to Kidney Transplantation. *Kidney Int* (2019) 95:1244–52. doi:10.1016/j.kint.2018.12.021
28. Khazanie P. REVIVAL of the Sex Disparities Debate. Are Women Denied, Never Referred, or Ineligible for Heart Replacement Therapies? *JACC Heart Fail* (2019) 7:612–4. doi:10.1016/j.jchf.2019.03.012
29. Gill JS, Hendren E, Dong J, Johnston O, Gill J. Differential Association of Body Mass Index with Access to Kidney Transplantation in Men and Women. *Clin J Am Soc Nephrol* (2014) 5:951–9. doi:10.2215/CJN.08310813
30. Bryce CL, Angus DC, Arnold RM, Chang CCH, Farrell MH, Manzarbeitia C, et al. Sociodemographic Differences in Early Access to Liver Transplantation Services. *Am J Transpl* (2009) 9:2092–101. doi:10.1111/j.1600-6143.2009.02737.x
31. United Nations Population Fund (UNFPA) Report (2025). Available online at: www.unfpa.org (Accessed: April 12, 2025).
32. Lepeytre F, Dahhou M, Zhang X, Boucquemont J, Sapir-Pichhadze R, Cardinal H, et al. Association of Sex with Risk of Kidney Graft Failure Differs by Age. *J Am Soc Nephrol* (2017) 28(10):3014–23. doi:10.1681/ASN.2016121380
33. Puoti F, Masiero L, Testa S, Vespasiano F, Oliveti A, Fiaschetti P, et al. Does Sex Matter in Solid Organ Transplantation? Analysis of 20-year Activity Data from the Italian National Deceased Donor Transplant Register. *J Sex Gend Specif Med* (2024) 10(3):115–29. doi:10.1723/4343.43282
34. Naibauer S, Branagan WT, Lehto S, Reynolds N, Mikulich-Gilbertson S, Page CE, et al. Attitudes Towards Living Organ Donation: A Cross-Sectional Survey Study. *Front Public Health* (2025) 13:1552393. doi:10.3389/fpubh.2025.1552393

Copyright © 2026 Cozzi, Carella, Puoti, Masiero, Forsythe, Manas, Nathan, Kaminski, Álvarez, Carmona, Mahíllo, Antoine, López-Fraga, Feltrin and Domínguez-Gil. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

ESOT | Transplant International

TYPE Original Research
PUBLISHED 22 May 2026
DOI 10.3389/ti.2026.16075

Check for updates

OPEN ACCESS

*CORRESPONDENCE
Nathalie M. Rock,
Nathalie.rock@hug.ch

RECEIVED 16 December 2025
REVISED 20 April 2026
ACCEPTED 22 April 2026
PUBLISHED 22 May 2026

CITATION
Rock NM, Frossard J, Vandelden C, Sparta G, DiBernardo S, Mack I, Parvex P, Balmer C, Marx Berger D, Berger C, Chehade H, Schuurmans M, Tschumi S, Mueller NJ, McLin VA and L'Huillier AG (2026) Burden of infectious diseases in children during the first year after solid organ transplantation.
Transpl. Int. 39:16075.
doi: 10.3389/ti.2026.16075

COPYRIGHT
© 2026 Rock, Frossard, Vandelden, Sparta, DiBernardo, Mack, Parvex, Balmer, Marx Berger, Berger, Chehade, Schuurmans, Tschumi, Mueller, McLin and L'Huillier. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

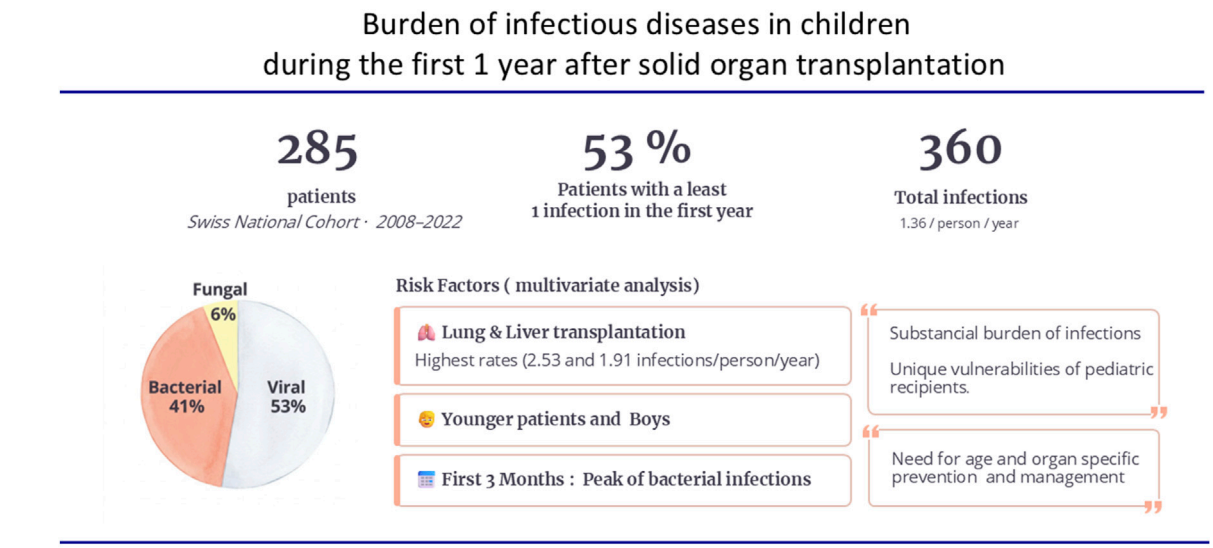
Burden of infectious diseases in children during the first year after solid organ transplantation

Nathalie M. Rock[1]*, Jaromil Frossard[2], Christian Vandelden[3], Giuseppina Sparta[4], Stefano DiBernardo[5], Ines Mack[6], Paloma Parvex[7], Christian Balmer[8], Daniela Marx Berger[9], Christoph Berger[10], Hassib Chehade[11], Macé Schuurmans[12], Sibylle Tschumi[13], Nicolas J. Mueller[10], Valérie A. McLin[1] and Arnaud G. L'Huillier[14] on behalf of the Swiss Transplant Cohort Study

[1]Pediatric Gastroenterology, Hepatology and Nutrition Unit, Division of Pediatric Specialties, Department of Pediatrics, Gynecology and Obstetrics, Swiss Pediatric Liver Center, University Hospitals of Geneva, University of Geneva, Geneva, Switzerland, [2]Swiss Transplant Cohort Study (STCS), University Hospital of Basel, Basel, Switzerland, [3]Transplant Infectious Diseases Unit, University Hospitals Geneva, Geneva, Switzerland, [4]Pediatric Nephrology, University Children's Hospital of Zurich, Zurich, Switzerland, [5]Pediatric Cardiology Service, Department of Woman-Mother-Child, Lausanne University Hospital, Lausanne, Switzerland, [6]Pediatric Infectious Diseases, University Children's Hospital of Basel, University of Basel, Basel, Switzerland, [7]Pediatric Nephrology, Division of Specialties, Department of Pediatrics, Gynecology and Obstetrics, University Hospitals of Geneva, University of Geneva, Geneva, Switzerland, [8]Pediatric Cardiology, University Children's Hospital of Zurich, Zurich, Switzerland, [9]Pediatric Nephrology, Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland, [10]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zürich, Switzerland, [11]Pediatric Nephrology Service, Department of Woman-Mother-Child, Lausanne University Hospital, Lausanne, Switzerland, [12]Pulmonology, University Hospital Zurich, Zurich, Switzerland, [13]Division of Pediatric Nephrology, Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland, [14]Pediatric Infectious Diseases Unit, Division of General Pediatrics, Department of Pediatrics, Gynecology and Obstetrics, University Hospitals of Geneva, University of Geneva, Geneva, Switzerland

Infections are a leading cause of morbidity and mortality in pediatric solid organ transplant recipients (SOT). Comprehensive data in this population is limited. We included pediatric SOT from the Swiss national cohort aged 0–18 years prospectively from 2008 to 2022. Using standardized definitions, all clinically relevant infections during the first year after transplant were analyzed. Associations with age, organ type, and rejection episodes were assessed. A total of 285 pediatric SOT were included, with kidney (41%) and liver (37%) transplants being the most common. During the first-year post-transplant, 53% (151/285) of patients experienced at least one infection, totaling 360. The overall incidence was 1.36 infection/person/year. Viral infections predominated (53%), followed by bacterial (41%) and fungal infections (6%). Patients receiving liver and lung transplants had higher infection rates (1.91 and 2.53 per person-year, respectively). In multivariate analysis type of transplant and male sex remained associated with increased risk of infection. Viral infections were overrepresented in younger recipients, while bacterial infections were most frequent in the first 3 months post-transplant. Pediatric SOT recipients face a substantial burden of infection. This underscores the need for specific prevention, early recognition, and coordinated management strategies to reduce infection-related morbidity.

KEYWORDS
immunosuppression, infection, opportunistic infection, pediatric, solid organ transplant (SOT), children transplantation, prophylaxis, PTLD



Introduction

Infections are not only a major cause of short- and long-term morbidity and mortality after solid organ transplantation (SOT) [1, 2], but also an important cause of hospital admission and graft failure [3–5]. The timeline of infections in the first year following SOT was first published more than 25 years ago: at this point, three different periods (0–1, 1–6 and >6 months) associated with different infectious risks were described [6]. A recent analysis of the Swiss Transplant Cohort Study (STCS) highlighted the substantial burden of infections in adult SOT recipients, with 55% experiencing at least one event during the first post-transplant year, predominantly bacterial [7]. However, these results cannot be directly extrapolated to children, whose susceptibility to infection is shaped by developmental and environmental factors: (1) immune system immaturity, (2) limited prior pathogen exposure and adaptive immunity, (3) possible incomplete immunization, and (4) higher exposure in daycare and school settings. In children, infection remains the most common cause of early death after SOT and continues to affect the quality of life for several years thereafter [2, 3, 5, 6]. To the best of our knowledge, no studies have systematically described the incidence and types of infectious complications in a large cohort of pediatric SOT recipients. Reports have generally focused on a single pathogen or on infections in a single organ transplant population. In a cohort of more than 2000 pediatric liver transplant recipients, more than half presented a serious post-transplant infection [8]. Similarly, infection is deemed responsible of 20% of deaths after pediatric kidney transplantation [9]. Therefore, a comprehensive multicenter analysis of post–pediatric SOT infections across various organ types can offer valuable insight into the overall infection burden and facilitate comparisons between transplant groups.

This study aimed to characterize infection incidence during the first post-transplant year in pediatric SOT recipients within the STCS nationwide cohort and to identify associations between infection, age, organ type, and rejection episodes [10].

Materials and methods

Study design

This is a prospective study nested in the cumulative recorded data of the STCS. All solid organ transplant recipients (SOT) of all ages transplanted in our country are prospectively enrolled within the STCS. The database, designed as a patient-case system, longitudinally captures organ- and patient-specific data, thus providing an ideal source of unbiased data. Clinical and laboratory information are collected at SOT, 6 and 12 months, and annually thereafter. At each visit, an infectious disease form is completed by an infectious disease physician. Regular monitoring and in-depth audits through

Abbreviations: SOT, solid organ transplant recipients; STCS, Swiss Transplant Cohort Study.

review process of randomly selected patients are performed by the STCS Central Data Center.

Ethical approval was obtained from all participating centers. Written informed consent was provided by patients or their legal guardians to participate to the STCS registry, and the study was approved by the scientific committee The present analysis was approved by the STCS Scientific Committee.

Patients

All SOT (kidney, heart, liver, lung, multi-organ transplant recipients) fulfilling the following criteria were included in the current study: (1) age <18 years at time of SOT; (2) enrolled in the STCS between the start of the registry (01.05.2008) and 31.12.2022, allowing at least 1 year of follow-up. Patients were censored at the last complete infectious disease form, loss of follow-up, new transplantation, graft-loss or after 1 year of follow-up, whatever came first.

Definitions

Infections

Inpatient and outpatient infections were identified by pediatric infectious diseases physicians with experience in transplant infectious diseases, using electronic hospital records and external documentation, according to prespecified rigorous and standardized definitions developed by the STCS infectious diseases working group [7], and based on guidelines and recommendations from the American Society of Transplantation and the European Conference on Infection in Leukemia [11, 12]. Clinically relevant infectious disease events (IDEs) included proven bacterial, probable/proven fungal, and probable/proven viral infections or syndromes; these are hereafter referred to as "infections." Given the absence of a consensus definition for opportunistic pathogens, we used a list validated by the STCS infectious disease working group, including CMV, EBV, VZV, HHV6, HHV8, adenovirus, BK polyomavirus, *Aspergillus* spp., *Pneumocystis, Zygomycetes, Microsporidia, Exophiala*, *Malassezia, Scedosporium, Trichophyton, Alternaria* and *Fusarium* spp., *Toxoplasma gondii, Cryptosporidium* spp., *Giardia lamblia*, *Leishmania* spp., *Strongyloides stercorales*, Isospora belli, N*ocardia* spp., *Listeria monocytogenes*, *Legionella* spp., non-tuberculous mycobacteria.

Treatments

The immunosuppressive drugs were recorded at time of the transplantation (−40 days, +14 days). Antimicrobial prophylactic drugs are reported from the day of transplantation to the end of follow-up, they were managed according to institution-specific guidelines based on international recommendations. In absence of exact day for treatment initiation, the first day of the month was imputed. Individual vaccination data were not available in the STCS registry at the time of analysis. Although vaccination policies varied slightly between centers, most followed the Swiss Federal Vaccination Commission schedule [13], with serology-based catch-up vaccination in some centers [14].

EBV and CMV risk stratification

The EBV and CMV risk stratification was based on donor (D) and recipient (R) serostatus as follows: high risk: D+/R-; low or intermediate risk: D+/R+, D-/R- or D-/R+.

Compatibility and rejection

ABO incompatibility in liver transplantation and donor type in kidney transplantation were recorded, based on the rationale that ABO incompatibility and deceased donor transplantation in kidney recipients are associated with increased immunosuppression. HLA compatibility was not available in the data base. Rejection was defined as biopsy-proven rejection. Management followed organ-specific, center-dependent protocols. The association between infection and rejection was assessed in two directions: rejection occurring within 30 days after infection, considering the potential impact of infections (e.g., CMV) or reduction in immunosuppression; and infection occurring within 90 days after rejection, reflecting the increased infectious risk associated with intensified immunosuppressive therapy.

Statistical analyses

Baseline characteristics were summarized as counts (percentages) for categorical variables and medians (interquartile range) for continuous variables. Cumulative incidence of first infection was estimated using competing risk methods, and incidence rates expressed per patient-year. Death, graft loss, and re-transplantation were considered as competing events. Incidence rates were calculated accounting for follow-up time using a Poisson generalized linear model, with the log of follow-up time included as an offset. Multivariable generalized linear and cause-specific hazard models identified risk factors adjusted for relevant variables. Detailed methods are available in Supplementary Material 1 [15–19].

Results

Baseline characteristics

Out of 8267 adult and pediatric patients transplanted in Switzerland during the study period and included in the STCS, 285 patients met the inclusion criteria and were included in the dataset (Supplementary Figure 1). The baseline characteristics of the cohort are presented in Table 1. Kidney and liver transplantation were the most common, representing 41% (116/285) and 37% (107/285) of all SOT. Liver transplant recipients were the youngest, with a median age at transplant of 1.7 years (IQR 0.8–9.7) whereas lung transplant recipients were the oldest with a median age 15.0 years (IQR 14.0–17.3). Three patients received combined liver-kidney transplants.

During the study follow-up, twelve patients died (4%). Graft loss occurred in eight (3%), leading to retransplantation in six (Table 1).

Immunosuppressive regimens per organ at baseline and throughout the first year are detailed in Table 1 and in Supplementary Figure 2.

10.3389/ti.2026.16075

TABLE 1 Baseline characteristics of pediatric organ transplant recipients included in the study.

Transplanted organ Number of patients	Kidney n = 116	Liver n = 107	Lung n = 14	Heart n = 45	Combined n = 3	Overall n = 285
Recipient age at SOT (yrs), median (IQR)	12.4 (5.7–16.4)	1.7 (0.8–9.7)	15.0 (14.0–17.3)	7.8 (1.5–14.1)	10.4 (2.4–11.6)	8.6 (1.8–15.1)
Recipient age category, n (%)						
<1 year	8 (6.9)	56 (52.3)	0 (0.0)	12 (26.7)	0 (0.0)	76 (26.7)
1–4.99 years	22 (19.0)	16 (15.0)	1 (7.1)	8 (17.8)	1 (33.3)	48 (16.8)
5–11.99 years	30 (25.9)	14 (13.1)	2 (14.3)	11 (24.4)	2 (66.7)	59 (20.7)
12–17.99 years	56 (48.3)	21 (19.6)	11 (78.6)	14 (31.1)	0 (0.0)	102 (35.8)
Recipient sex (male), n (%)	67 (57.8)	61 (57.0)	6 (42.9)	14 (31.1)	1 (33.3)	149 (52.3)
Previous transplant history, n (%)	7 (6.0)	2 (1.9)	0 (0.0)	0 (0.0)	1 (33.3)	10 (3.5)
Donor age at donation (yrs), median (IQR)	38.5 (25.0–45.0)	22.0 (12.0–43.0)	34.0 (25.0–41.0)	9.0 (2.0–24.0)	26.0 (10.0–44.0)	32.0 (16–43.0)
Donor sex (male), n (%)	67 (57.8)	58 (54.2)	7 (50.0)	16 (35.6)	1 (33.3)	149 (52.3)
CMV risk stratification, n (%)						
High risk	44 (38.3)	14 (13.6)	4 (28.6)	15 (33.3)	0 (0.0)	77 (27.5)
Low or intermediate risk	71 (61.7)	89 (86.4)	10 (71.4)	30 (66.7)	3 (100.0)	203 (72.5)
EBV risk stratification, n (%)						
High risk	42 (36.5)	40 (38.5)	2 (16.7)	13 (29.5)	1 (33.3)	98 (35.3)
Low or intermediate risk	73 (63.5)	64 (61.5)	10 (83.3)	31 (70.5)	2 (66.7)	180 (64.7)
Induction drugs						
Basiliximab, n (%)	71 (61.2)	92 (86.0)	12 (85.7)	13 (28.9)	3 (100.0)	191 (67.0)
ATG, n (%)	2 (1.7)	1 (0.9)	0 (0.0)	30 (66.7)	2 (66.7)	35 (12.3)
Immunosuppressive drugs[a]						
MMF n (%)	113 (97.4)	15 (14.0)	14 (100.0)	40 (88.9)	3 (100.0)	185 (64.9)
TAC, n (%)	79 (68.1)	106 (99.1)	5 (35.7)	24 (53.3)	1 (33.3)	215 (75.4)
CsA, n (%)	40 (34.5)	3 (2.8)	10 (71.4)	20 (44.4)	1 (33.3)	74 (26.0)
GC, n (%)	113 (97.4)	78 (72.9)	14 (100.0)	44 (97.8)	3 (100.0)	252 (88.4)
Other, n (%)	4 (3.4)	1 (0.9)	1 (7.1)	7 (15.6)	1 (0.0)	14 (5)
Outcome[b], n (%)						
Death (1 year)	0 (0.0)	5 (4.7)	2 (14.3)	2 (4.4)	2 (66.7)	11 (3.9)
Dropout (1 year)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
End follow-up (<1 year)	2 (1.7)	2 (1.9)	0 (0.0)	2 (4.4)	0 (0.0)	6 (2.1)
Graft loss, PNF (1 year)	3 (2.6)	3 (2.8)	2 (14.3)	0 (0.0)	0 (0.0)	8 (2.8)
Number of infections (1year), n (%)						
0	67 (57.8)	36 (33.6)	5 (35.7)	24 (53.3)	2 (66.7)	134 (47.0)
1	28 (24.1)	23 (21.5)	3 (21.4)	12 (26.7)	1 (33.3)	67 (23.5)
2	9 (7.8)	18 (16.8)	3 (21.4)	8 (17.8)	0 (0.0)	38 (13.3)
3+	12 (10.3)	30 (28.0)	3 (21.4)	1 (2.2)	0 (0.0)	46 (16.1)

(*Continued*)

TABLE 1 Continued

Transplanted organ Number of patients	Kidney n = 116	Liver n = 107	Lung n = 14	Heart n = 45	Combined n = 3	Overall n = 285
Infections incidence rate[b]	1.00 (0.82; 1.19)	1.91 (1.65; 2.19)	2.53 (1.68; 3.62)	0.74 (0.51; 1.03)	-	1.36 (1.22; 1.51)

SOT, solid organ transplant; ATG, anti-thymocyte globulin; IQR, interquartile range; CMV, cytomegalovirus; EBV, Epstein-Barr virus; MMF, mycophenolate mofetil; TAC, tacrolimus; CsA, cyclosporine; GC, glucocorticoids.
[a]All immunosuppressive drugs recorded (within 14 days after and 30 days before transplantation).
[b]Censored after graft losses, infections incidence rate : infection/patient/year PNF: Primary non Function.
CMV/EBV risk stratification based on donor (D) and recipient (R) serostatus: high risk: D+/R-; low or intermediate risk: D+/R+, D-/R- or D-/R+.

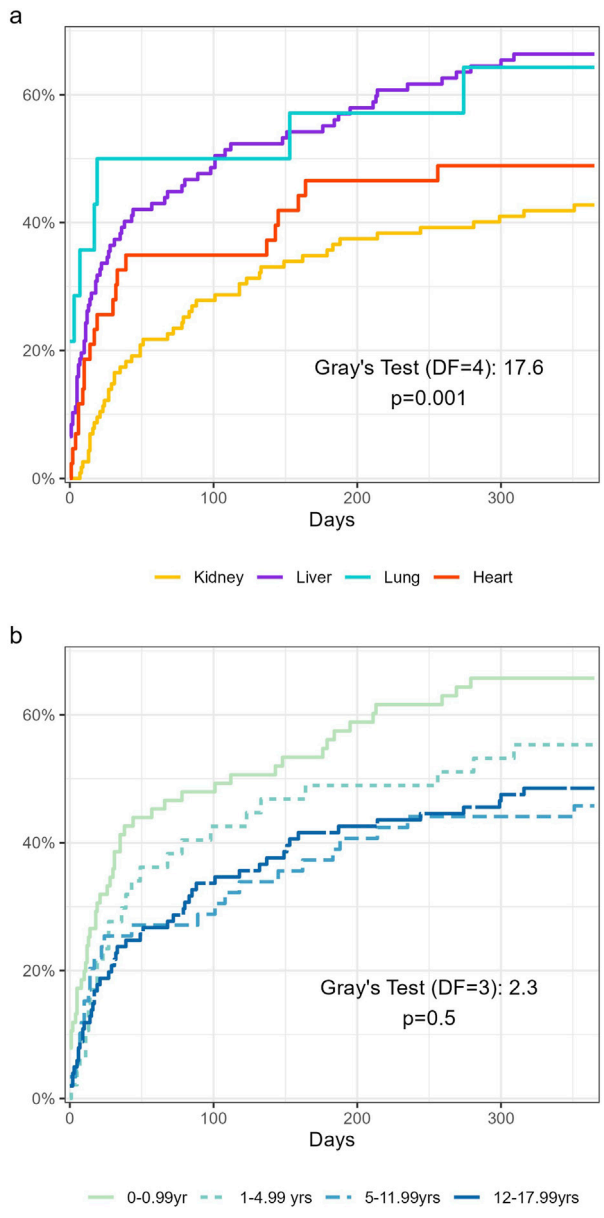


FIGURE 1
Breakdown of infections between **(a)** organs **(b)** age groups. All organs include 1 infection from combined transplant not displayed in the Panel **(a)**.

Prophylactic strategies are shown in Supplementary Figure 3. Prophylaxis against *Pneumocystis jirovecii* was given to 94% (267/285) for a median of 348 days (IQR 186–261). Additionally, 73% (207/285) received antiviral prophylaxis for a median of 185 days (IQR 116–288), mainly (val)ganciclovir in 68% (194/285). Antifungal prophylaxis was used in 17% (48/285), mostly in lung or combined transplant recipients.

Infectious diseases events

Amongst the 285 patients included in the study, 53% (n = 151) presented at least one infection during the first year after SOT. A total of 360 infections were documented; 16% of patients had ≥3 events (Table 1) and 29% at least 2 infectious events. The infection incidence rate was 1.36 infection/patients/year (95% confidence interval [CI]: 1.22–1.51).

The breakdown of infections between organs is depicted in Figure 1a. Patients after lung and liver transplantation exhibited the highest incidence of infection (2.53 [95%CI: 1.68–3.62] and 1.91 [95% CI: 1.61–2.19], respectively) and heart transplants the lowest (0.74 [95%CI: 0.51–1.03]). The cumulative incidence of infection significantly differed between organs (p = 0.001) (Figure 2a). Among, the three combined transplants, one gastrointestinal infection with multiple bacteria was observed.

The distribution of infection among age group is presented in Figure 1b. Sixty-four percent of patients <1 year of age presented with at least one infection during the first year after SOT (49/76), compared to 54% (26/48), 46% (27/59) and 48% (49/102) for those between 1 and <5, between 5 and <12, and between 12 and < 18 years, respectively. Amongst patients aged <1 year at time of transplant, the infection incidence rate was 2.41 (95% CI: 2.07–2.79), compared to 0.96 (95% CI: 0.70–1.27), 0.84 (95% CI: 0.62–1.11) and 1.06 (95% CI: 0.86–1.28) in those between 1 and <5, between 5 and <12, and between 12 and <18 years, respectively. The cumulative incidence of infection is described in Figure 2b.

Forty-two patients with living-donor kidney transplants experienced 53 infections (1.26 infections per patient), compared with 58 infections among 74 patients with deceased-donor transplants (0.78 infections per patient).

Burden of infectious diseases events

Amongst the 360 infections; 53% were caused by viruses (n = 189), followed by bacteria (41% n = 149]) and fungi (6% [n = 22]) (Figure 1).

Viral infections

Amongst the 189 viral infections, proven infections were documented in 110 (58%), probable infections in 69 (37%), and viral syndromes in 10 (5%) cases. Respiratory viruses predominated,

10.3389/ti.2026.16075

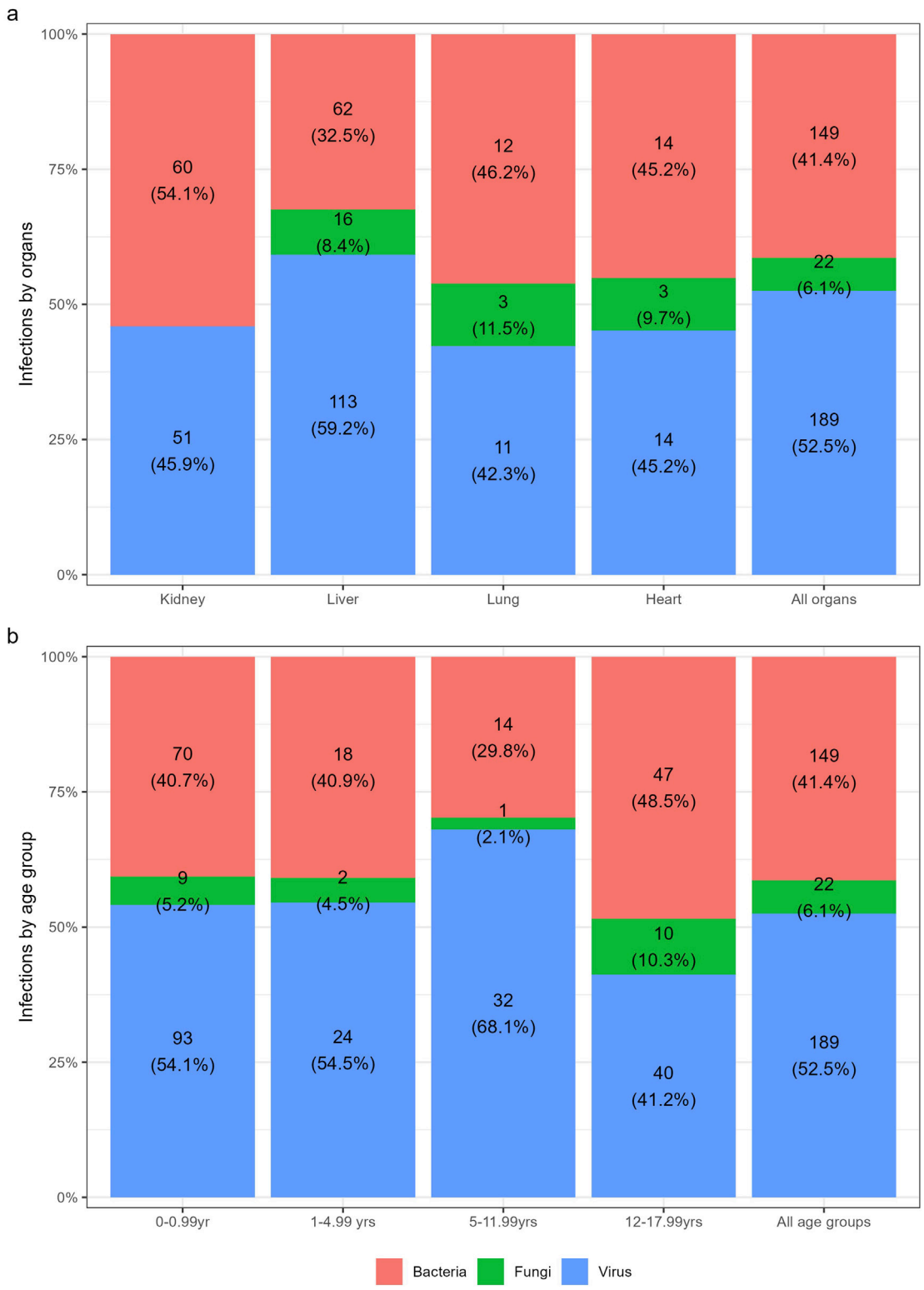


FIGURE 2
Cumulative incidence of infections between **(a)** organs **(b)** age groups. All organs include 1 infection from combined transplant taken in consideration for the gray test.

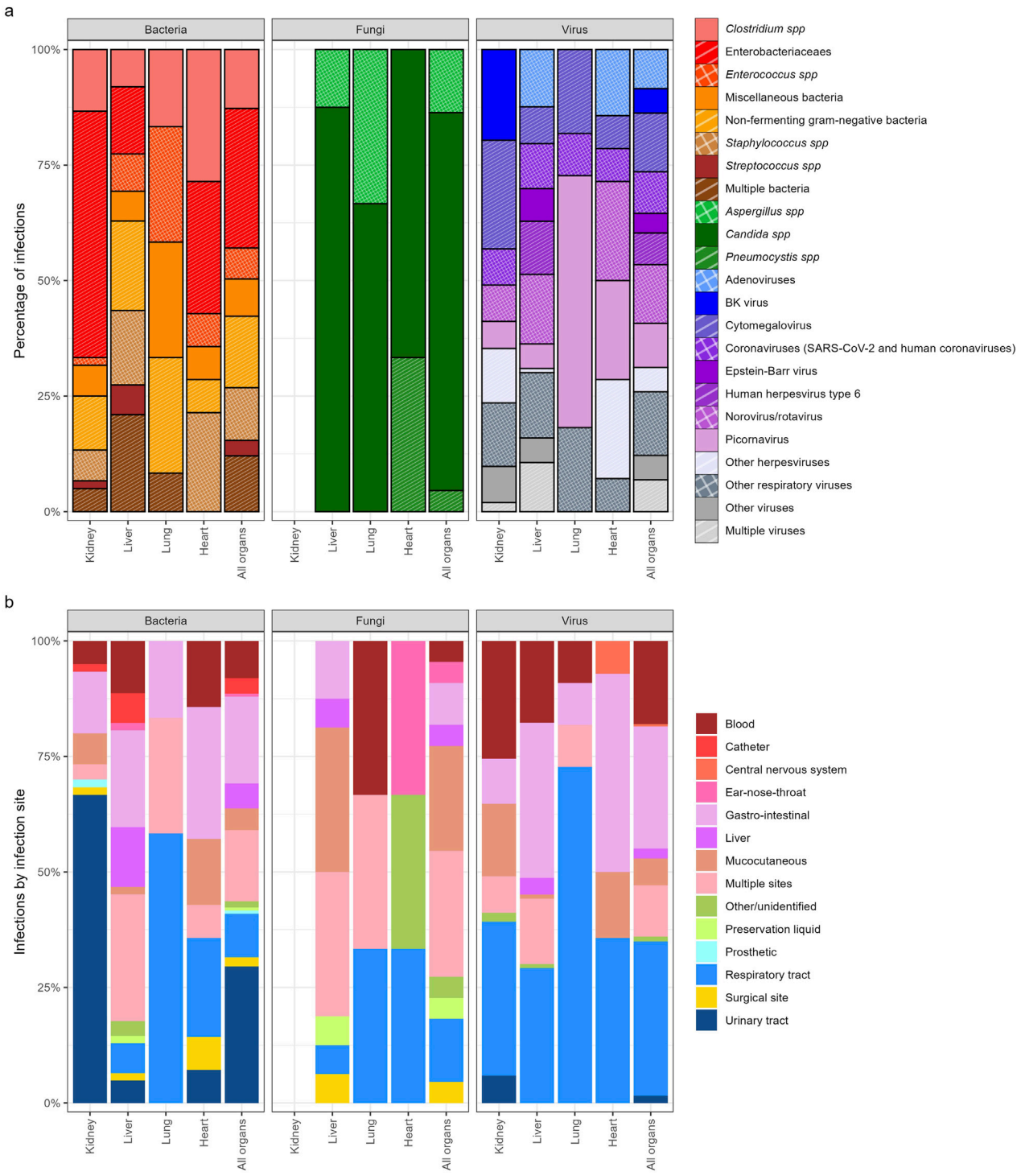


FIGURE 3
(a) Causal Infectious agent in bacterial, fungal and viral infections by organ. **(b)** Infectious site of bacterial, fungal and viral infections by organ.

followed by CMV (13%, 24/189) of all viral infections (Figure 3a; Supplementary Table 1a). Sixty percent of viral infections occurred in liver transplant recipients (113/189). Respiratory and gastrointestinal systems were most affected.

Around half of the viral infections occurred in children <1 year at SOT (49% [93/189]) (Supplementary Table 1b). Twelve EBV infections occurred in 10 patients, half of whom were stratified as EBV high risk at transplantation. Four patients developed post-transplant lymphoproliferative disorder (PTLD) between 0 and 160 days after EBV infection. Additionally, 27 CMV infections were recorded in 25 patients, including 15 stratified as high risk at transplant. Most CMV episodes (19/27) occurred in the absence of antiviral prophylaxis, whereas 30% (8/27) were breakthrough episodes.

10.3389/ti.2026.16075

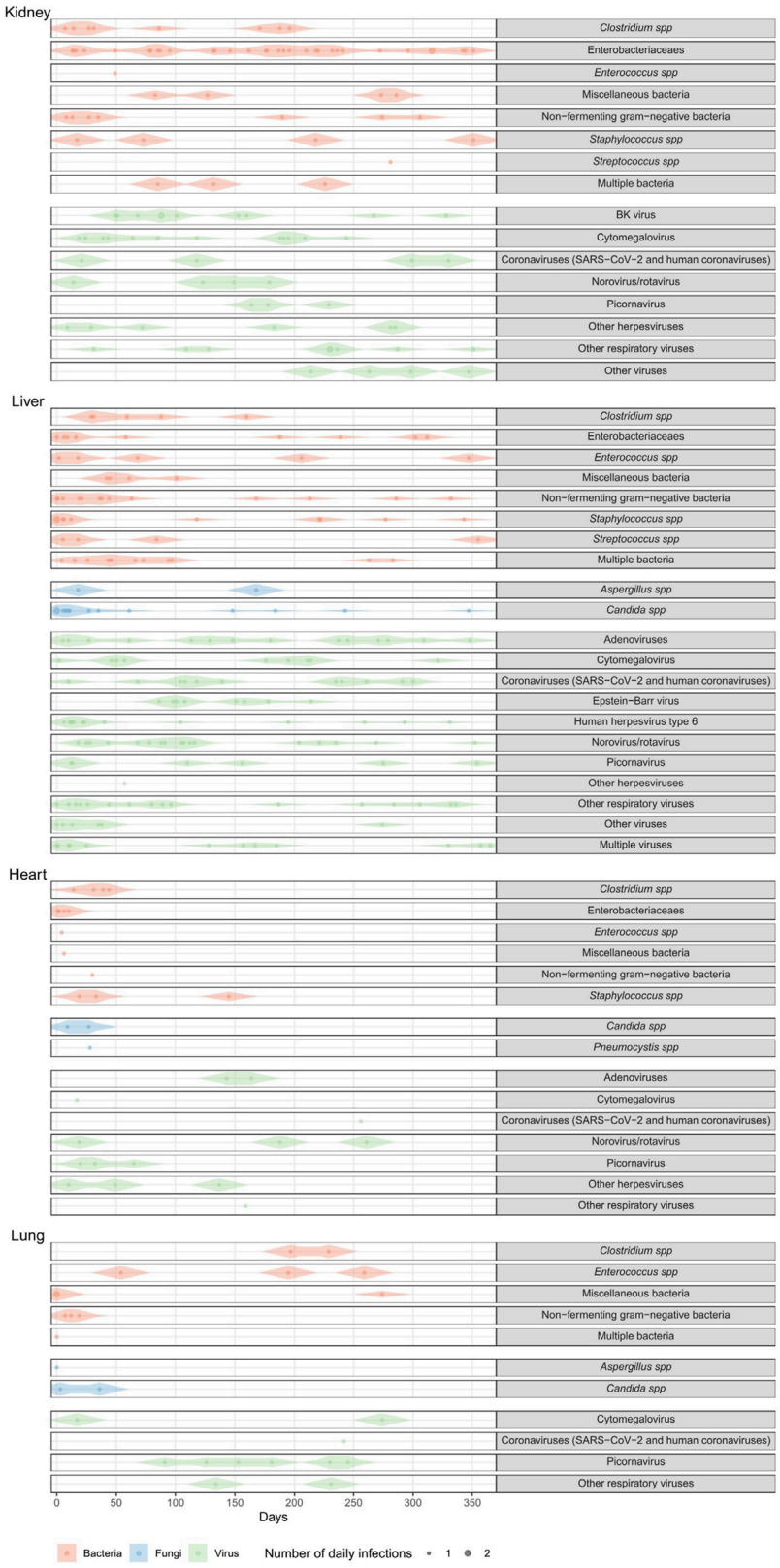


FIGURE 4
Violin representation of infections over time during the first year after transplant.

10.3389/ti.2026.16075

TABLE 2 Comparison of patients with and without infection.

Characteristic Number of patients	Infections n = 151	No infections n = 134	Univariate IRR (95% CI), p-value	Multivariate IRR (95% CI), p-value[a]
Transplanted organ, n (%)				
Kidney	49 (32.5)	67 (50.0)		
Liver	71 (47.0)	36 (26.9)	2.16 (1.47–3.18), p < 0.001	2.14 (1.38–3.34) p < 0.001
Lung	9 (6.0)	5 (3.7)	2.99 (1.34–7.15) p = 0.007	4.09 (1.79–10.1) p < 0.001
Heart	21 (13.9)	24 (17.9)	0.74 (0.42–1.29) p = 0.29	0.87 (0.49–1.53) p = 0.62
Combined	1 (0.7)	2 (1.5)		
Recipient age at transplant (yrs), median (IQR)	6.3 (1.4–14.3)	10.5 (2.9–15.6)	0.96 (0.94–0.99) p = 0.009	0.99 (0.95–1.02) p = 0.39
Recipient sex (male), n (%)	84 (55.6)	65 (48.5)	1.54 (1.07–2.21) p = 0.016	1.44 (1.01–2.06) p = 0.038
Previous transplant history, n (%)	4 (2.6)	6 (4.5)		
CMV risk stratification, n (%)				
High risk	44 (29.7)	33 (25.0)	0.85 (0.57–1.28) p = 0.43	1.04 (0.69–1.56) p = 0.86
Low or intermediate risk	104 (70.3)	99 (75.0)		
Unknown	3 (2.0)	2 (1.5)		
EBV risk stratification, n (%)				
High risk	57 (38.0)	41 (32.0)	1.19 (0.83–1.73) p = 0.43	1.22 (0.83–1.80) p = 0.29
Low or intermediate risk	93 (62.0)	87 (68.0)		
Unknown	1 (0.7)	6 (4.5)		
Inductions drugs[b]				
Basiliximab, n (%)	113 (74.8)	78 (58.2)	1.91 (1.28–2.85) p = 0.001	1.59 (0.98–2.60) p = 0.057
ATG, n (%)	12 (7.9)	23 (17.2)	0.35 (0.18–0.67) p = 0.002	1.05 (0.37–2.94) p = 0.92
Immunosuppressive drugs				
MMF, n (%)	84 (55.6)	101 (75.4)	0.52 (0.36–0.75) p = 0.001	0.79 (0.37–1.71) p = 0.51
TAC, n (%)	107 (70.9)	108 (80.6)	0.86 (0.57–1.30) p = 0.48	0.83 (0.37–1.81) p = 0.64
CsA, n (%)	49 (32.5)	25 (18.7)	1.22 (0.82–1.84) p = 0.32	1.66 (0.76–3.66) p = 0.21
GC, n (%)	129 (85.4)	123 (91.8)	0.71 (0.41–1.18) p = 0.19	0.99 (0.58–1.67) p = 0.21
Other, n (%)	7 (4.6)	6 (4.5)	0.46 (0.18–1.20) p = 0.11	0.85 (0.31–2.28) p = 0.73
Number of different IS, median (IQR)	3 (2–3)	3 (2–3)	0.7 (0.56, 0.88), p = 0.002	0.98 (0.72, 1.34) p = 0.9

[a]IRR derived from negative binomial generalized linear model. Effects highlighted in gray are adjusted for Organs, Sex, Age, Gender, CMV Serology and EBV Serology. Effects highlighted in blue are additionally adjusted for Basiliximab, ATG, MMF/EC-MPA, TAC, CsA, GC, Other IS. Effect highlighted in green are adjusted for the set RF1, Basiliximab and ATG.
[b]All immunosuppressive drugs recorded (within 14 days after and 30 days before transplantation).
IRR: Incidence rate ratio; IQR: interquartile range; yrs: years; CMV: Cytomegalovirus; EBV: Epstein-Barr virus, ATG: anti-thymocyte globulin;
IS, Immunosuppressor. MMF, Mycophenolate mofetil. TAC, Tacrolimus. CsA, cyclosporine A. GC, Glucocorticoid.
CMV/EBV risk stratification based on donor (D) and recipient (R) serostatus: high risk: D+/R-; low or intermediate risk: D+/R+, D-/R- or D-/R+.

Bacterial infections

Amongst the 149 bacterial infections, *E. coli* was the most commonly detected pathogen in 17% of cases (25/149), followed by *Clostridium* spp. (13% [19/149]) and *Pseudomonas* spp. (13% [19/149]) (Figure 3a; Supplementary Table 1a). A total of 45% (68/149) of bacterial infections were caused by Gram-negative organisms. Most cases of bacterial infections occurred in liver (42% [62/149]) and kidney (40% [60/149]) transplant recipients. Around half of the bacterial infections occurred in children <1 year at SOT (47% [70/149]) (Supplementary Tables 1a,b). Urinary tract infections predominated in kidney recipients, and respiratory infections in lung and heart recipients.

Thirteen patients (liver [n = 6], kidney [n = 6]), lung [n = 1] transplant recipients) experienced at least one infection caused by a multi-drug resistant (MDR) bacteria, totaling 19 episodes. Of the 19 episodes of infections caused by MDR bacteria, the most common organisms were MDR *Enterobacter* spp. (n = 7) and

E. coli spp. (n = 6). Other identified MDR bacteria were *Pseudomonas* spp. (n = 3), *Klebsiella* spp. (n = 2) and *Acinetobacter* spp (n = 1). No carbapenemase-producing Enterobacterales (CPE) or methicillin-resistant *Staphylococcus aureus* (MRSA) were identified.

Fungal infections

Amongst the 22 fungal infections, proven infection was documented in 16 (73%), the remaining being documented as probable fungal infection. The most frequently observed pathogen was *Candida* albicans, representing 59% (13/22) of fungal infections (Figure 3a; Supplementary Tables 1a,b). Death occurred in 3/22 cases (13.6%) 2 candidas and one other fungi, none of which were receiving antifungal prophylaxis, while 4/22 infections (18.2%) occurred despite prophylaxis.

Vaccine-preventable pathogens

Among 360 infections, 27 were attributed to vaccine-preventable pathogens (6%). Of these, 12 infections were caused by rotavirus, seven by influenza, six by varicella-zoster virus, one by *Haemophilus* influenzae type b and one by hepatitis B virus (donor-derived).

Opportunistic pathogens

Among 360 infections, 83 (23%) were secondary to opportunistic pathogens. These pathogens were mostly viruses (93% [77/83]), such as CMV (n = 24), adenoviruses (n = 16), HHV6 (n = 13), and BK virus (n = 10), followed by EBV (n = 8) and VZV n = 6). Other opportunistic pathogens were rare (*Aspergillus* spp [n = 3], non-tuberculosis mycobacteria ([n = 2]; *Pneumocystis* spp [n = 1]).

Site of infections

Most occurred in abdominal sites (liver, gastrointestinal site and urinary tract - 39%,140/360), followed by respiratory infections (22%, 80/360) (Figures 3a,b; Supplementary Table 2).

Timeline of infections

The burden of infections over time is presented by organ in Figure 4. Bacterial infections predominated in the first 3 months (56%, (84/149)), mainly *Clostridium* spp, mixed species, and *Pseudomonas* spp. *E. coli* infections occurred throughout the year (Supplementary Table 3).

Viral infections remained steady; EBV appeared mainly between 3 and 6 months, CMV throughout, and gastrointestinal viruses year-round. Most fungal infections occurred in the first month, mainly *Candida* spp (Supplementary Table 3).

Infections by organ

Regarding bacterial infections, in the kidney, Gram-negative bacteria predominated, with *E. coli* accounting for 17 cases (28.3%), followed by *Klebsiella spp.* (8; 13.3%) and *Pseudomonas spp.* (8; 13.3%), while gram-positive organisms remained less frequent. In the liver, infections were more evenly distributed, with 22/62 (35.5%) Gram-negative and 25/62 (40.3%) Gram-positive bacteria, alongside 13/62 (21%) polymicrobial cases. In the lung, the distribution was heterogeneous, with notable proportions of *Enterococcus spp.* (3/12; 25%) and mycobacteria (2/12; 16.7%), and no clear predominance of Gram-negative organisms. In the heart, Gram-positive bacteria dominated (5/7; 71.4%), mainly *Clostridium spp.* (2/7; 28.6%) and staphylococci (1/7; 14.3%), whereas Gram-negative bacteria were rare (1/7; 14.3%) and polymicrobial infections uncommon.

Regarding viruses, in the kidney, infections were mainly due to BK virus (10/51; 19.6%) and cytomegalovirus (12/51; 23.5%), whereas the liver showed a broader distribution including adenovirus (14/113; 12.4%), HHV-6 (13/113; 11.5%), coronaviruses (11/113; 9.7%), and 12/113 (10.6%) multiple viral infections. In the lung, picornaviruses predominated (6/11; 54.5%), while the heart displayed a low and heterogeneous viral distribution without a dominant pathogen.

Four patients liver-transplanted of a ABO incompatibly context experienced 9 infections (2.25 infections per patient). Forty-two patients with living-donor kidney transplants experienced 53 infections (1.26 infections per patient), compared with 58 infections among 74 patients with deceased-donor transplants (0.78 infections per patient).

Management of infections

Among the 360 infections, information regarding inpatient vs. outpatient management was available in 290 (81%). Among those, 58% (169/290) required hospitalization for management while 42% (122/290) were managed on an outpatient basis. Ninety-nine percent (146/148) of bacterial infections were treated by antibacterial therapy. Antiviral therapy was administered in 30% (55/185) of viral infections. All fungal infections were treated with antifungals. Additionally, a reduction of immunosuppression was reported in 10% of infections for which information was available (34/335). Of these cases, 29 involved viral infections (11 CMV; 6 EBV; 6 BK virus).

Among the 11 patients who died, seven had an active infection at the time of death. Five deaths were attributed to multiorgan failure secondary to infection, including three due to invasive fungal infections (one Aspergillus spp with multisystemic involvement and two *Candida* spp affecting the respiratory and gastrointestinal tract) and two due to bacterial sepsis (Herbaspirillum spp. in blood and *Bacteroides fragilis* from a gastrointestinal source). The remaining two patients died from non-infectious causes (cerebrovascular disease and postoperative hemorrhage), both associated with concurrent infection.

Risk factors for infections

Demographics of patients with (n = 151) and without infections (n = 134) are compared in Table 2. In a univariate model, liver and lung transplantation were associated with an increased infection incidence rate ratio (IRR) (2.16; $p < 0.001$ and 2.99; $p < 0.007$, respectively). A younger recipient age as well as male sex were also associated with an increased IRR (0.96; $p = 0.009$ and 1.54; $p = 0.016$, respectively).

In a multivariate model, only liver and lung transplantation as well as male sex remained associated with an increased infection incidence rate ratio (2.14; $p < 0.001$, 4.09; $p < 0.001$, 1.44; $p = 0.038$ respectively). (Table 2). No associations were found with immunosuppressive regimen or number of drugs (Table 2). Organ specific analyses did not identify any additional risk factors for infections beyond male sex (Supplementary Figure 5).

Association with rejection

During the follow-up period, 155 episodes of biopsy-proven rejections were observed with a median time of 51 days after transplantation (IQR 18–166) in 85 patients. Fifteen percent (24/155) episodes of rejection occurred within 30 days after an infection (Supplementary Table 4). In the multivariate model, no significant risk of rejection was found in the 30 days following any infection (HR 1.08; 95% Cl 0.57–2.06; $p = 0.800$).

Twenty-five episodes of rejection were followed by at least one infection within 90 days, totaling 43 infections (one infection in 16 cases, >1 infection in 9 cases) (Supplementary Table 4). In the multivariate model, rejection was not identified as a risk factor of infection (HR 1.08; 95% Cl 0.58–1.99; $p = 0.800$). Supplementary Figure 4 displays the timeline between rejection and infections by organ and by patient.

Discussion

This nationwide study of pediatric SOT during the first year after transplantation highlights several findings: (1) more than half of patients experienced at least one infectious event; (2) incidence of infection was highest in younger recipients; (3) liver and lung transplantation, as well as male sex were independently associated with an increased risk of infections (5) viral infections accounted for the largest proportion of infections; (6) bacterial infections predominated during the first 3 months, with a large proportion due to Gram-negative organisms (6) distinct organ-specific microbiological patterns were observed (7) and the burden of fungal infection was considerable, with 3 of 22 fungal infections resulting in death.

To our knowledge, this is the first comprehensive and standardized characterization of the infectious burden within the first year after pediatric SOT in a nationwide cohort. Most studies have focused on a single type of infection or on severe infections [20, 21], a single type of transplanted organ [8, 22], or data collection was restricted to the immediate early post-SOT period [23]. While organ-specific studies are essential, our objective is complementary: to provide an overall view of the infectious burden across pediatric SOT and enable comparisons between transplant groups, that share underlying immunosuppressive mechanisms. Our data showed that approximately 50% of pediatric SOT recipients presented at least one infection during the first year after transplant, in line with previous reports after pediatric liver transplantation [8]. Notably, one fifth of patients experienced >3 infections. Nearly half of infections required hospitalization. The challenge of invasive diagnostic and therapeutic procedures in children (venous access, biopsies of the infected sites,...), the impact on quality of life, and the economic burden of these infections were not analyzed in this study but are likely to be considerable [24].

At an incidence rate of 1.36 infection, the incidence of infection in our cohort was very similar to adult SOT recipients using the same design, definitions, and study population [7]. However, infection patterns differed substantially between children and adults, supporting the need for age-specific preventive and management strategies.

Infections were more frequent in younger patients, likely to immune immaturity and more frequent behavioural exposure. Young children lack antigen-specific adaptive responses and therefore rely on stronger but less specific innate responses [25, 26]. Lung transplant recipients had the highest incidence of infections, likely attributable to intense immunosuppression, airway exposure to pathogens and impaired mucociliary clearance [27–29]. Liver transplant recipients also had a high incidence of infections, despite a lower immunosuppression [8], and even after adjusting for age. This may reflect the liver immunologic role, cirrhosis-related immune defects [30–35] and the role of basiliximab induction. Male sex remained an independent risk factor, consistent with known sex-based immune differences and possible behavioral factors, including treatment non-adherence [36–47].

More than half of infections were viral, contrasting with the adult study where bacterial infections predominated [7]. Viral infections were even more frequent in younger children and occurred year-round, reflecting transitions from donor-derived and immunosuppression-related risk to community exposure after return to school or daycare. Respiratory and gastrointestinal viruses were most common, mirroring pediatric viral epidemiology [48–50], followed by herpesviruses, reflecting their burden after pediatric SOT [51–54]. These findings emphasize the need for heightened vigilance for viral infections in routine pediatric follow-up, early testing for respiratory pathogens in order to avoid unnecessary prolonged empiric antibiotherapy, importance of immunization in the community for vaccine-preventable diseases immunization and infection control measures such as masks, social distancing and hand hygiene whenever possible in case of sustained viral circulation in schools and daycare.

Bacterial infections predominated in the early months, reflecting intensified immunosuppression and post-operative complications. Like in adult SOT recipients [7], *E. coli* was the most frequent cause of bacterial infections, of which 24% were MDR. [12]. The high prevalence of Gram-negative pathogens in this cohort supports the adaptation of empirical antibacterial therapy toward broader-spectrum coverage in cases of suspected bacterial infection. These findings also support the importance of early postoperative surveillance cultures in febrile patients and emphasize the need for close multidisciplinary coordination between transplant teams and community pediatricians to ensure timely detection and rapid referral for suspected severe infections.

Moreover, our findings reveal clear organ-specific microbiological patterns. Kidney infections were largely driven by enteric Gram-negative bacteria, consistent with a urinary or digestive origin, whereas liver infections displayed a mixed and frequently polymicrobial profile, supporting a biliary or intra-abdominal source [55, 56]. Lung infections were more heterogeneous and included opportunistic pathogens, suggesting a role for host-related factors such as immunosuppression. In contrast, heart infections were predominantly caused by Gram-positive bacteria, reflecting

typical endovascular infections associated with skin flora and biofilm formation.

Viral infections also exhibited organ-specific distributions, with latent viruses predominating in the kidney and a broader, more diverse spectrum in the liver, possibly reflecting younger age and primary exposure to common viruses. Lung infections were mainly driven by respiratory viruses, whereas cardiac involvement remained rare and nonspecific.

Although the number of reported fungal infections remained low, the outcome was fatal in 13% of cases. This raises the question of whether the indications for antifungal prophylaxis in SOT recipients, rarely applied in our cohort, should be expanded, and of the clinical situations in which screening for fungal colonization should be considered.

Less than a quarter of infections in our dataset were caused by opportunistic pathogens. This is probably overestimated given the fact that some viral pathogens considered as opportunistic by the STCS infectious diseases working group might indeed be opportunistic in the adult setting, but might simply reflect primary community infection in children (i.e., VZV, adenovirus). Overall, the relatively low burden of opportunistic infections likely reflects effective prophylaxis, underscoring adherence to standardized protocols and ongoing education of families and healthcare providers. Also, only 6% of infections were attributed to vaccine-preventable pathogens. While this may suggest a potential contribution of the pre-transplant immunization to post-transplant protection, this could not be verified in our cohort as individual immunization charts were not available. [14]. These findings nonetheless support the importance of ensuring up to date vaccination before transplantation and post-transplant catch-up when feasible.

No significant association was found between rejection episodes and infections. This may reflect limited power and pathogen-specific differences in the risk of rejection [57]. In this cohort, steroid-free regimens were not associated with a reduced risk of infection. However, this finding may be subject to selection bias, as most patients received steroid-based therapy. Contrary to our initial hypothesis, recipients of deceased-donor kidney transplants did not exhibit a higher infection rate, as the number of infections per patient was greater in the living-donor group.

Limitations of our study include the sample size limiting conclusion of subgroup analyses, possible reporting bias toward severe infections (as 60% required hospitalization), and underreporting of milder community-acquired cases. The absence of a pediatric control group limits comparison with the general population, and the results may not be generalized to other settings with different epidemiology or clinical practices. In addition, detailed data on immunosuppressive drug dosing and levels, treatment of rejection were unavailable restricting analysis of their association with infection. As with all registry-based studies, our findings may also be affected by loss to follow-up, missing or incomplete data, and variability in data reporting across centers.

In conclusion, this study provides a comprehensive overview of the infectious burden in the first year following pediatric SOT. More than half of patients experienced at least one clinically relevant infection, with viral infections predominated highlighting the unique vulnerabilities of pediatric recipients. The higher risk of infection was for liver and lung transplant recipients. These findings underscore the need for age and organ specific prevention and management strategies, including optimized vaccination, early diagnostics, and tailored antimicrobial approaches.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by IRB review board - university hospital basel. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation to the STCS cohort study was provided by the participants' legal guardians/ next of kin.

Author contributions

NR, AL, JF conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. JF also performed the statistical analyses and extracted the data from the Swiss Transplant Cohort Study database. CV, NM, and VM conceptualized and designed the study and reviewed and revised the manuscript. GS, SD, IM, PP, CBa, DM, CBe, HC, MS and ST contributed to data collection and critically reviewed the manuscript for important intellectual content.

Group members of Swiss Transplant Cohort Study

Member of the Swiss Transplant Cohort Study: Patrizia Amico, Adrian Bachofner, Vanessa Banz, Sonja Beckmann, Guido Beldi, Christoph Berger, Ekaterine Berishvili, Annalisa Berzigotti, Françoise-Isabelle Binet, Pierre-Yves Bochud, Petra Borner, Sanda Branca, Anne Cairoli, Emmanuelle Catana, Yves Chalandon, Philippe Compagnon, Sabina De Geest, Sophie De Seigneux, Michael Dickenmann, Joëlle Lynn Dreifuss, Thomas Fehr, Sylvie Ferrari-Lacraz, Andreas Flammer, Jaromil Frossard, Déla Golshayan, Nicolas Goossens, Fadi Haidar, Jürg Halter, Christoph Hess, Sven Hillinger, Hans Hirsch, Patricia Hirt, Linard Hoessly, Uyen Huynh-Do, Franz Immer, Nina Khanna, Michael Koller, Angela Koutsokera, Andreas Kremer, Thorsten Krueger, Christian Kuhn, Arnaud L'Huillier, Bettina Laesser, Frédéric Lamoth, Roger Lehmann, Alexander Leichtle, Oriol Manuel, Hans-Peter Marti, Michele Martinelli, Valérie McLin, Katell Mellac, Aurélia Merçay, Karin Mettler, Sara Christina Meyer, Nicolas Müller, Jelena Müller, Ulrike Müller-Arndt, Mirjam Nägeli, Dionysios Neofytos, Jakob Nilsson, Manuel Pascual, Rosmarie Pazeller, David Reineke, Juliane Rick, Fabian Rössler, Silvia Rothlin, Thomas Schachtner, Stefan Schaub, Dominik Schneidawind, Macé Schuurmans, Simon Schwab, Thierry Sengstag, Daniel Sidler, Federico Simonetta, Jürg Steiger, Guido Stirnimann, Ueli Stürzinger, Christian Van Delden,

Jean-Pierre Venetz, Jean Villard, Julien Vionnet, Laura Walti, Caroline Wehmeier, Patrick Yerly.

Funding

The author(s) declared that financial support was received for this work and/or its publication. The Swiss Transplant Cohort Study is supported by the Swiss National Science Foundation (SNSF, http://www.snf.ch), Unimedsuisse and the Transplant Centers.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2026.16075/full#supplementary-material

References

1. Green M. Introduction: infections in solid organ transplantation. *Am J Transpl* (2013) 13(Suppl. 4):3–8. doi:10.1111/ajt.12093

2. Fishman JA. Infection in organ transplantation. *Am J Transpl* (2017) 17(4):856–79. doi:10.1111/ajt.14208

3. Dharnidharka VR, Stablein DM, Harmon WE. Post-transplant infections now exceed acute rejection as cause for hospitalization: a report of the NAPRTCS. *Am J Transpl* (2004) 4(3):384–9. doi:10.1111/j.1600-6143.2004.00350.x

4. Hamandi B, Husain S, Grootendorst P, Papadimitropoulos EA. Clinical and microbiological epidemiology of early and late infectious complications among solid-organ transplant recipients requiring hospitalization. *Transpl Int* (2016) 29(9):1029–38. doi:10.1111/tri.12808

5. Parasuraman R, Abouljoud M, Jacobsen G, Reddy G, Koffron A, Venkat KK. Increasing trend in infection-related death-censored graft failure in renal transplantation. *Transplantation* (2011) 91(1):94–9. doi:10.1097/tp.0b013e3181fdd96c

6. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med* (1998) 338(24):1741–51. doi:10.1056/NEJM199806113382407

7. van Delden C, Stampf S, Hirsch HH, Manuel O, Meylan P, Cusini A, et al. Burden and timeline of infectious diseases in the first year after solid organ transplantation in the Swiss transplant cohort study. *Clin Infect Dis* (2020) 71(7):e159–e69. doi:10.1093/cid/ciz1113

8. Shepherd RW, Turmelle Y, Nadler M, Lowell JA, Narkewicz MR, McDiarmid SV, et al. Risk factors for rejection and infection in pediatric liver transplantation. *Am J Transpl* (2008) 8(2):396–403. doi:10.1111/j.1600-6143.2007.02068.x

9. Foster BJ, Dahhou M, Zhang X, Platt RW, Hanley JA. Change in mortality risk over time in young kidney transplant recipients. *Am J Transpl* (2011) 11(11):2432–42. doi:10.1111/j.1600-6143.2011.03691.x

10. Koller MT, van Delden C, Muller NJ, Baumann P, Lovis C, Marti HP, et al. Design and methodology of the swiss transplant cohort study (STCS): a comprehensive prospective nationwide long-term follow-up cohort. *Eur J Epidemiol* (2013) 28(4):347–55. doi:10.1007/s10654-012-9754-y

11. Humar A, Michaels M, AiwgoID M. American society of transplantation recommendations for screening, monitoring and reporting of infectious complications in immunosuppression trials in recipients of organ transplantation. *Am J Transpl* (2006) 6(2):262–74. doi:10.1111/j.1600-6143.2005.01207.x

12. De PB, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the european organization for research and treatment of cancer/invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (EORTC/MSG) consensus group. *Clin Infect Dis* (2008) 46(12):1813–21. doi:10.1086/588660

13. Federal Office of Public Health. *Swiss federal vaccination Commission*. Swiss Immunization Schedule. Available online at: https://www.bag.admin.ch/en/vaccinations-and-prevention (Accessed July 11, 2025).

14. L'Huillier AG, Wildhaber BE, Belli DC, Diana A, Rodriguez M, Siegrist CA, et al. Successful serology-based intervention to increase protection against vaccine-preventable diseases in liver-transplanted children: a 19-yr review of the Swiss national reference center. *Pediatr Transpl* (2012) 16(1):50–7. doi:10.1111/j.1399-3046.2011.01600.x

15. Gray RJ. A class of K-Sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* (1988) 16(3):1141–54. doi:10.1214/aos/1176350951

16. R Core Team. *R: a Language and environment for statistical computing*. Foundation for Statistical Computing (2024). Available online at: https://www.R-project.org/ (Accessed July 11, 2025).

17. Wickham H, Averick M, Bryan J, Chang W, D'Agostino McGovan L, Francois R, et al. Welcome to the tidyverse. *J Open Source Softw* (2019) 4(43):1686.

18. Therneau TM, Grambsch PM. *Modeling survival data: extending the cox model*. New York, NY: Springer (2000). doi:10.1007/978-1-4757-3294-8

19. Venables WN, Ripley BD. *Modern applied statistics with*. New York, NY: Springer (2002). doi:10.1007/978-0-387-21706-2

20. Waller KMJ, De La Mata NL, Wyburn KR, Hedley JA, Rosales BM, Kelly PJ, et al. Notifiable infectious diseases among organ transplant recipients: a data-linked cohort study, 2000-2015. *Open Forum Infect Dis* (2022) 9(8):ofac337. doi:10.1093/ofid/ofac337

21. Moller DL, Sorensen SS, Wareham NE, Rezahosseini O, Knudsen AD, Knudsen JD, et al. Bacterial and fungal bloodstream infections in pediatric liver and kidney transplant recipients. *BMC Infect Dis* (2021) 21(1):541. doi:10.1186/s12879-021-06224-2

22. Dohna Schwake C, Guiddir T, Cuzon G, Benissa MR, Dubois C, Miatello J, et al. Bacterial infections in children after liver transplantation: a single-center surveillance study of 345 consecutive transplantations. *Transpl Infect Dis* (2020) 22(1):e13208. doi:10.1111/tid.13208

23. Onyearugbulem C, Williams L, Zhu H, Gazzaneo MC, Melicoff E, Das S, et al. Risk factors for infection after pediatric lung transplantation. *Transpl Infect Dis* (2018) 20(6):e13000. doi:10.1111/tid.13000

24. Hogan J, Pietrement C, Sellier-Leclerc AL, Louillet F, Salomon R, Macher MA, et al. Infection-related hospitalizations after kidney transplantation in children: incidence, risk factors, and cost. *Pediatr Nephrol* (2017) 32(12):2331–41. doi:10.1007/s00467-017-3737-x

25. Semmes EC, Chen JL, Goswami R, Burt TD, Permar SR, Fouda GG. Understanding early-life adaptive immunity to guide interventions for pediatric health. *Front Immunol* (2020) 11:595297. doi:10.3389/fimmu.2020.595297

26. Kollmann TR, Kampmann B, Mazmanian SK, Marchant A, Levy O. Protecting the newborn and young infant from infectious diseases: lessons from immune ontogeny. *Immunity* (2017) 46(3):350–63. doi:10.1016/j.immuni.2017.03.009

27. Trachuk P, Bartash R, Abbasi M, Keene A. Infectious complications in lung transplant recipients. *Lung* (2020) 198(6):879–87. doi:10.1007/s00408-020-00403-9

28. Dettori M, Riccardi N, Canetti D, Antonello RM, Piana AF, Palmieri A, et al. Infections in lung transplanted patients: a review. *Pulmonology* (2024) 30(3):287–304. doi:10.1016/j.pulmoe.2022.04.010

29. Magda G. Opportunistic infections post-lung transplantation: viral, fungal, and mycobacterial. *Clin Chest Med* (2023) 44(1):159–77. doi:10.1016/j.ccm.2022.10.012

30. Piano S, Bunchorntavakul C, Marciano S, Rajender Reddy K. Infections in cirrhosis. *Lancet Gastroenterol Hepatol* (2024) 9(8):745–57. doi:10.1016/S2468-1253(24)00078-5

31. Bernsmeier C, van der Merwe S, Perianin A. Innate immune cells in cirrhosis. *J Hepatol* (2020) 73(1):186–201. doi:10.1016/j.jhep.2020.03.027

32. Hasa E, Hartmann P, Schnabl B. Liver cirrhosis and immune dysfunction. *Int Immunol* (2022) 34(9):455–66. doi:10.1093/intimm/dxac030

33. Wyke RJ, Rajkovic IA, Williams R. Impaired opsonization by serum from patients with chronic liver disease. *Clin Exp Immunol* (1983) 51(1):91–8.

34. Campbell AC, Dronfield MW, Toghill PJ, Reeves WG. Neutrophil function in chronic liver disease. *Clin Exp Immunol* (1981) 45(1):81–9.

35. Ono Y, Watanabe T, Matsumoto K, Ito T, Kunii O, Goldstein E. Opsonophagocytic dysfunction in patients with liver cirrhosis and low responses to tumor necrosis factor-alpha and lipopolysaccharide in patients' blood. *J Infect Chemother* (2004) 10(4):200–7. doi:10.1007/s10156-004-0321-7

36. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* (2003) 348(16):1546–54. doi:10.1056/NEJMoa022139

37. Forsyth KS, Jiwrajka N, Lovell CD, Toothacre NE, Anguera MC. The conneXion between sex and immune responses. *Nat Rev Immunol* (2024) 24(7):487–502. doi:10.1038/s41577-024-00996-9

38. Bianchi I, Lleo A, Gershwin ME, Invernizzi P. The X chromosome and immune associated genes. *J Autoimmun* (2012) 38(2-3):J187–92. doi:10.1016/j.jaut.2011.11.012

39. Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. *Hum Reprod Update* (2005) 11(4):411–23. doi:10.1093/humupd/dmi008

40. Zimmermann P, Curtis N. Factors that influence the immune response to vaccination. *Clin Microbiol Rev* (2019) 32(2):e00084-18. doi:10.1128/CMR.00084-18

41. Klein SL, Jedlicka A, Pekosz A. The Xs and Y of immune responses to viral vaccines. *Lancet Infect Dis* (2010) 10(5):338–49. doi:10.1016/S1473-3099(10)70049-9

42. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol* (2016) 16(10):626–38. doi:10.1038/nri.2016.90

43. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. *Nat Rev Immunol* (2008) 8(9):737–44. doi:10.1038/nri2394

44. Burra P, Zanetto A, Schnabl B, Reiberger T, Montano-Loza AJ, Asselta R, et al. Hepatic immune regulation and sex disparities. *Nat Rev Gastroenterol Hepatol* (2024) 21(12):869–84. doi:10.1038/s41575-024-00974-5

45. Gray WN, Holbrook E, Morgan PJ, Saeed SA, Denson LA, Hommel KA. Transition readiness skills acquisition in adolescents and young adults with inflammatory bowel disease: findings from integrating assessment into clinical practice. *Inflamm Bowel Dis* (2015) 21(5):1125–31. doi:10.1097/MIB.0000000000000352

46. Boucquemont J, Pai ALH, Dharnidharka VR, Hebert D, Furth SL, Foster BJ. Gender differences in medication adherence among adolescent and young adult kidney transplant recipients. *Transplantation* (2019) 103(4):798–806. doi:10.1097/TP.0000000000002359

47. Vaisbourd Y, Dahhou M, Zhang X, Sapir-Pichhadze R, Cardinal H, Johnston O, et al. Differences in medication adherence by sex and organ type among adolescent and young adult solid organ transplant recipients. *Pediatr Transpl* (2023) 27(2):e14446. doi:10.1111/petr.14446

48. Walker CLF, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet* (2013) 381(9875):1405–16. doi:10.1016/S0140-6736(13)60222-6

49. Collaborators GL. Age-sex differences in the global burden of lower respiratory infections and risk factors, 1990-2019: results from the global burden of disease study 2019. *Lancet Infect Dis* (2022) 22(11):1626–47. doi:10.1016/S1473-3099(22)00510-2

50. Bulata-Pop I, Simionescu B, Bulata B, Junie LM. Epidemiology and diagnostic accuracy of respiratory pathogens in pediatric populations: insights from global studies. *Cureus* (2024) 16(9):e68652. doi:10.7759/cureus.68652

51. Pergam SA, Limaye AP, Astidco P. Varicella zoster virus in solid organ transplantation: guidelines from the American society of transplantation infectious diseases community of practice. *Clin Transpl* (2019) 33(9):e13622. doi:10.1111/ctr.13622

52. Yamada M, L'Huillier AG, Green M. A focused review of epstein-barr virus infections and PTLD in pediatric transplant recipients: guidance from the IPTA and ECIL guidelines. *J Pediatr Infect Dis Soc* (2024) 13(Suppl. ment_1):S31–S8. doi:10.1093/jpids/piad097

53. L'Huillier AG, Dipchand AI, Ng VL, Hebert D, Avitzur Y, Solomon M, et al. Posttransplant lymphoproliferative disorder in pediatric patients: survival rates according to primary sites of occurrence and a proposed clinical categorization. *Am J Transpl* (2019) 19(10):2764–74. doi:10.1111/ajt.15358

54. L'Huillier AG, Dipchand AI, Ng VL, Hebert D, Avitzur Y, Solomon M, et al. Posttransplant lymphoproliferative disorder in pediatric patients: characteristics of disease in EBV-seropositive recipients. *Transplantation* (2019) 103(11):e369–e74. doi:10.1097/TP.0000000000002898

55. Bonnel AR, Bunchorntavakul C, Reddy KR. Immune dysfunction and infections in patients with cirrhosis. *Clin Gastroenterol Hepatol* (2011) 9(9):727–38. doi:10.1016/j.cgh.2011.02.031

56. Leber B, Mayrhauser U, Rybczynski M, Stadlbauer V. Innate immune dysfunction in acute and chronic liver disease. *Wien Klin Wochenschr* (2009) 121(23-24):732–44. doi:10.1007/s00508-009-1288-2

57. Higdon LE, Tan JC, Maltzman JS. Infection, rejection, and the connection. *Transplantation* (2023) 107(3):584–95. doi:10.1097/TP.0000000000004297

ESOT | Transplant International

TYPE Original Research
PUBLISHED 22 May 2026
DOI 10.3389/ti.2026.15722

Check for updates

OPEN ACCESS

*CORRESPONDENCE
Helena Bugacov,
helena.bugacov@icahn.mssm.edu

RECEIVED 10 October 2025
REVISED 29 January 2026
ACCEPTED 04 May 2026
PUBLISHED 22 May 2026

CITATION
Bugacov H, Cusmai C, Li K, Montal AM, Dawodu G, Sun T, Tuminello S, Gulati S, Tseng K-C, Bernstein JT, Laskey D, Seethamraju H and Scheinin S (2026) Identical versus compatible blood typing: investigating best practices in lung transplantation.
Transpl. Int. 39:15722.
doi: 10.3389/ti.2026.15722

COPYRIGHT
© 2026 Bugacov, Cusmai, Li, Montal, Dawodu, Sun, Tuminello, Gulati, Tseng, Bernstein, Laskey, Seethamraju and Scheinin. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Identical versus compatible blood typing: investigating best practices in lung transplantation

Helena Bugacov[1]*, Cristina Cusmai[1], Kenneth Li[1], Anne Michelle Montal[1], Gbalekan Dawodu[1], Tian Sun[1], Stephanie Tuminello[1], Shubham Gulati[1], Kuo-Chang Tseng[2], Joshua Taylor Bernstein[3], Daniel Laskey[1], Harish Seethamraju[1] and Scott Scheinin[1]

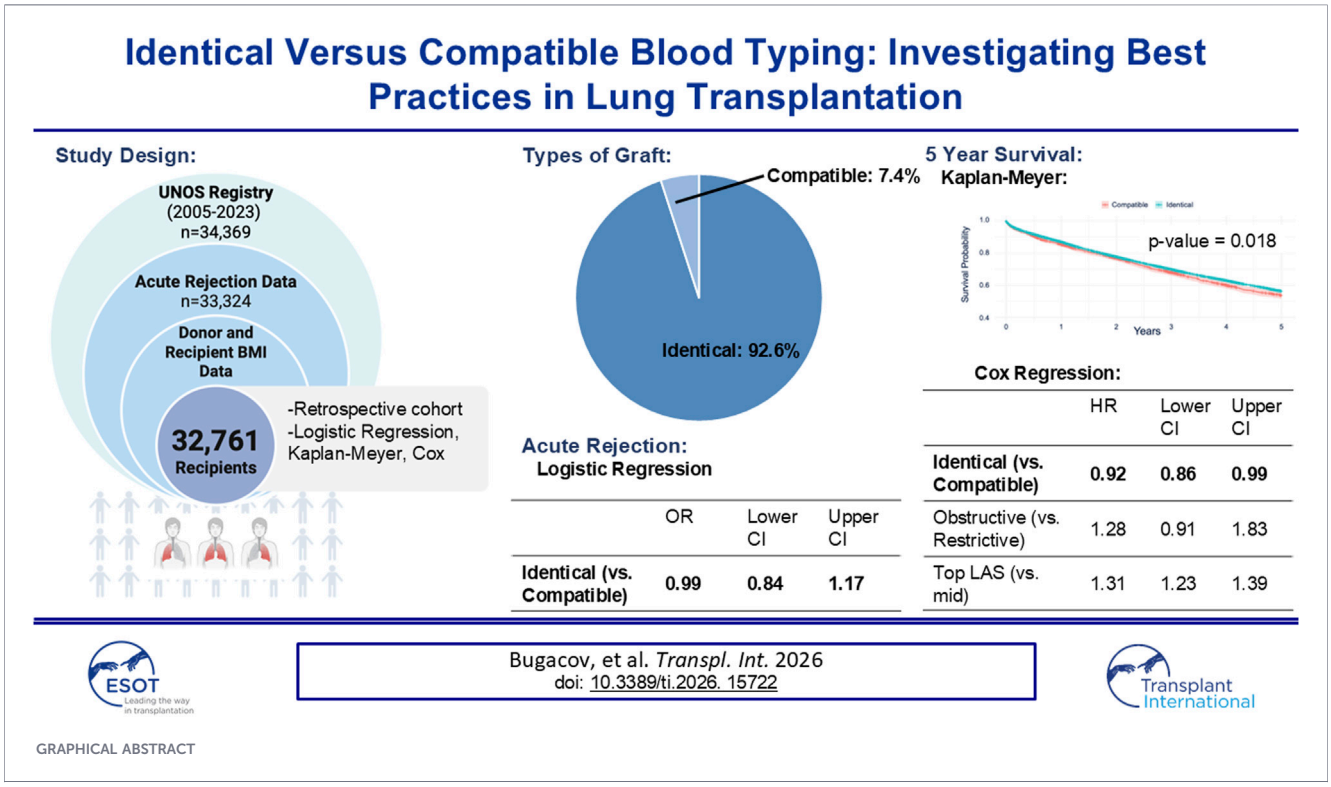
[1]Department of Thoracic Surgery, Icahn School of Medicine at Mount Sinai, New York, NY, United States, [2]University of California Los Angeles Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, Los Angeles, CA, United States, [3]Stevens Institute of Technology School of Business, Hoboken, United States

This study investigated acute rejection in ABO-compatible versus ABO-identical lung transplants from 2005–2023, with a secondary objective of comparing 5-year survival. Lung transplantation improves quality of life and survival; however, organ scarcity remains a major challenge. While ABO-identical matching has traditionally been preferred, evolving allocation policies and research have increased the use of ABO-compatible transplants to expand the donor pool. A retrospective cohort study using the UNOS database included adult recipients (n = 32,761). Comparisons were made between ABO-identical (n = 30,347) and ABO-compatible (n = 2,414) groups. Logistic regression assessed acute rejection, and Kaplan-Meier and Cox proportional hazards models evaluated 5-year survival. There was no significant difference in acute rejection (p = 0.99; OR = 1.03, 95% CI 0.86–1.21). ABO-identical transplants showed improved 5-year survival (p = 0.019; HR = 0.91, 95% CI 0.85–0.98), with benefits limited to recipients with obstructive lung disease (p = 0.043) and those in the highest LAS quartile (p = 0.014). The differential benefit of this modest association between ABO-identical matching and survival in this subpopulation remains unclear. Overall, ABO-compatible transplantation safely expands donor availability without increasing rejection risk.

KEYWORDS
ABO blood group system, ABO blood type, lung, lung transplant, allocation

Introduction

Lung transplantation offers improved quality of life and survival, with approximately 88.4% 1-year survival rates in 2018–2023 [1]. Globally, the incidence of lung transplant surpasses more than 4,600 cases annually, the majority being bilateral, with a median survival of 6.2 years in the adult population [2]. In 2022, 2,743 lung transplants were performed, a number that has been gradually increasing since the pandemic, alongside the addition of 3,161 candidates to the waiting list [3]. However, organ scarcity remains a significant challenge [3]. Donor-recipient matching is an evolving strategy aimed at optimizing the best organ for the most medically urgent recipient [3]. Prior to 2023, lung allocation was determined by a classification-based system [4]. Candidates were initially arranged into ordered groups based on blood type identical and within



250 miles of the donor hospital [5]. Within each group, the candidates were then ranked preferentially by Lung Allocation Scores (LAS) [5].

In early 2023, the lung allocation policy converted to a continuous distribution framework, which utilizes a composite allocation score (CAS) to determine the preferential order of candidates when a medically suitable donor becomes available [5]. This change was implemented to improve fairness, decrease waitlist mortality, increase access to lung transplants for the most medically urgent candidates, and improve patient outcomes in lung transplant allocation [5]. The Lung CAS includes nine candidate attributes, which include two components of the LAS. These are expected 1-year waiting list mortality without a transplant (WLAUC), expected 5-year post-transplant survival, blood type matching, CPRA (HLA antibody sensitization), height, pediatric status, prior living donor status, travel efficiency (including travel and transportation costs), and proximity efficiency [5]. Blood type matching (ABO-compatible, see Methods "ABO Matching") allows recipients with harder-to-match blood types to have increased priority for potential donors compared to those with more common blood types, providing a recipient with more prospective donors, compared to blood type identical matching [5].

Traditionally, ABO-identical matching has been preferred in lung transplantation due to the perceived lower risk of rejection [6]. Non-identical ABO or ABO-compatible lung transplantation is an area of ongoing research to expand the donor pool for recipients, with prior studies suggesting good outcomes with ABO compatible transplants [6–9]. These studies were, however, limited due to sample size and single-center studies, for instance, investigating 325 patients between 1990 and 2016 [9]. Taghavi et al. examined 6,655 adult double lung transplantations from May 2005 to December 2011, and their multivariate analysis demonstrated no association with long-term or short-term mortality [8]. There was no clarity, however, on whether acute and chronic rejection were more common among ABO compatible organs.

Our study builds upon previous research by comparing outcomes between recipients of identical and compatible ABO lung transplants, focusing on patient survival and acute rejection rates. Acute rejection is a clinically meaningful marker of immune injury due to the possibility of ABO-incompatibility triggering acute or hyperacute antibody-mediated graft rejection [10] and complications such as passenger lymphocyte syndrome [11], as well as it being a risk factor associated with the development of chronic lung allograft dysfunction [12]. 5-year survival is a robustly captured endpoint in UNOS that has notably been incorporated in the lung allocation policy to prioritize candidates, reflecting consensus that this endpoint is an important measure of transplant benefit [13]. The aim of our study is to gain insight into the role of ABO compatibility in optimizing lung transplant outcomes and inform clinical decision-making to enhance donor organ utilization.

Materials and Methods

Study design and population

United Network for Organ Sharing (UNOS) is a non-profit organization contracted by the federal government to manage organ donation and allocation. The Standard Transplant Analysis and Research data files, a public-access dataset, were obtained from the UNOS registry. All lung transplants, both single and double,

performed in the United States from June 2005 to June 2023 were examined. ABO compatible transplants were compared to ABO identical transplants, with an endpoint of risk-adjusted all-cause mortality. Acute rejection, which was defined as any recorded acute rejection episode in the follow-up window of our dataset, was used as a secondary endpoint.

Study population (inclusion/exclusion criteria)

We included all de-identified lung transplants in the UNOS registry from June 2005-June 2023 with donor-recipient ABO match categorized as ABO-identical or compatible. We excluded pediatric recipients, recipients without an acute rejection episode status classification, recipients without a recipient BMI or associated donor BMI, and cases without ischemic time. Re-transplantations and multi-organ transplants were not excluded. For survival analyses, recipients missing survival time were excluded and follow-up was censored at 5 years.

Primary exposure

The ABO blood group compatibility was classified into "Identical" and "Compatible."

Primary outcome

The primary outcome used in our analysis was risk-adjusted all-cause mortality.

Confounding variables

Additional variables examined included recipient age, donor age, lung transplant type (single or double), recipient gender, and medical conditions of the recipient before transplantation, categorized as "hospitalized but not ICU", "Intensive Care", or "Not Hospitalized". We also maintained the four major categories from LAS in this analysis, including obstructive lung disease, pulmonary hypertension, cystic fibrosis, and restrictive lung disease [14]. We also used the UNOS data set to calculate age difference as the absolute age difference between the recipient and donor. We calculated BMI differences as the absolute difference in BMI between the recipient and donor, and height differences as the absolute height difference between the recipient and donor. The initial Lung Allocation Score was cut at the 25th (33.74) and 75th (44.96) percentiles to define three groups (below 1st, 1st–4th, above 4th).

Statistical analysis

Univariate comparisons between groups based on ABO compatibility and acute rejection event used chi-square tests for categorical variables and t-tests for continuous variables. Statistical significance was defined as a two-tailed p-value of less than 0.05. Multivariable logistic regression was utilized to assess the association between ABO status and acute rejection ABO status and ICU status, ICU status and blood type, and high vs. low LAS score as a function of blood type.

Kaplan-Meier survival analysis was used to estimate overall survival probabilities over 5 years post-transplant, capped at 1825 days (5 Years), and the status of each patient (alive or deceased). A Cox proportional hazards model was used to assess the impact of ABO status on survival, adjusting for age, allocation quartile, and disease category, transplant type, and gender.

Data organization, analysis, manipulation, visualization, and statistical analysis were performed using R statistical software while running and utilizing the following packages: survival, survminer, dplyr, ggplot2, tidyverse, readxl, and compareGroups [14–19].

Ethics statement

According to our institution's IRB office this study does not meet the criteria for IRB approval as this study does not include identifiable human subjects. This study only contains de-identified UNOS data and is not interacting with any participants or obtaining identifiable data from other sources.

ABO matching

ABO blood grouping, also known as blood type, is the presence or absence of antigens, labeled A and B, on the surface of a red blood cell (RBC) [20]. In the absence of one or both antigens, antibodies against the antigen are formed [21]. It is these antibodies that cause mismatch reactions. People whose red blood cells display only the A antigen generate serum anti-B antibodies and are labeled as type A[21]. Conversely, those with B-antigen have anti-A-antibodies and are considered type B. Individuals with both A and B antigens do not produce any antibodies and are labeled AB. Lastly, people expressing neither antigen are considered O-type and generate antibodies to both A- and B-type antigens [21].

ABO matching has been a significant cornerstone of transplantation [22]. Type O recipients can only receive blood from donors who are also Type O, as they have circulating antibodies to both A and B antigens [22]. Type A can receive organs from type A or O donors and Type B can receive organs from type B or O donors [22]. Type AB individuals do not have antibodies; therefore, they can receive donors from all blood types. When a recipient and donor are matched to the same ABO type (e.g., a Type A recipient receiving a Type A donor), this is referred to as ABO-identical matching. Minor ABO-incompatibility, or ABO-compatible transplantation, occurs with a blood type O donor lung transplanted into A, B, or AB recipients, or a blood type A and B donor lung transplanted into a AB recipient [22].

Major ABO-incompatibility occurs when an organ with A or B antigens is transplanted into a recipient with corresponding antibodies, most seen when blood type O patients receive lungs from A, B, or AB donors. ABO-incompatible cases have been done only inadvertently due to clerical errors [7, 23, 24].

Results

During the study period, 34,369 patients underwent lung transplantation, as reported by the UNOS database. Pediatric patients under the age of 18 years were excluded, leaving

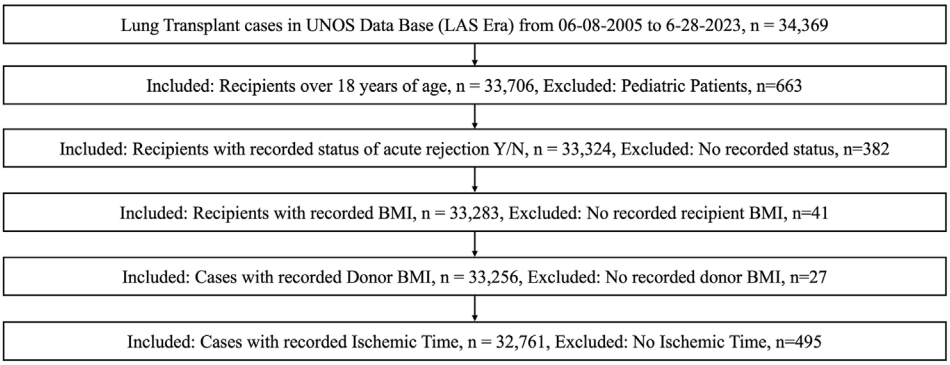


FIGURE 1
Schematic representing cohort selection.

TABLE 1 **Summary of patient characteristics (Univariate/Unadjusted analysis).**

Variable	Compatible, n = 2,414	Identical, n = 31,235	p-value
Acute Rejection			0.99
No	2251 (93.2%)	28289 (93.2%)	
Yes	163 (6.75%)	2058 (6.78%)	
Recipient Gender			0.437
F	997 (40.5%)	12031 (39.6%)	
M	1437 (59.5%)	18316 (60.4%)	
Recipient Age	58.4 (12.0)	57.1 (12.6)	<0.001
Recipient BMI	25.3 (4.35)	25.5 (4.55)	0.005
Medical Condition			0.002
Intensive Care	285 (11.8%)	3888 (12.8%)	
Hospitalized – Not ICU	193 (8.00%)	3016 (9.94%)	
Not Hospitalized	1936 (80.2%)	23443 (77.2%)	
Disease Stratification			<0.001
Cystic Fibrosis	170 (7.04%)	2464 (8.12%)	
Obstructive	835 (34.6%)	7619 (25.1%)	
Other	233 (9.65%)	3496 (11.5%)	
Restrictive	1176 (48.7%)	16768 (55.3%)	
Lung Transplantation			<0.001
Single	798 (33.1%)	8419 (27.7%)	
Double	1612 (66.9%)	21920 (72.3%)	
Allocation Quartile			<0.001
Top	496 (20.5%)	7802 (24.0%)	
Middle	1134 (47.0%)	15276 (50.3%)	
Bottom	784 (32.5%)	7269 (24.0%)	

33,706 adult patients. These were screened for documentation of acute rejection episodes (33,324). Patients with missing data for body mass index (BMI) from either the donor or the recipient were also excluded, as were patients with no recorded ischemic time, resulting in a final retrospective cohort of n = 32,761 (Figure 1). Of this, 30,347 transplants occurred with identical ABO matching, and 2,414 occurred with compatible matching.

Acute rejection

In the univariate analysis (Table 1), there was no significant difference in gender or acute rejection between identical ABO and compatible matching. The ABO compatible group had an older mean age (58.4 in compatible vs. 57.1 in identical) (age, $p < 0.001$) and a similar BMI (25.3 in compatible and 25.5 identical) (BMI, $p = 0.005$). There was a small, but statistically significant difference in the ABO identical group being more likely to be transplanted from the ICU (12.8% in identical vs. 11.8% in compatible) and non-ICU hospitalizations (9.9% in identical vs. 8.0% in compatible). In contrast, the ABO compatible group was more likely to be transplanted from an outpatient setting (80.2% in compatible vs. 77.2% in identical). (Medical conditions, $p = 0.002$). Patients with low LAS scores are likely to be on the waitlist for a long time as they are not a priority due to their LAS score, which is calculated by their disease severity as a factor. As a result, they are more likely to have compatible ABO matching because they would not otherwise receive a transplant. Additionally, to examine if ABO-compatible grafts were used in more clinically stable patients, we fit a multivariate logistic regression model with ABO-identical vs. ABO-compatible matching as the outcome. We found a modest increase in use of compatible donors in ICU cases vs. non-ICU-cases (OR 1.26, 95% CI 1.04–1.52). We also fit a multivariate logistic regression model with ICU vs. non-ICU status as the outcome, and found more O type patients (who can only receive ABO-identical grafts) in the ICU (OR 1.16, 95% CI 1.07–1.24). Additionally, we fit a multivariate logistic regression model with high LAS vs. non-high LAS as the outcome and found that O type patients were also in the highest allocation quartile (OR 1.09, 95% CI 1.03–1.15).

Comparing recipient diagnosis, patients with obstructive disease were more likely to undergo ABO compatible matching (34.6% in compatible vs. 25.1% in identical). Higher use of ABO-compatible donors in patients with obstructive disease likely reflects real-world patterns in center allocation of lungs. Specifically, patients with obstructive disease were more likely to fall into a lower LAS score (65% of obstructive vs. 9.6% and 13.8% of restrictive and other diagnoses, $p < 0.001$) and be transplanted from an outpatient setting (92.1% of obstructive vs. 73.8% and 69.8% of restrictive and other diagnoses, $p < 0.001$). Centers may be more willing to accept ABO-compatible organs to expand donor utilization and shorten wait times for this population of patients. In comparison, restrictive (55.3% identical vs. 48.7% compatible), cystic fibrosis (8.12% identical vs. 7.04% compatible), and all other diagnoses (which includes less ubiquitous diagnoses such as Kartagener's syndrome, common variable immune deficiency, or associated diagnoses such as pulmonary hypertension) (11.5% identical vs. 9.65% compatible) were more likely to undergo ABO identical matching (recipient diagnoses, $p < 0.001$). 33.1% of recipients with ABO compatible matching underwent single-lung transplantation. In contrast, 27.7% of recipients with ABO identical matching underwent single-lung transplantation (lung transplant type, $p < 0.001$, Table 1). When stratified by allocation score, the top third and middle tier scores were more likely to receive an ABO identical matching (24.0% and 50.3% in top and middle third) versus compatible (20.5% and 47% in top and middle third). The lower third of allocation scores, however, were more likely to have ABO compatible matching (32.5%) compared to ABO identical (24.0%). (LAS score, $p < 0.001$). Reviewing episodes of acute rejection, there was no significant difference found between ABO identical matching and ABO compatible matching (acute rejection, $p = 0.990$).

Based on the univariate results, we adjusted for recipient age, gender, medical condition, and disease type in the logistic regression model (Table 2). Recipients with restrictive disease and the "other" category were at an increased odds of acute rejection compared to the cystic fibrosis phenotype (Odds Ratio [OR] = 1.28, 95% Confidence Interval [CI]: 1.05–1.56), (OR 1.28, 95% CI = 1.05–1.56). Female recipients also had lower odds of acute rejection than their male counterparts (OR = 0.83, CI: 0.76–0.90). There was no significant risk of acute rejection for the recipient, regardless of medical conditions (Hospitalized-Not ICU, Intensive Care, or Not Hospitalized), when adjusting for confounders identified in the univariate analysis (Table 2).

When adjusted for age, gender, medical condition, disease category, and lung transplant type, the multivariate analysis showed no significant difference in acute rejection between the ABO identical and compatible matching (Table 2).

Overall survival

A Cox proportional hazards regression was used to further investigate the impact of covariates on 5-year survival. Five year survival is reported by the ISHLT data base as it best assesses survival immunogenicity; shorter survival, such as 1 year survival often reflects mortality from infection and acute rejection risk [2]. The factors included gender, ABO status, allocation quartile, disease category (grouped into cystic fibrosis, obstructive, restrictive, and other), and transplant type (single vs. double). The model revealed that ABO-identical matches were associated with a decreased risk of death (Hazard Ratio [HR] = 0.91, 95% CI = 0.85–0.98). Additionally, the highest age quartile of the recipient (HR = 1.48, 95% CI = 1.39–1.58) and the highest allocation score quartile (HR = 1.29, 95% CI = 1.20–1.36) were associated with an increased risk of death. Lastly, recipients with disease in the "other" category were associated with increased risk of death (HR 1.37, 95% CI = 1.25–1.49) (Table 3).

Across all patients analyzed, the Kaplan-Meier 5-year survival curve demonstrated a significant survival benefit towards ABO-identical matching compared to compatible matching ($p = 0.02$) (Figure 2).

A Kaplan-Meier survival analysis was used to compare the 5-year survival for the four different disease categories: cystic fibrosis, obstructive, restrictive, and other. The analysis revealed a significant difference in survival among the different disease groups ($p < 0.0001$). Cystic fibrosis had a significantly improved 5-year

TABLE 2 Multivariate/Adjusted analysis. Logistic regression - Relative odds of Acute rejection episode confounding for ABO status using logistic regression recipient age, recipient gender, medical condition and disease category. Identical blood type, Hospitalized not ICU and Cystic fibrosis were reference categories for analysis.

Comparison	Odds Ratio	Lower CI	Upper CI
ABO Identical vs Compatible	0.99	0.84	1.17
Intensive Care Unit (ICU) vs Not Hospitalized	1.25	1.09	1.42
Hospitalized, not ICU vs Not Hospitalized	1.11	0.95	1.28
Obstructive vs Cystic Fibrosis	1.18	0.95	1.46
Restrictive vs Cystic Fibrosis	1.21	0.99	1.48
Other vs Cystic Fibrosis	1.23	1.01	1.51
Top Quartile Allocation Score vs Middle Quartile	1.22	1.09	1.36
Bottom Quartile Allocation Score vs Middle Quartile	0.98	0.86	1.11
Single vs. Double Transplant	0.68	0.62	0.76

TABLE 3 Adjusted overall survival investigated using logistic and Cox proportional hazards regression, adjusted for sex, age, allocation quartile, and disease category.

Comparison	Hazards Ratio	Lower .95	Upper .95
ABO Identical vs Compatible	0.92	0.86	0.99
Top LAS vs Middle LAS	1.31	1.23	1.39
Bottom LAS vs Middle LAS	1.07	1.02	1.13
Obstructive vs Cystic Fibrosis	1.04	0.95	1.13
Restrictive vs Cystic Fibrosis	1	0.92	1.08
Other vs Cystic Fibrosis	1.32	1.21	1.45
Single vs. Double Transplant	0.78	0.75	0.81

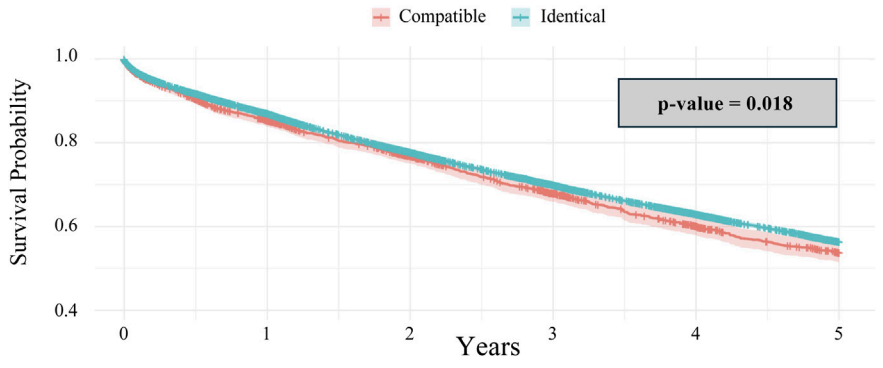


FIGURE 2
Kaplan-Meier 5-year survival analysis of ABO Compatible vs. Identical Groups.

survival, with the other categories having the worst survival outcomes (Figure 3). When assessing stratification between disease processes, only obstructive disease was found to have a significant difference in survival between ABO identical and ABO compatible groups (p = 0.038) (Figure 4). Restrictive, cystic fibrosis, and the other group did not demonstrate a significant survival difference between identical and compatible matching.

Another Kaplan-Meier survival analysis compared the 5-year survival rates of the three allocation score categories: below 1st, 1st–4th, and above 4th, with LAS scores as follows: below_1st = 0–33.74, 1st-4th = 33.75–44.95, and above_4th = 44.96–100. The analysis revealed a significant difference in survival among these three groups, with recipients in the first quartile having the highest 5-year survival rate and those in the

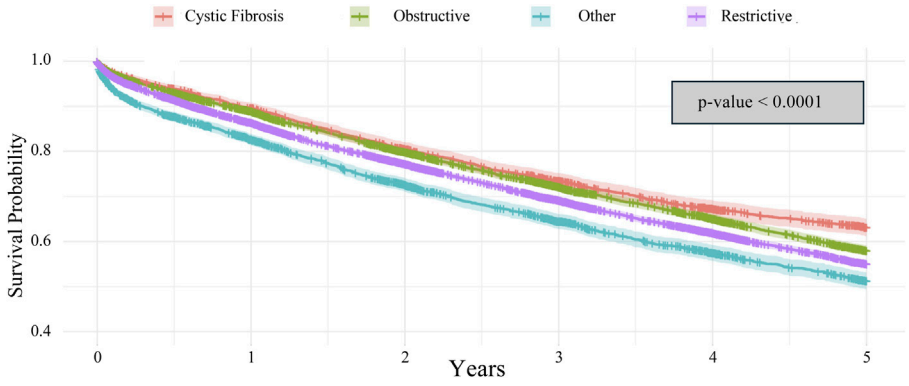
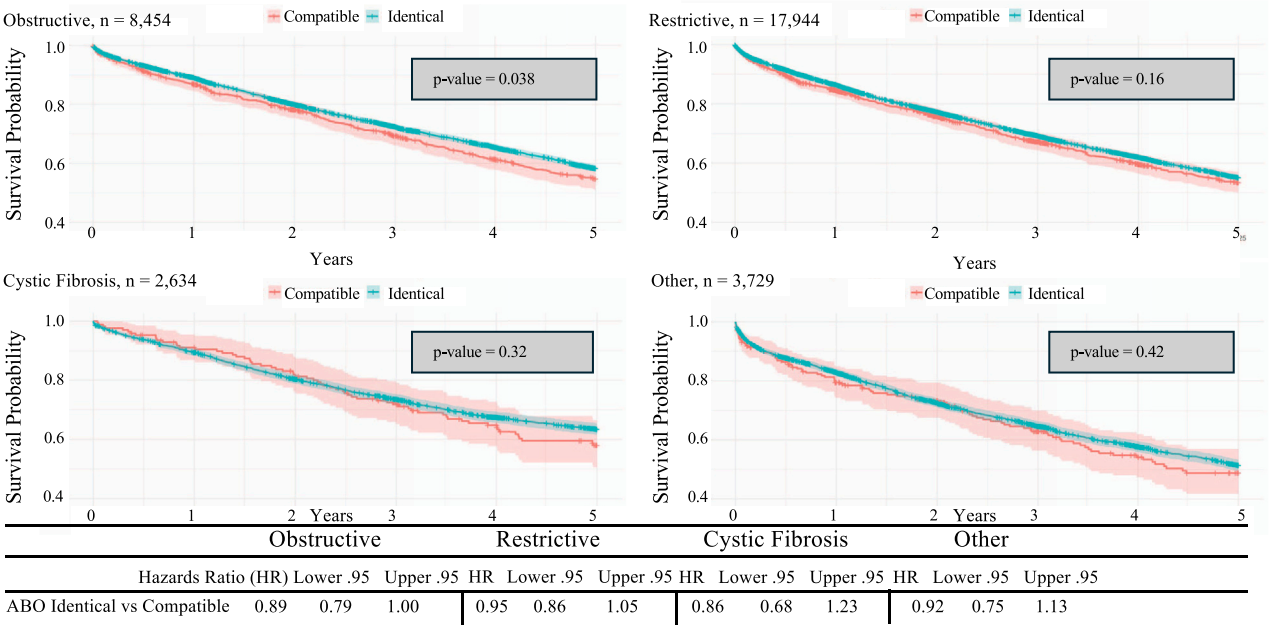


FIGURE 3
Kaplan-Meier 5-year survival analysis of lung transplant recipients characterized by lung disease.



	Obstructive			Restrictive			Cystic Fibrosis			Other		
Hazards Ratio (HR)	Lower .95	Upper .95	HR	Lower .95	Upper .95	HR	Lower .95	Upper .95	HR	Lower .95	Upper .95
ABO Identical vs Compatible	0.89	0.79	1.00	0.95	0.86	1.05	0.86	0.68	1.23	0.92	0.75	1.13

FIGURE 4
Kaplan-Meier 5-year survival analysis of lung transplant recipients categorized by ABO identical vs. compatible status receiving lung transplantation stratified by lung disease.

lowest quartile having the poorest ($p < 0.0001$) (Figure 5). When further stratified into allocation score tiers, only the top third of allocation scores demonstrated significant survival with ABO identical matching ($p = 0.014$); the middle and lowest tiers found no significant difference (Figure 6).

Lastly, when comparing single and double lung transplantation, there was a significant difference in overall survival (Figure 7) which is consistent with previously published highlighting a survival advantage in double lung transplantation [25, 26]. However, when stratified by ABO compatibility, there is no statistical difference in either the single or double lung transplantation groups, regardless of whether ABO identical or ABO compatible matching occurred (Figure 8).

Discussion

In sum, our work utilized the UNOS database to evaluate outcomes in ABO matching in lung transplantation. Two endpoints were examined: acute rejection and overall survival. Further sub-analysis was performed comparing ABO matching within recipient diagnosis, lung allocation score breakdown, and single versus double lung transplantation. After adjusting for confounding variables, our multivariate analysis demonstrated no significant risk of acute rejection when ABO compatible donors were used compared to the ABO identical group.

When comparing all lung transplants across the board, during the study period, our findings suggest improved long-term survival

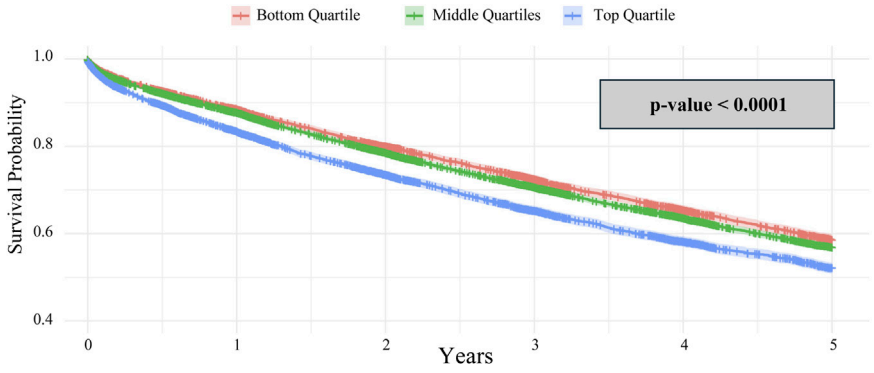
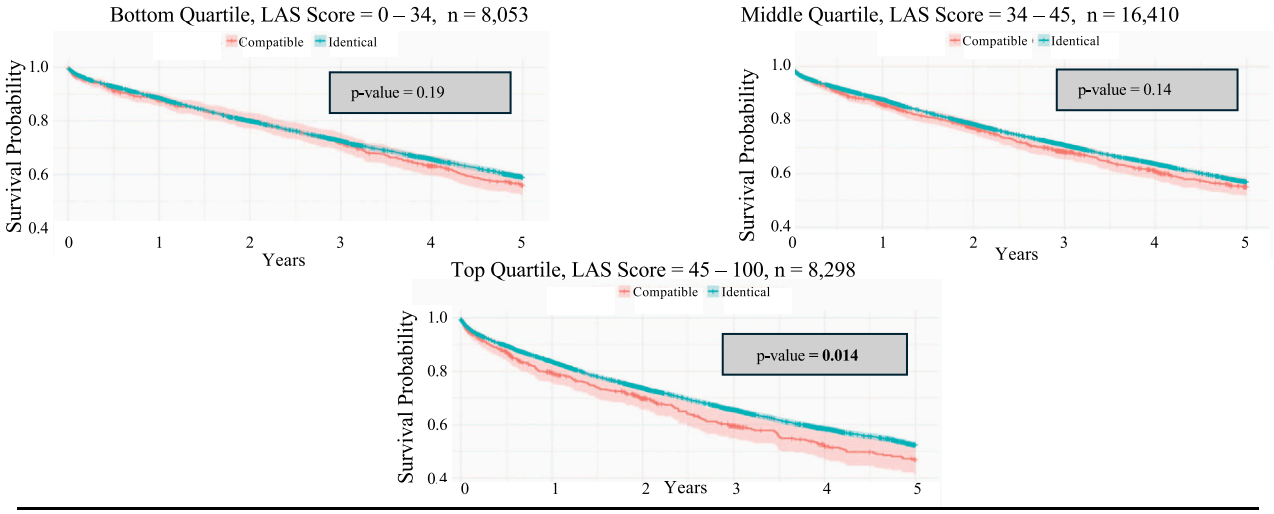


FIGURE 5
Kaplan-Meier 5-year survival analysis of lung transplant recipients categorized by lung allocation score quartile.



	Top Quartile			Middle Quartile			Bottom Quartile		
Hazards Ratio (HR)	Lower .95	Upper .95		HR	Lower .95	Upper .95	HR	Lower .95	Upper .95
ABO Identical vs Compatible	0.86	0.75	1.00	0.93	0.84	1.03	0.93	0.83	1.05

FIGURE 6
Kaplan-Meier 5-year survival analysis of lung transplant recipients categorized by lung allocation score quartile and stratified by ABO identical vs. compatible status.

with ABO identical lung transplants. However, it was found that ABO compatible donors were significantly more likely to undergo a single lung transplant than a double lung transplant. A double lung transplant is widely known to have improved long-term survival compared to a single lung transplant [25]. When the survival data were analyzed after stratifying for transplant type, double versus single, no significant long-term survival difference was found between ABO compatible and ABO identical lung transplant recipients.

We evaluated the long-term survival of ABO compatible versus ABO identical lung transplantation based on recipient diagnosis: obstructive, restrictive, cystic fibrosis, and a fourth category, which included less ubiquitous diagnoses such as Kartagener's syndrome, common variable immune deficiency, or associated diagnoses such as pulmonary hypertension. We found no significant difference in overall survival in all diagnostic categories except for obstructive disease. Obstructive lung disease is the only diagnosis found to be associated with better survival with ABO-identical transplantation. The biological basis for decreased survival with ABO compatible remains unclear and warrants further investigation considering our findings reflect those of an observational study with retrospective analysis of the database. Based on this, it can be inferred that for other disease categories, ABO-compatible transplantation is a viable option with favorable long-term outcomes.

We then stratified the data by allocation score, dividing it into three parts: the lowest, middle, and top tiers. It was found that only the top tier, with the highest allocation scores, showed statistically significant differences between ABO-identical and ABO-compatible

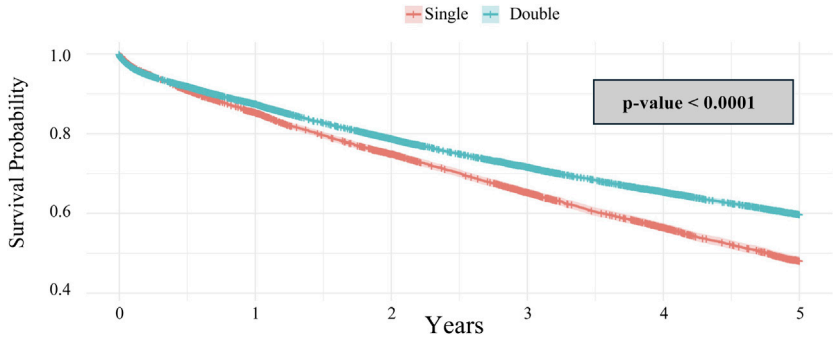
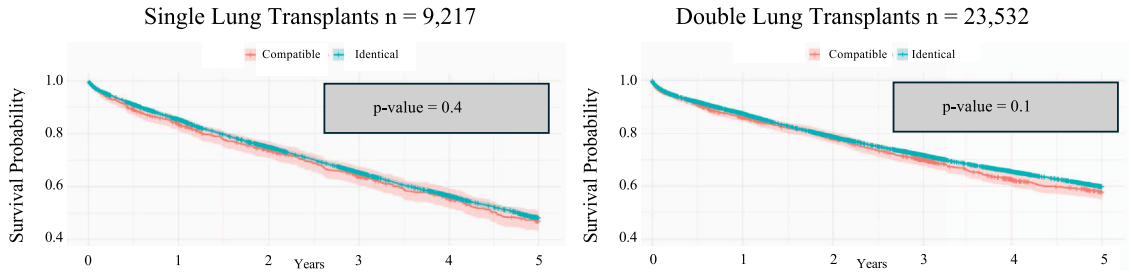


FIGURE 7
Kaplan-Meier 5-year survival analysis of lung transplant recipients categorized by single or double lung transplantation.



	Single Lung Transplant			Double Lung Transplant		
	Hazards Ratio	Lower .95	Upper .95	Hazards Ratio	Lower .95	Upper .95
ABO Identical vs Compatible	0.93	0.84	1.04	0.92	0.84	1.01

FIGURE 8
Kaplan-Meier 5-year survival analysis of lung transplant recipients categorized by ABO identical vs. compatible status receiving lung transplantation stratified by single or double lung transplantation.

transplantation in terms of overall survival. All other allocation scores showed no significant differences in survival; therefore, an ABO-compatible transplant is a reasonable option.

Chronic rejection is a major driver of reduced long-term survival after lung transplant [27, 28]. Given that immunogenicity drives risk for rejection and consequent mortality, the primary outcome of acute rejection is a useful proxy for understanding the role of ABO-compatible and ABO-identical blood typing. Fewer HLA mismatches, particularly class I, have been shown to significantly decrease the rate of chronic rejection and the development of bronchiolitis obliterans, thus influencing survival [29]. This effect has been demonstrated in the lab as well as in humans. Donor-specific anti-HLA antibodies appear to correlate with elevated defensin levels, which promote sustained inflammation and epithelial proliferation, leading to chronic rejection [30]. Class II HLA mismatching predisposes the recipient to acute rejection [29, 31]. HLA matching chronic rejection is further demonstrated in areas of the world where lobar lung transplantation is performed. Living-donor lobar lung transplant recipients appear to have immunological advantages, such as a reduced incidence and delayed onset of chronic rejection, as well as fewer *de novo* donor-specific antibodies, which may translate to improved outcomes [32]. The immunological benefits are potentially owing to HLA similarities due to blood-related donors [32]. The alloimmune response after transplant clearly plays an important role in the development of rejection and therefore significantly affects graft function both in the short and long term. Our primary analyses were limited to acute rejection events captured in the registry and all-cause long-term survival, and we were not able to assess HLA mismatch burden or clinician-diagnosed chronic rejection. An area for future study will be to test the effect of HLA mismatching in ABO-identical and compatible transplants on long-term survival in datasets that include detailed HLA typing endpoints.

We find that ABO compatible lung transplantation of both single and double lungs does not increase the risk of acute rejection. Given that single lung transplant recipients may begin at an immunological disadvantage, our findings may further support

the usage of ABO compatible lung allocation as opposed to strictly ABO identical matching. Additional research is needed to examine the development of chronic rejection and its effect on long-term survival in the context of ABO compatible lung transplantation. Going one step further, ABO compatibility in lung transplantation remains in an evolutionary phase, as successful ABO-incompatible living-donor lobar lung transplantation has been reported [33].

While our findings indicate that ABO compatibility does not significantly influence acute rejection rates, it is associated with differences in survival outcomes among patients receiving a lung transplant for obstructive lung disease and for patients in the highest quartile of lung allocation scores. However, this effect was modest. This may be due to residual confounding in patients with obstructive disease and high LAS, or differential biological vulnerability to immune-mediated injury in high-risk phenotypes, such as due to passenger lymphocyte syndrome [34]. When considering factors for matching recipients and donors, results from this study underscore the importance of considering disease-specific and allocation score factors when evaluating the need for ABO identical matching. Based on our analysis, identical matching is not required for most lung transplant cases, which could shorten a patient's waitlist time and increase the number of donor lungs available for transplantation [6].

The advent of *ex vivo* lung perfusion (EVLP) has shown tremendous promise in the field of lung transplantation, particularly in evaluating marginally acceptable organs for pre-treatment and improving organ quality [35]. An area of future direction related to the topic of this article is the possibility of converting a type A organ to type O, thereby creating a universal donor through enzymatic pre-treatment of donor lungs using EVLP [26, 35–37]. More research is needed with this novel technology, which could markedly increase ABO-compatible organs to broaden the donor pool.

These results should be evaluated in consideration of several limitations. At the same time, adjusted models accounted for several confounders, such as ABO status, recipient age, gender, medical condition, and disease classification, as an observational study can still introduce bias due to confounding. One limitation is that CLAD is a major determinant of late mortality after lung transplantation. However, CLAD is not available in a standardized form in the UNOS dataset we analyzed [38]. We therefore used acute rejection and 5-year survival as complementary endpoints. Another limitation is that our acute rejection endpoint is not time-to-event and may be affected by early death, because time-to-first acute rejection was not available in a consistent timestamped manner in our dataset. In addition, a further limitation of this study is its retrospective design, which spans from 2005 to 2023. Although the analysis spanning almost two decades may be considered a strength, variations in documentation and technology could inherently introduce several potential biases in the data set, such as evolving diagnostic and reporting standards, advancements in transplant care, and LAS implementation since its first implementation in May of 2005, in alignment with this study's starting point. Since the conclusion of our study period, the LAS scoring system has been replaced by continuous allocation scoring; therefore, the findings may not be directly applicable to today's lung transplant patients. Following the implementation of continuous distribution for lung allocation in the United States, we observed a significant increase in ABO-compatible transplants–doubling from 14% to 28% of annual lung transplants. The principle from our study would still be relevant, that while we believe there is a role for ABO compatible lung matching, the sickest patients may benefit from ABO identical organs.

These findings underscore the importance of considering both disease-specific factors and allocation scoring when assessing the potential benefits of ABO-matching. While identical matching may be modestly associated with a survival advantage in specific high-risk subgroups, our results support the broader use of ABO-compatible organs, which could reduce waitlist times and expand access to transplantation without increasing the risk of acute rejection while also selecting for the best candidates for compatible matching.

Conclusion

ABO compatible lung transplants can safely be performed as there is no significant difference in acute rejection, provides a larger pool of donors, and increases access to lung transplantation. Caution needs to be taken with specific subsets of recipients, such as those in the top LAS quartile, due to their higher 5-year survival with ABO identical matching.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

HB, GD, SS, KL, and SG were responsible for conceptualization with study design, data extraction, statistical analysis, figure generation, and manuscript preparation with HB serving as the first author. ST and KL led the implementation of proper statistics and programming, JB, K-CT, ST, and KL contributed to coding, data processing, and implementation of statistical analyses. GD and SG were responsible for data cleaning, study design and implementation. KL, CC and TS assisted in drafting and editing the manuscript and making figures. DL, HS, DG, AM, and SS provided expert clinical guidance, validated the interpretation of transplant-related variables, and contributed to the critical revision of the manuscript for scientific accuracy and coherence. All authors participated in discussions of study findings, reviewed the final manuscript, and approved its submission. Each author agrees to be accountable for all aspects of the work and to ensure that any questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The authors(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2026.15722/full#supplementary-material

References

1. Singh TP, Hsich E, Cherikh WS, Perch M, Hayes D, Jr, Lewis A, et al. The international thoracic organ transplant registry of the international society for heart and lung transplantation: 2025 annual report of heart and lung transplantation. *J Heart Lung Transpl* (2025) 44:1857–73. doi:10.1016/j.healun.2025.04.014

2. ISHLT. *ISHLT_Fast-Facts.pdf*. Addison, Texas: International Society for Heart and Lung Transplantation (2025). Available online at: https://www.ishlt.org/docs/default-source/default-document-library/ishlt_fast-facts.pdf? (Accessed January 5, 2026).

3. Valapour M, Lehr CJ, Schladt DP, Swanner K, Poff K, Handarova D, et al. *OPTN/SRTR 2023 annual data report: lung* (2023). 1600–6143.

4. Yang Z, Bai YZ, Yan Y, Hachem RR, Witt CA, Vazquez Guillamet R, et al. *Validation of a novel donor lung scoring system based on the updated lung composite allocation score* (2025). 1600–6143.

5. OPTN. *Guide_To_Calculating_Lung_Composite_Allocation_Score.pdf*. OPTN Lung Committee deliberations (2022).

6. Fakhro M, Larsson H, Malmsjo M, Algotsson L, Lindstedt S. ABO-identical matching has no superiority in long-term survival in comparison to ABO-compatible matching in lung transplantation. *J Cardiothorac Surg* (2019) 14(1):24. doi:10.1186/s13019-019-0846-6

7. Snell GI, Holmes M, Levvey BJ, Shipp A, Robertson C, Westall GP, et al. *Lessons and insights from ABO-incompatible lung transplantation* (2013). 1600–6143.

8. Taghavi S, Jayarajan SN, Furuya Y, Komaroff E, Shiose A, Leotta E, et al. Examining ABO compatible donors in double lung transplants during the era of lung allocation score. (2014). 1552–6259.

9. Taghavi S, Jayarajan SN, Furuya Y, Komaroff E, Shiose A, Leotta E, et al. *Single-lung transplantation with ABO-compatible donors results in excellent outcomes* (2014). 1557–3117.

10. Chen-Yoshikawa TF. ABO blood type incompatible lung transplantation. *J Thorac Dis* (2023) 15(6):3437–42. doi:10.21037/jtd-23-48

11. Salerno CT, Burdine J, Perry EH, Kshettry VR, Hertz MI, Bolman RMI. Donor-derived antibodies and hemolysis after abo-compatible but nonidentical heart-lung and lung transplantation1. *Transplantation* (1998) 65(2):261–4. doi:10.1097/00007890-199801270-00021

12. Pavlisko EN, Neely ML, Kopetskie H, Hwang DM, Farver CF, Wallace WD, et al. Prognostic implications of and clinical risk factors for acute lung injury and organizing pneumonia after lung transplantation: data from a multicenter prospective cohort study. *Am J Transpl* (2022) 22(12):3002–11. doi:10.1111/ajt.17183

13. UNOS. New lung allocation policy in effect (2025). Available online at: https://unos.org/news/new-lung-allocation-policy-in-effect/#:~:text=,five%20points (Accessed January 2, 2026).

14. dplyr. *A grammar of data manipulation* (2025).

15. Subirana ISH, Vila J. Building bivariate tables: the compare Groups package for R. *J Stat Softw* (2014). doi:10.18637/jss.v057.i12

16. Kassambara AKM, Biecek P, Pabian S. Survminer: drawing survival curves using "ggplot2.". (2024). Available online at: https://cran.r-project.org/web/packages/survminer/index.html (Accessed December 20, 2025).

17. *Create elegant data visualisations using the grammar of graphics*. (2025). Available online at: https://ggplot2.tidyverse.org/ (Accessed December 21, 2025).

18. Wickham H, Averick M, Bryan J, Chang W, McGowan LDA, François R, et al. Welcome to the tidyverse. *J Open Source Softw* (2019). doi:10.21105/joss.01686

19. *Read excel files*. (2025). Available online at: https://readxl.tidyverse.org/ (Accessed December 30, 2025).

20. Storry JR, Olsson ML. *The ABO blood group system revisited: a review and update* (2009). 0894–203X.

21. Usmani A, Morris GP, Murphey C. *The increasing need for ABO blood group genotyping and quality assurance implications for laboratory implementation* (2024). p. 1879–166.

22. Chen-Yoshikawa TF. *ABO blood type incompatible lung transplantation* (2023). 2072–1439.

23. Pierson RN, 3rd, Loyd JE, Goodwin A, Majors D, Dummer JS, Mohacsi P, et al. Successful management of an ABO-mismatched lung allograft using antigen-specific immunoadsorption, complement inhibition, and immunomodulatory therapy. Addison, Texas: International Society for Heart and Lung Transplantation (2002). 79–84.

24. Banner NR, Rose ML, Cummins D, De Silva M, Pottle A, Lyster H, et al. Management of an ABO-Incompatible lung transplant. *Am J Transplant* (2004) 4(7):1192–6. doi:10.1111/j.1600-6143.2004.00438.x

25. Subramanian MP, Meyers BF. *Bilateral versus single lung transplantation: are two lungs better than one? 2018* (2025). 2072–1439.

26. Weingarten N, Mehta AC, Budev M, Ahmad U, Yun J, McCurry K, et al. *Single vs double lung transplantation in older adults: a propensity-matched analysis* (2025). p. 1931–3543.

27. Bos S, Vos R, Van Raemdonck DE, Verleden GM. *Survival in adult lung transplantation: where are we in 2020?* (2020). 1531–7013.

28. Van Herck A, Verleden SE, Vanaudenaerde BM, Verleden GM, Vos R. *Prevention of chronic rejection after lung transplantation* (2017). 2072–1439.

29. Peltz M, Edwards LB, Jessen ME, Torres F, Meyer DM, et al. *HLA mismatches influence lung transplant recipient survival, bronchiolitis obliterans and rejection: implications for donor lung allocation* (2011). 1557–3117.

30. Saini D, Angaswamy N, Tiriveedhi V, Fukami N, Fukami N, Ramachandran S, Hachem R, et al. *Synergistic effect of antibodies to human leukocyte antigens and defensins in pathogenesis of bronchiolitis obliterans syndrome after human lung transplantation* (2010). 1557–3117.

31. Renaud-Picard B, Koutsokera A, Cabanero M, Martinu T. Acute rejection in the modern lung transplant era. *Semin Respir Crit Care Med* (2021) 42(03):411–27. doi:10.1055/s-0041-1729542

32. Nakajima D, Date H. Living-donor lobar lung transplantation. *J Thorac Dis* (2021) 13(11):6594–601. doi:10.21037/jtd-2021-07

33. Nakajima D, Yuasa I, Kayawake H, Tanaka S, Yamada Y, Yutaka Y, et al. *The first successful case of ABO-incompatible living-donor lobar lung transplantation following desensitization therapy* (2023). p. 1600–6143.

34. Kohl MM, Schwarz S, Jaksch P, Muraközy G, Kurz M, Schönbacher M, et al. High rate of passenger lymphocyte syndrome after ABO minor incompatible lung transplantation. *Am J Respir Crit Care Med* (2024) 209(8):995–1000. doi:10.1164/rccm.202306-1107OC

35. Wang AA-O, Ribeiro RA-O, Ali AA-O, et al. Ex vivo *enzymatic treatment converts blood type A donor lungs into universal blood type lungs. 2022* (2023). p. 1946–6242.

36. Noda K, Furukawa M, Chan EG, Sanchez PG. Expanding donor options for lung transplant: extended criteria, donation after circulatory death, ABO incompatibility, and evolution of *Ex Vivo* lung perfusion. *Transplantation* (2023) 107(7):1440–51. doi:10.1097/tp.0000000000004480

37. Thabut G, Mal H. Outcomes after lung transplantation. *J Thorac Dis* (2017) 9(8):2684–91. doi:10.21037/jtd.2017.07.85

38. Todd JL, Weigt SS, Neely ML, Grau-Sepulveda MV, Mason K, Sever ML, et al. Prognosis and risks for probable chronic lung allograft dysfunction: a prospective multicenter study. *Am J Respir Crit Care Med* (2025) 211(2):239–47. doi:10.1164/rccm.202403-0568OC

ESOT | Transplant International

TYPE Original Research
PUBLISHED 29 May 2026
DOI 10.3389/ti.2026.16293

Check for updates

OPEN ACCESS

*CORRESPONDENCE
Bart M. Vanaudenaerde,
bart.vanaudenaerde@kuleuven.be

†These authors have contributed equally to this work

RECEIVED 23 January 2026
REVISED 18 April 2026
ACCEPTED 01 May 2026
PUBLISHED 29 May 2026

CITATION
Kaes J, Hooft C, Jin X, Heigl T, Liu H, Pollenus E, Prenen F, Beeckmans H, Kerckhof P, Vanstapel A, Van Slambrouck J, Mercurio M, Zapata-Ortega M, Aerts G, Geudens V, Vermaut A, Vanvuchelen L, Somers A, Verbeylen L, Vanluyten C, Barbarossa A, Mohamady Y, Özsoy B, Zajacova A, Tielemans B, Yildirim AO, Bos S, De Sadeleer L, Godinas L, Rojas Quintero J, Polverino F, Van den Steen PE, Ceulemans LJ, Vos R and Vanaudenaerde BM (2026) Blood vessels as primary site of rejection in murine lung transplantation. *Transpl. Int.* 39:16293. doi: 10.3389/ti.2026.16293

COPYRIGHT
© 2026 Kaes, Hooft, Jin, Heigl, Liu, Pollenus, Prenen, Beeckmans, Kerckhof, Vanstapel, Van Slambrouck, Mercurio, Zapata-Ortega, Aerts, Geudens, Vermaut, Vanvuchelen, Somers, Verbeylen, Vanluyten, Barbarossa, Mohamady, Özsoy, Zajacova, Tielemans, Yildirim, Bos, De Sadeleer, Godinas, Rojas Quintero, Polverino, Van den Steen, Ceulemans, Vos and Vanaudenaerde. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

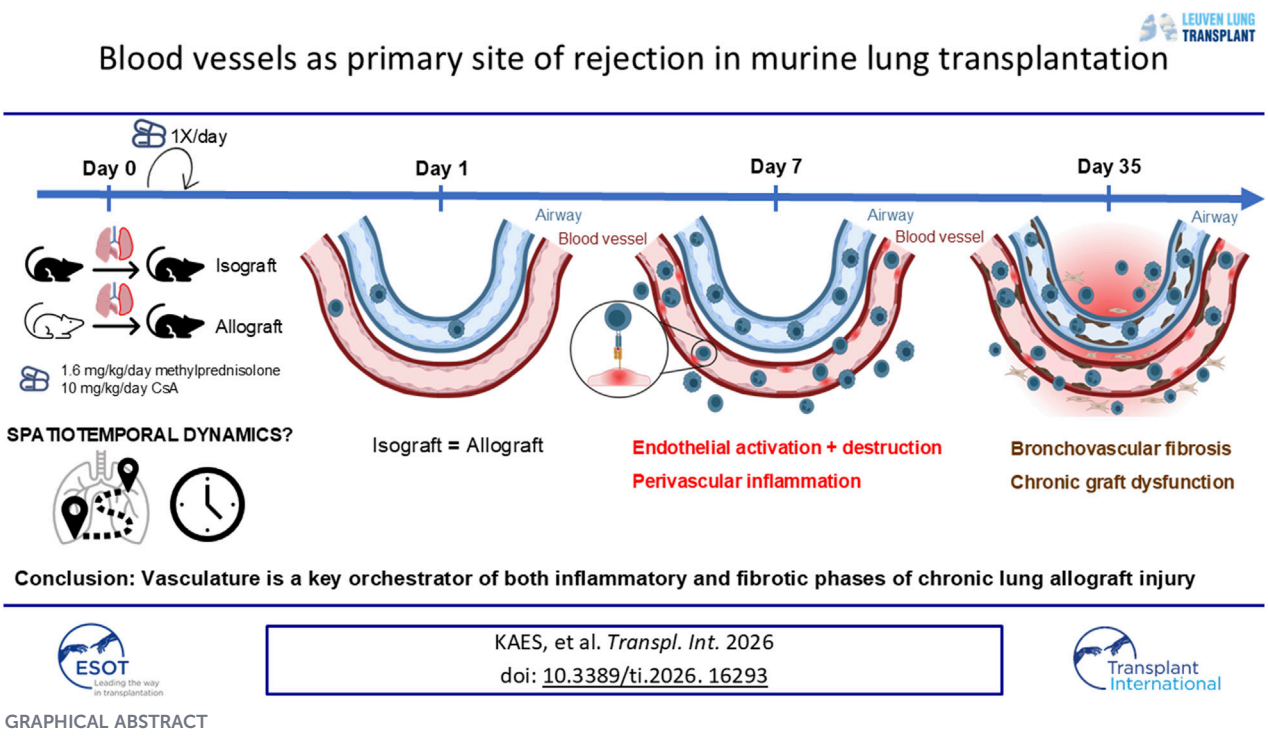
Blood vessels as primary site of rejection in murine lung transplantation

Janne Kaes [1‡], Charlotte Hooft [1‡], Xin Jin [1], Tobias Heigl [1], Hengshuo Liu[2], Emilie Pollenus [3], Fran Prenen [3], Hanne Beeckmans [1], Pieterjan Kerckhof [1], Arno Vanstapel [4], Jan Van Slambrouck [1,5], Martina Mercurio [1], Marta Zapata-Ortega [1], Gitte Aerts [1], Vincent Geudens [1], Astrid Vermaut [1], Lise Vanvuchelen [1], Anse Somers [1], Lara Verbeylen [1], Cedric Vanluyten [1,5], Annalisa Barbarossa [1,5], Yousry Mohamady [1], Balin Özsoy [1], Andrea Zajacova [1,6], Birger Tielemans [1], Ali Onder Yildirim [2], Saskia Bos [1,6], Laurens De Sadeleer [1,6], Laurent Godinas [1,6], Joselyn Rojas Quintero [7], Francesca Polverino [7], Philippe E. Van den Steen [3], Laurens J. Ceulemans [1,5], Robin Vos [1,6] and Bart M. Vanaudenaerde [1*]

[1]Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), KU Leuven, Leuven, Belgium, [2]Institute of Lung Health and Immunity (LHI), Helmholtz Institute, Munich, Germany, [3]Laboratory of Immunoparasitology, Department of Microbiology, Immunology and Transplantation, Rega Institute for Medical Research, KU Leuven, Leuven, Belgium, [4]Translational Cell and Tissue Research, KU Leuven and UZ Gasthuisberg, Leuven, Belgium, [5]Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium, [6]Department of Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium, [7]Pulmonary and Critical Care, Department of Medicine, Baylor College of Medicine, Houston, TX, United States

Survival after lung transplantation lags that of other solid organ transplants. Long-term survival is hampered primarily due to chronic lung allograft dysfunction (CLAD) development. It remains elusive how (chronic) rejection is organized within the lung graft over time post-transplant. Using a model of orthotopic left lung transplantation in major mismatched mouse strains with daily immunosuppression, we aimed to study the spatiotemporal dynamics of (chronic) rejection, using micro-computed tomography imaging, flow cytometric analyses and spatial proteomics. Endothelial cells demonstrated early activation and destruction (day 7 post-transplant). The accompanying early inflammation at the vascular compartment, progressed towards aberrant tissue repair resulting in irreversible bronchovascular fibrosis and chronic graft dysfunction. We provide new insights in the spatiotemporal dynamics of (chronic) rejection with a vascular-oriented onset that may have future implications for diagnosis and treatment in clinical lung transplantation.

KEYWORDS
blood vessels, chronic lung allograft dysfunction (CLAD), chronic rejection, flow cytometry, lung transplantation, murine orthotopic left lung transplantation, spatial proteomics



Introduction

Lung transplantation is the only curative treatment for end-stage lung diseases. Despite advances in donor selection, surgical techniques, and immunosuppressive strategies, survival after lung transplantation lags that of other solid organ transplants with a median survival of only 6 years post-transplantation [1–3]. Beyond the first post-transplant year, survival is predominantly limited by the development of chronic lung allograft dysfunction (CLAD) [1, 4, 5]. CLAD is clinically defined by an irreversible decline in lung function and represents an umbrella term encompassing heterogeneous pathological processes. It is not exclusively defined by rejection, but rather as a broad term for irreversible loss of lung function. Three clinical phenotypes of CLAD are currently recognized, including, 'bronchiolitis obliterans syndrome' (BOS), 'restrictive allograft syndrome' (RAS) and a mixed phenotype [6]. These phenotypes reflect the complexity of CLAD from a clinical point of view. Importantly, this CLAD definition does not provide insights into the underlying drivers of graft injury [1, 5]. CLAD has historically been conceptualized as a predominantly airway-centered disease, with clinical and research efforts largely focused on bronchiolar pathology [7–9]. However, this airway-centric view contrasts with established paradigms of vascular chronic rejection that is well characterized in other solid organ transplants, where chronic rejection has been perceived as a vessel-centered process in which persistent immunological and endothelial activation induces thrombosis, intimal proliferation, and vascular remodeling act as hallmarks of chronic allograft vasculopathy [10–12].

The apparent disconnect between lung transplantation and other solid organs is therefore striking, particularly given the shared immunological principles governing allograft rejection. Considering transplant rejection can be described as an immune-mediated recognition of the donor graft HLA antigens as 'non-self', where both cellular and humoral mechanisms of the innate and adaptive immune system get involved [13].

So, despite vascular chronic rejection being well characterized in other transplanted organs and some studies within the field of lung transplantation reporting perivascular inflammation histologically, its central role and the temporal and spatial relationships between vascular injury and graft dysfunction have never been investigated in the context of lung transplantation, and direct evidence in human lung allografts remains limited [9, 11, 12, 14]. This conceptual gap has contributed to an incomplete understanding of chronic lung allograft injury and may partially explain the lack of effective targeted therapies [1, 15, 16].

Importantly, the traditional dichotomous classification of rejection into "acute" and "chronic" forms complicates interpretation. In clinical practice, rejection cannot be regarded as a binary or purely temporal process. Lung transplant recipients may experience chronically ongoing antibody-mediated rejection, recurrent or persistent episodes of acute rejection, or overlapping immunopathological processes resulting in chronic graft injury [17]. Distinguishing "chronic" rejection as a pathophysiological mechanism from chronically ongoing forms of "acute" rejection is therefore essential [12, 18–20]. Controlled experimental models may act as a valuable tool to obtain essential and fundamental information on the spatiotemporal dynamics of vascular involvement in (chronic) rejection [21–24].

Building on these observations, we hypothesize that (chronic) rejection in lung transplantation may originate in the vascular compartment with a significant role for endothelial cells. We aim to map the temporal and spatial progression of vascular pathology in

a murine lung transplant model to understand how vascular injury contributes to chronic graft dysfunction. We will use our murine model of rejection after orthotopic left lung transplantation and use advanced methodologies including multicolor flow cytometry, *in vivo* and *ex vivo* μCT imaging and spatial proteomics.

Materials and methods

Orthotopic mouse left lung transplantation and study design

Mice (male) were purchased from Janvier Labs (Le Genest-Saint-Isle, France) and transplanted between eight to 10 weeks of age. Recipients were C57BL/6N (H-2K^b) and donors were either C57BL/6N (H-2K^b) for isograft transplantation or BalbC (H-2K^d) for allograft transplantation. Serial sacrifice was performed at three different time points, on post-operative day 1, 7 and 35. All mice were housed in a conventional facility with individually ventilated cages (IVC) and received *ad libitum* standard chow and water. Orthotopic left lung transplantation was performed as previously described [22, 25, 26]. After surgery, mice were allowed to recover on a heating pad overnight and received buprenorphine for the following 72 h. Both isografts and allografts received daily subcutaneous immunosuppression consisting of 10 mg/kg/day cyclosporine (Sandimmun®, Novartis, Vilvoorde, Belgium) and 1.6 mg/kg/day methylprednisolone (SoluMedrol®, Pfizer, Brussels, Belgium) started immediately after transplantation. The specifics of the study design are illustrated in Figure 1A. The experimental procedure was approved by the Ethical Committee for Animal Research at KU Leuven (P194/2019). To determine leukocyte and endothelial cell numbers and activation, flow cytometry was performed on the entire left lung graft at the three timepoints (n = 5–6/group/timepoint). Longitudinal, non-terminal *in vivo* μCT imaging was performed on day 1, 7 and 35 in the grafts (n = 6/group) of the flow cytometry experiment sacrificed day 35. Terminal exsanguination with retro-orbital blood collection was performed, prior to sacrifice for measuring the cyclosporine A trough level by an immunoassay (Dimension® RXL, Siemens Medical solutions, Diamond diagnostics, USA) (Supplementary Figure S1). The experiment with isografts and allografts was repeated for histological analyses (n = 4–5/group/timepoint). At the time of sacrifice, lungs were perfused with saline and inflated, followed by perfusion with 4% PFA at 4 °C for 24 h. The grafts were subsequently embedded in paraffine and processed into 4 μm thick sections which were stained with Hematoxylin-Eosin and Masson's trichrome. Images were taken with an Olympus BX61 microscope. The percentage of collagen in a stained lung section with Masson's trichrome was quantified using QuPath 0.3.2 with a personalized Pixel Classifier created with the 'Train Pixel Classifier' tool.

Flow cytometric analysis to quantify leukocyte and endothelial cell numbers and activation

At time of autopsy, the transplanted lung was removed and cells were isolated as previously described [27]. The lung was extracted and collected in RPMI buffer [RPMI GlutaMAX/FCS (5%)/ 1% penicillin/streptomycin/ 0.1% beta-mercaptoethanol], minced and incubated for 30 min at 37 °C in digestion medium consisting of 2 mg/mL collagenase D and 0.1 mg/mL DNase I in RPMI buffer. Subsequently, lung tissue was homogenized using a 20-gauge needle and new digestion medium was added, followed by a second incubation period of 15 min at 37 °C. Cells were washed and red blood cell lysed using 0.83% NH_4Cl/10 mM Tris at 37 °C and passed through a 70 μm nylon cell strainer. After a last washing step, live leukocytes were counted in a Bürker chamber with trypan-blue staining.

For the flow cytometry 1.5-3 million lung cells were used. Cells were incubated with a viability dye, Zombie Aqua (Biolegend, San Diego, CA, USA) or Zombie UV (Biolegend), together with Mouse Fc block (MACS Miltenyi Biotec.) for 15 min at room temperature. After washing twice, cells were stained with a panel of monoclonal antibodies (Supplementary Table S1) dissolved in Brilliant stain buffer (BD Biosciences, Erembodegem, Belgium) for 20 min at 4 °C. After surface staining, 100,000 or 200,000 live single cells were analyzed per sample with a BD LSR Fortessa Flow cytometer (BD Biosciences). The flow cytometric panels used allow to quantify viable cells, leukocytes, endothelial cells numbers and activation status (Supplementary Table S1). For the activation status we used MHC1/2 (central for T cell activation), adhesion molecules ICAM-1 (present on leukocytes and endothelial cells) and VCAM-1 (present on endothelial cells). Data were analyzed with FlowJo v10 software (FlowJo LLC, Ashland, OR, USA) and cells were gated according to predefined gating strategies (Supplementary Figure S2). The absolute number of leukocytes and endothelial cells were calculated by the percentage of CD45$^+$ and CD45$^-$ CD31$^+$ cells, respectively, among the live cells multiplied by the total number of live cells determined with the Bürker chamber.

In vivo and *ex vivo* μCT imaging to identify and locate rejection

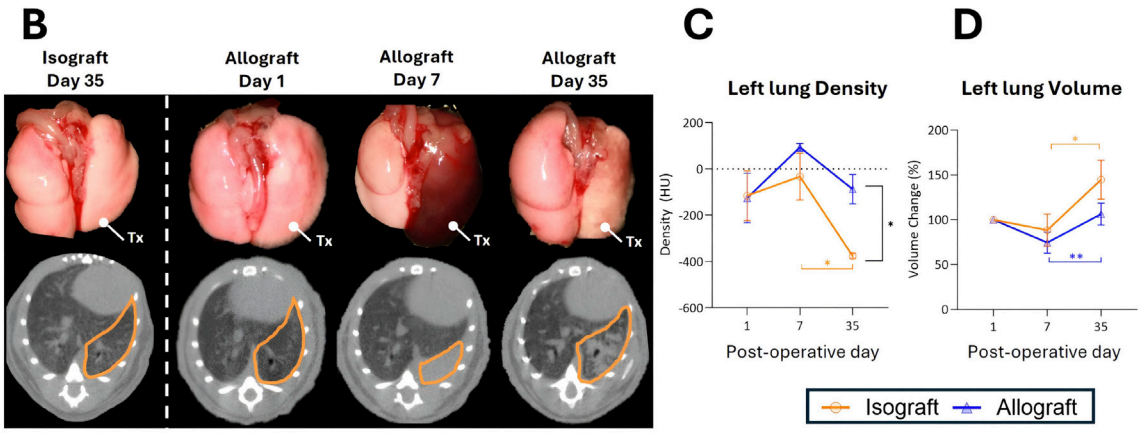
For *in vivo* μCT imaging free-breathing mice were scanned with a whole-body small animal μCT scanner (SkyScan 1278, Bruker μCT, Kontich, Belgium). Animals were anesthetized with isoflurane (2% in pure oxygen) and placed in supine position. Following scan parameters were used: 50 kVp X-ray source, 350 μA current, 1 mm aluminum X-ray filter and 150 ms exposure time per projection acquiring projections with 0.9° increments over a total angle of 220°. Acquisition resulted in a respiratory-weighted reconstructed 3D dataset with an isotropic voxel size of 50 μm in a total scan time of 3 min, associated with a radiation dose exposure of 69–89 mGy [28]. The images were reconstructed with the following parameters: smoothing of one, beam-hardening correction of 10%, post-alignment and ring artefact reduction were optimally set for each individual scan. Images were processed and calibrated to Hounsfield units (HU) as described before [29]. Image reconstruction, analysis and quantification were performed using NRecon, DataViewer and CTAn software provided by the manufacturer. Quantification of total lung volume and mean lung density was performed for a manually delineated region of interest (ROI), resulting in a volume of interest (VOI) on the transversal μCT images at end-expiration.

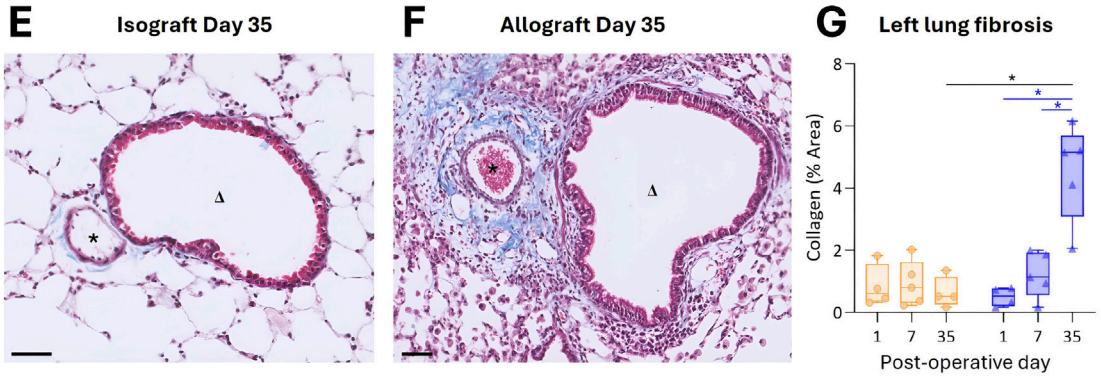
For *ex vivo* μCT imaging separate transplant allograft, isograft and non-transplant control mice were used (Figure 1A). The lungs were fixated as previously described and chemically dehydrated in a graded series of ethanol concentrations followed by hexamethyldisilazane

10.3389/ti.2026.16293

A

	Isograft			Allograft			Control	
Post-operative time point	Day 1	Day 7	Day 35	Day 1	Day 7	Day 35	C57BL/6	BalbC
Flow cytometry + *in vivo* microCT*	n=5	n=6	n=6*	n=6	n=6	n=6*	n=0	n=0
Histology — Histological analyses	n=4	n=5	n=4	n=4	n=5	n=5	n=2	n=2
Histology — *Spatial Proteomics*	*1*	*1*	*1*	*3*	*3*	*3*	*0*	*0*
Ex vivo microCT	n=2	n=3	n=0	n=2	n=2	n=2	n=2	n=2





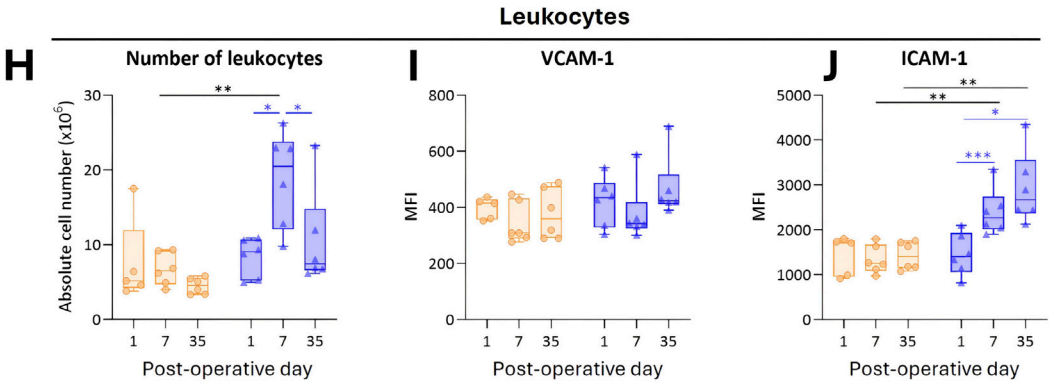


FIGURE 1
Study design and standard elements of the murine orthotopic left lung transplantation. **(A)** Orthotopic left lung transplantation was performed to create isografts (C57BL/6 NRj in C57BL/6 NRj) and allografts (Balb/cJRj in C57BL/6 NRj). *In vivo* μCT was performed on the same groups of mice used for flow cytometry sacrificed on day 35. Animals used for histology were also used to perform spatial proteomics. **(B)** Representative macroscopic pictures of lung blocs with the corresponding μCT images. The left transplanted lung is indicated with Tx and delineated in yellow on μCT sections. **(C)** Mean lung density difference in left transplanted lung, calculated from end-expiratory μCT images. Mean is shown with error bars indicating SEM. **(D)** Evolution of total lung volume of left transplanted lung with relative change compared to the measurement of day one. Volumes were calculated based on end-

(*Continued*)

FIGURE 1 (Continued)
expiratory μCT images. Data is expressed as mean with SEM. **(E,F)** Masson's trichrome images of isograft and allograft on day 35 after transplantation, collagen deposition is indicated in blue. Scale indicates 50 μm; * = blood vessel; Δ = airway. **(G)** Collagen staining intensity was quantitatively calculated in tissue sections stained with Masson's trichrome using QuPath software. **(H)** Flow cytometry was used to determine absolute numbers of leukocyte cells and to determine the surface expression of adhesion molecules on these leukocytes **(I)** ICAM-1 and **(J)** VCAM-1. Data are shown as box-and-whisker plots (box: median with interquartile range, whiskers: full data distribution) with each dot representing an individual mouse sample. Tx = transplanted; HU = Hounsfield units; ISO = isograft; ALLO = allograft; MFI = mean fluorescence intensity.

(Sigma-Aldrich, Overijse, Belgium) submersion overnight. Dried lungs were scanned using a Skyscan 1272 μCT scanner (Bruker, Kontich, Belgium) with a resolution of 3.5 μm. 3D images were reconstructed using the NRecon software (version 1.7.0.4, Bruker microCT, Kontich, Belgium) and 3D segmentations of airway lumina, arteries and veins was performed semi-automatically by ITK-SNAP software [30].

Bulk spatial GeoMx proteomics to validate vessel orientated rejection in lung sections

GeoMX spatial proteomic profiling was performed to determine the spatial localization of different immune-related proteins of interest. By selecting specific regions of interest based on the anatomical location, we performed a regional analysis subdividing airways, arteries, veins, and parenchyma (Figures 5A,B). Formalin-fixed and paraffin-embedded (FFPE) lung tissue sections (4 μm) were obtained from one isograft at each time point (day 1, 7 and 35) and three allografts at each timepoint. For each tissue section, three regions of interest (ROIs) were selected and paired for the parenchyma, bronchioles, arteries, and veins (total of 12 ROIs), based on the anatomical orientation in the H&E image. For the spatial proteomics, the GeoMx assay and platform was performed at the F Polverino lab in Baylor (Houston, USA). Tissue sections were incubated with 47 oligo-labelled primary antibodies of interest (Supplementary Table S2) and analyzed using the Nanostring GeoMx Digital Spatial Profiler as per manufacturer's instructions. The detection antibodies comprised three fixed panels of the GeoMx assay (GeoMx immune cell profiling panel, GeoMx immune activation status panel, GeoMx immune cell typing panel).

Statistical analysis

Data analysis was performed using GraphPad statistical software (Prism, version 10, San Diego, CA, USA). To compare the different groups one-way ANOVA was used. To compare the different time points in isografts or allografts, a mixed effects model with Šidák multiple comparisons test was conducted. To compare isografts and allografts, a mixed effect model with Tukey's multiple comparisons *post hoc* was used. A p-value of <0.05 was considered significant. Differential protein expression analyses (spatial proteomics) were performed to compare allografts and isografts in different compartments of the lung. Third quartile normalization was performed on the obtained expression matrix to allow comparison between samples. Of the 47 included proteins, 35 were assigned to a specific cluster (structural, hematopoietic, innate immunity, adaptive immunity, stromal and proliferation). To be able to pool multiple proteins per cluster, expression values were scaled to Z-scores for each protein separately. Statistical analysis on these differences was performed using mixed modeling in R (version 4.2.2), using the "lmer" function. The model used a full factorial design between graft (isograft and allograft), day (1, 7, 35) and tissue type (airway, artery, vein, parenchyma), with notation "graft*day*tissue". Different mouse individuals were included as random effect. The least squares method ("emmeans" function) was used to perform pairwise comparisons between allograft and isograft.

Results

Lung morphology and density after murine orthotopic single lung transplantation

Isografts maintained normal macroscopic appearance throughout follow-up, whereas allografts progressively developed yellow discoloration with patchy dark areas by day 35 (Figure 1B). Longitudinal *in vivo* μCT revealed normal morphology in both groups on day 1; by day 7, allografts showed complete consolidation corresponding to atelectasis, while isografts remained aerated. On day 35, patchy dense regions persisted in allografts, contrasting with preserved isograft structure. Quantitative analysis confirmed these changes: mean lung density was significantly higher in allografts compared to isografts on day 35 (-87 ± 154 HU vs. -376 ± 27 HU, $p = 0.016$), while isografts showed a modest decline in density over time ($p = 0.043$) (Figure 1C). Lung volumes increased from day 7 to 35 in both groups (isograft $p = 0.04$; allograft $p = 0.008$) with no overall differences between both groups (Figure 1D). Histology confirmed these findings by preserved parenchymal architecture without cellular infiltrates or connective tissue deposition and fibrosis formation in isografts versus bronchovascular inflammation and fibrosis in allografts on day 35 (Figures 1E–G; Supplementary Figure S3).

Flow cytometry for leukocyte and endothelial cell numbers and activation status

The number of leukocytes ($CD45^+$) significantly increased in the allograft left lung on day 7 ($p = 0.037$) but decreased again on day 35 ($p = 0.020$) (Figure 1H). These leukocytes significantly presented more ICAM-1 on their surface on day 7 ($p = 0.0026$) and 35 ($p = 0.0045$) compared to isografts, while no change in VCAM-1 was observed (Figures 1I,J).

Endothelial cell ($CD31^+$) numbers remained stable in isografts. In contrast, allografts showed a significant reduction on day 7 compared to day 1 ($p = 0.024$), which only partially recovered by day 35 ($p = 0.199$) (Figure 2A). Endothelial cells showed to be activated, as VCAM-1 was significantly increased on day

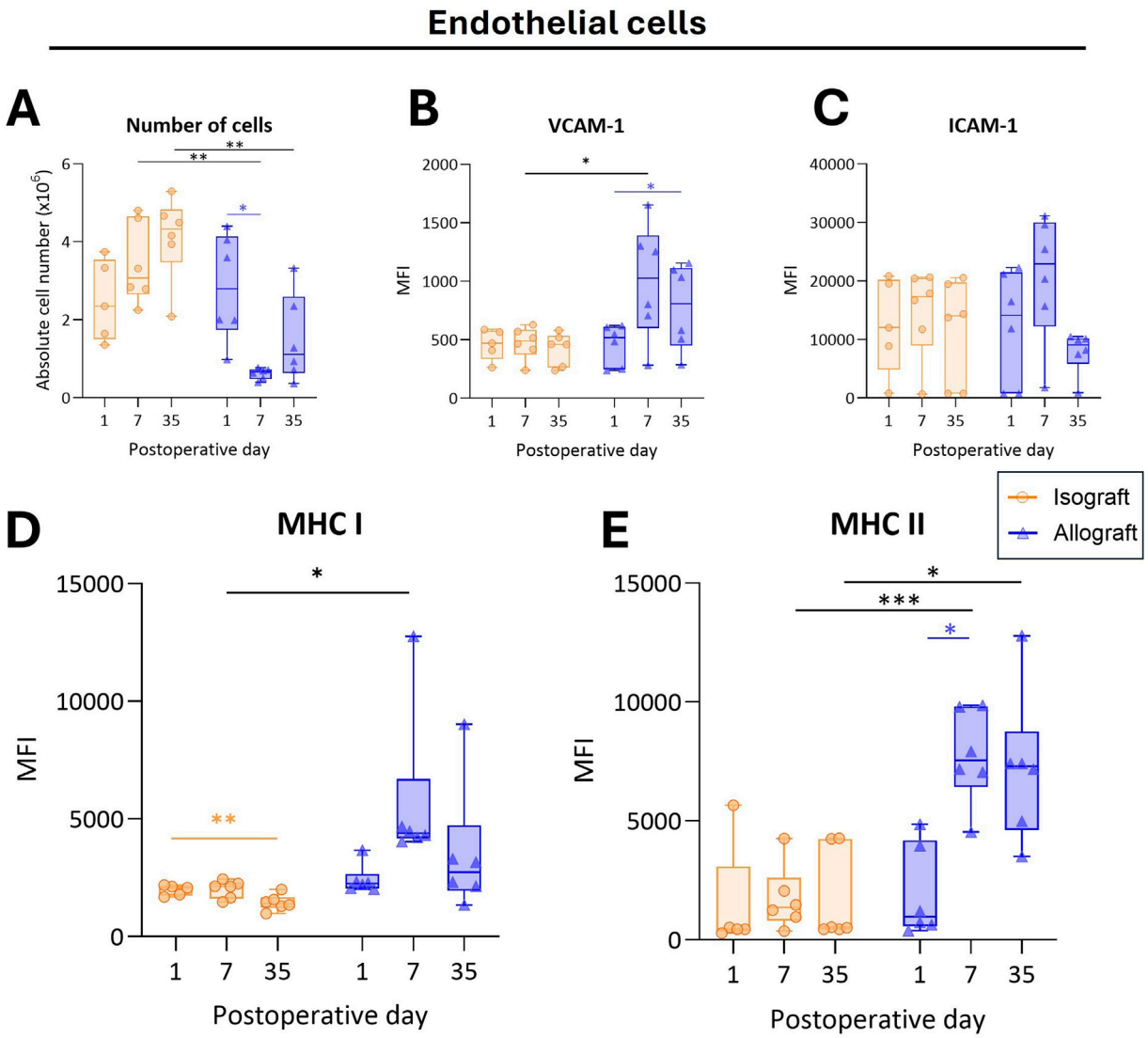


FIGURE 2
Total endothelial cell numbers and endothelial surface expression of adhesion and MHC molecules in the murine left transplanted lung. Isograft (C57BL/6NRj in C57BL/6NRj) and allograft (Balb/cJRj in C57BL/6NRj) transplantations were performed and sacrificed at indicated time points. **(A)** Absolute number of CD31$^+$ endothelial cells. **(B–E)** Flow cytometry was used to determine the surface expression of adhesion molecules (VCAM-1 and ICAM-1) and MHC molecules (MHC I and II) on CD31$^+$ endothelial cells. Data are shown as box-and-whisker plots (box: median with interquartile range, whiskers: full data distribution), with each dot representing an individual mouse sample. EC = endothelial cells; Leuko = leukocytes; MFI = mean fluorescence intensity.

7 compared to isografts ($p = 0.047$) and remained increased on day 35 versus day 1 ($p = 0.049$) (Figure 2B). No change in ICAM-1 expression by endothelial cells was observed (Figure 2C). Endothelial MHCI and MHCII expression were increased in allografts compared to isografts on day 7 ($p = 0.045$; $p = 0.0002$, respectively) and MHCII remained significantly increased on day 35 ($p = 0.006$) (Figures 2D,E).

Histological visualization of vessel-centered rejection

Isografts showed preserved vascular, airway, and pleural architecture, with minimal focal edema on day 1 that resolved by day 35. Allografts displayed a vascular driven pathology. On day 1, the multifocal intra-alveolar edema was accompanied by subtle perivascular changes (Figure 3). By day 7, dense cuff-like perivascular infiltrates dominated, composed of lymphocytes and histiocytes, frequently accompanied by pleural extension. On day 35, these infiltrates became organized and shifted in composition toward plasma cell–rich cuffs with fewer lymphocytes, paralleled by progressive perivascular fibrosis (Figure 3; Supplementary Figure S3). The parenchyma showed edema on day 1 that was largely resolved in isografts but more extensive in allografts (Figure 3). The airways remained preserved in isografts, whereas allografts demonstrated peribronchial fibrosis on day 35 (Figure 3; Supplementary Figure S3).

10.3389/ti.2026.16293

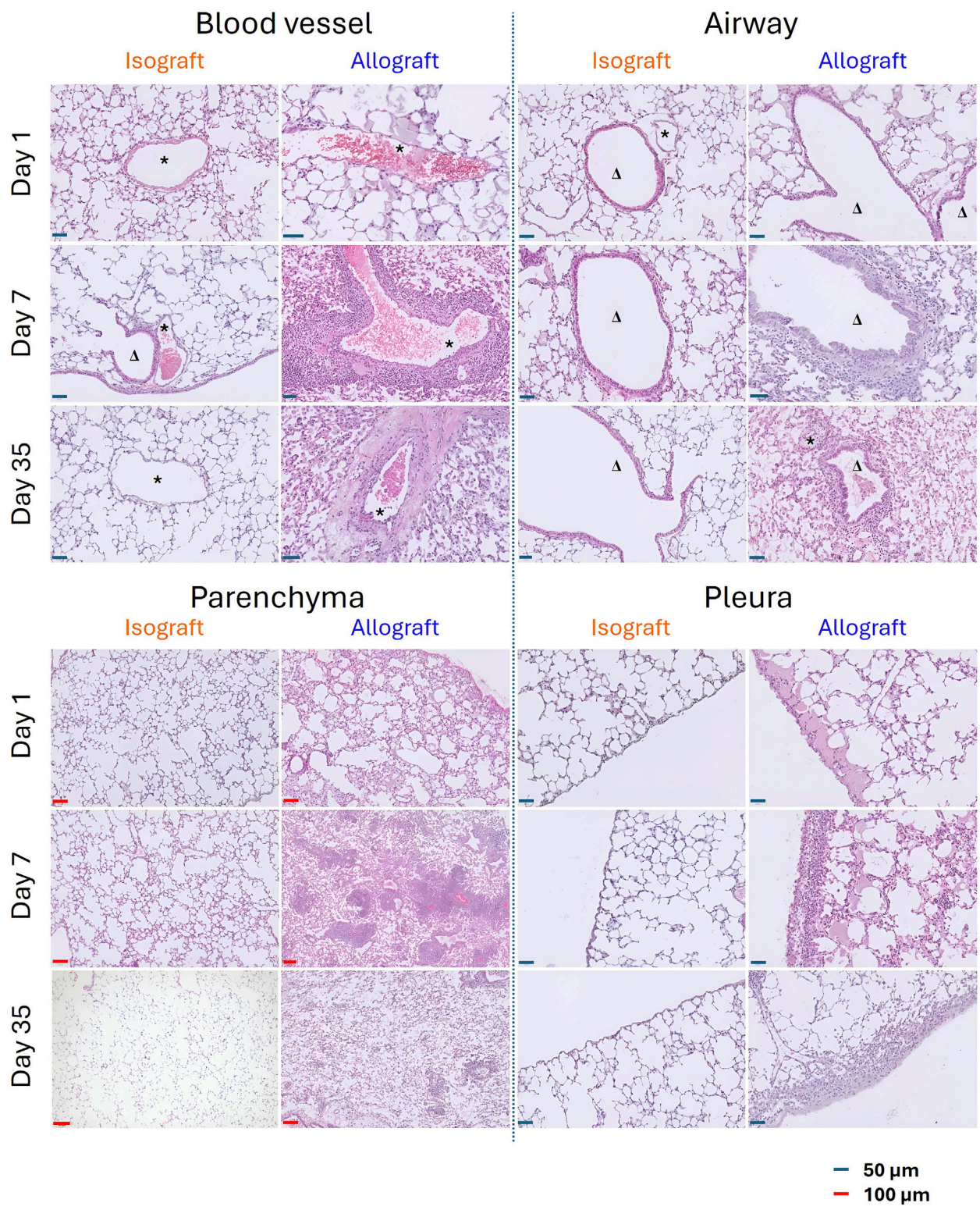


FIGURE 3
Representative histological images of isografts and allografts of the different compartments (blood vessel, airway, parenchyma, and pleura) over time. Representative Hematoxylin-Eosin (H&E) staining of the different groups on day 1, 7, and 35 after transplantation (n = 4/5). Scale bar of parenchymal images indicates 100 µm, scale bar of all other images indicates 50 µm, * = blood vessel; Δ = airway.

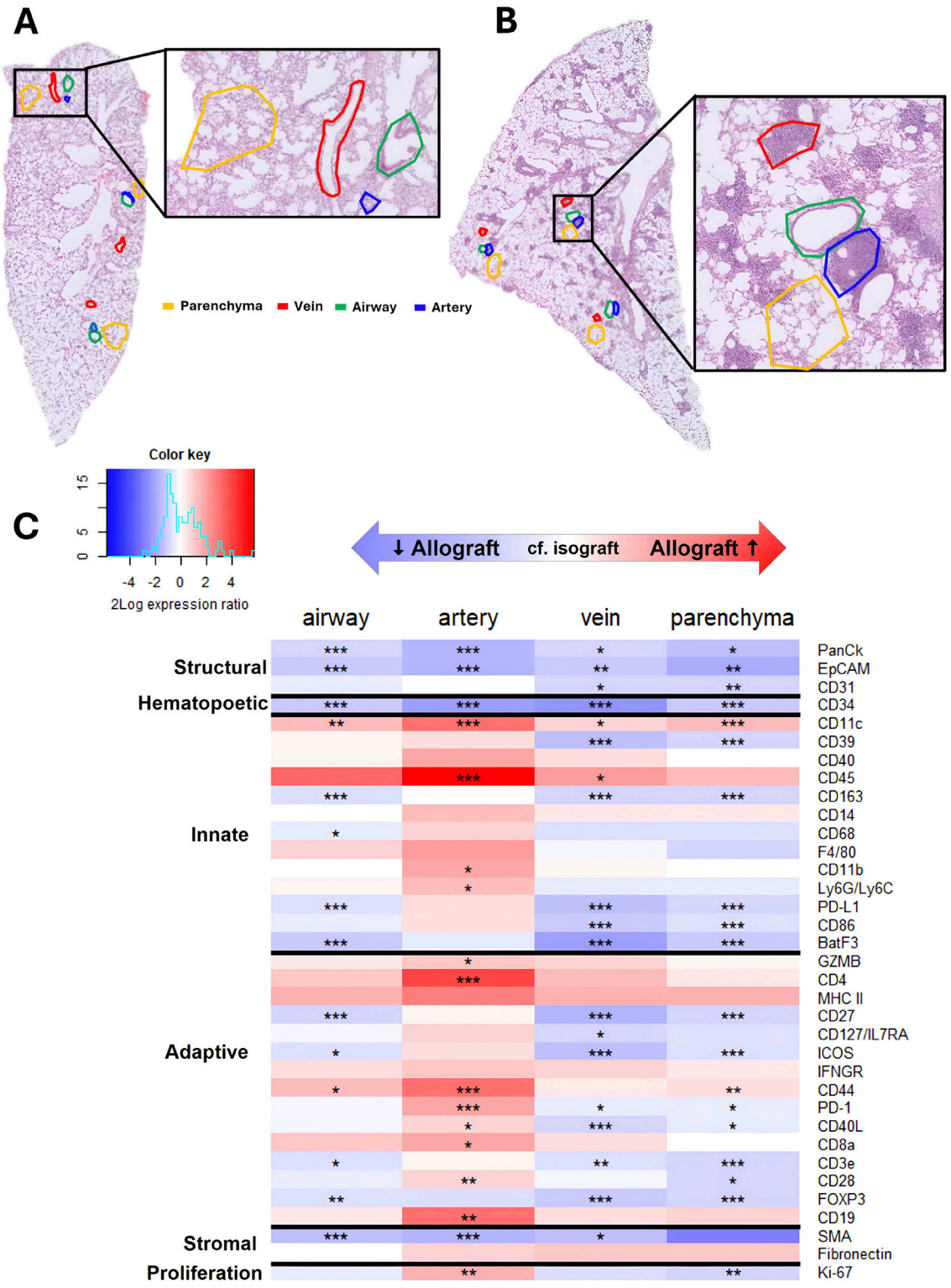


FIGURE 4
Spatial proteome analysis at regions of interest: artery, vein, airway, and parenchyma. **(A,B)** Example of allograft on day 1 and day 35 after transplantation with regions of interest (ROIs), yellow indicates parenchyma, red vein, green airway, and blue artery. **(C)** Heatmap of spatial proteomics according to the anatomical location of the immune process in the transplanted lung. Protein expression levels were quantified around the airways, arteries, veins and in the parenchyma region of interest in formalin-fixed paraffin embedded (FFPE) tissue sections from the left transplanted lungs of isografts (C57BL/6NRj in C57BL/6NRj) (n = 1/time point) and allografts (Balb/cJRj in C57BL/6NRj) (n = 3/time point) by NanoString GeoMX digital spatial

(*Continued*)

FIGURE 4 (Continued)
profiling. On day 1, no significant differences between allograft and isograft were observed. Data of day 1 was discarded for this figure (and excluded from the model). Additionally, since no major differences were observed between day 7 and day 35, data of day 7 and 35 were pooled together for simplicity of the figure. This was performed by still including day 7 and 35 in the model but only performing pairwise comparisons between allograft and isograft for all tissue regions. Z-score differences between allograft and isograft were hence computed for each cluster and tissue region separately (colors). The mixed model provided p-values of the pairwise comparisons are indicated on the figure.

Bulk spatial GeoMx proteomics confirm vessel orientated rejection

2D-UMAP projection of all included samples, based on normalized protein expression, showed isografts at all timepoints clustering together with allograft day 1, while a second cluster consisted of allograft day 7 and 35 together (Supplementary Figure S4). Indeed, no significant differences were found comparing isografts and allografts on day 1. To continue, based on this clustering, data of allograft day 7 and 35 were pooled and this was compared to isograft (Figure 4C). We observed a higher expression of most of the proteins at the arterial regions in allografts compared to isografts. Particularly CD45 (pan leukocyte marker), CD4 and CD44 (T cell markers) were more present around the arteries of allografts compared to isografts ($p < 0.001$; $p = 0.001$; $p = 0.002$, respectively) and the other structures. Expression of CD19 (B cell marker) was also higher around the arteries of allografts compared to isografts ($p = 0.006$). Both innate and adaptive immune markers were more expressed in the allografts' arteries compared to isografts and other structures. The expression of CD11c (dendritic cell marker) was increased in allografts in the parenchyma ($p = 0.001$) and around the arteries ($p = 0.006$) and airways ($p = 0.029$), compared to isografts. Protein expression of immune regulatory markers CD39, CD163, PD-L1 and FoxP3 decreased in the allograft's parenchyma ($p < 0.001$; $p < 0.001$; $p < 0.001$; $p < 0.001$) and veins ($p < 0.001$; $p < 0.001$; $p < 0.001$; $p = 0.002$) compared to isografts. Expression of other adaptive immunity markers CD27, ICOS and CD40L (T cell activation markers) were significantly less detected in allografts' vein compared to isografts ($p < 0.001$; $p < 0.001$; $p < 0.001$). EpCAM and PanCK (epithelial markers) were decreased in allografts' airways ($p < 0.001$; $p < 0.001$) in comparison to isografts. Smooth muscle actin (SMA) was significantly lower in allografts' airways ($p < 0.001$) and arteries ($p < 0.001$). However, fibronectin seemed to be higher in allografts, although not significant. Ki-67 (proliferation marker) was expressed more highly around the arteries and parenchyma of the allografts compared to the other structures, and to isografts ($p = 0.023$; $p = 0.023$).

3D visualization by *ex vivo* µCT imaging to locate rejection

Ex vivo µCT was performed on donor controls, isografts, and allografts on day 1, 7, and 35, enabled segmentation of the airway tree, pulmonary arteries, and veins (Figure 5). Donor control lungs (Balb/c and C57BL/6) and isografts demonstrated preserved morphology of both airway and vascular compartments at all time points. Allografts appeared normal on day 1, with intact airways and vasculature comparable to controls. In contrast, by day 35, allografts exhibited marked vascular pathology: arteries and veins were narrowed, collapsed, and embedded within dense fibrotic regions. Notably, airway structures appeared intact without evidence of distortion or malformation and airway obstruction was only found secondary and in severe stages of rejection.

Discussion

This study demonstrated a vasculature and endothelial cell centered onset of rejection in a mouse model of chronic lung rejection. Our findings indicate that endothelial cells are key in the immune response of acute rejection (day 7) and the fibrotic remodeling of chronic rejection (day 35) around the arteries, analogous to chronic vascular injury observed in other solid organ transplants.

We previously characterized the alloimmune response in this mouse transplant model with both innate and adaptive immune cells involved [22, 25]. In this study we confirmed the temporal relation between immune activation on day 7 (with little fibrosis), and organized fibrosis on day 35 in the allografts. As such, day 7 may be regarded as acute rejection and day 35 may be regarded as chronic rejection. In the current study, we observed an early (day 7) loss of endothelial cells that coincided with this inflammatory peak of the acute phase of rejection. Moreover, early lymphocyte activation and leukocyte adhesion to the endothelium was enhanced by endothelial cell activation with increased expression of VCAM-1 and increased expression of ICAM-1 in leukocytes. The parallel increase in MHC molecules on endothelial cells (especially MHCII) further supports the leading role for the endothelium in orchestrating the immune response, by activating the adaptive immune system with its antigen-presenting capacity, directly activating T-helper cells. Jambusaria et al. demonstrated that lung endothelial cells express higher levels of immunoregulatory genes than those from the brain or heart, underscoring their unique immune-modulating capacity [31]. Carmeliet et al. further introduced the concept of "immunomodulatory endothelial cells" (IMECs), a specialized subset capable of engaging directly in immune signaling [32]. Histology and especially the spatial proteomics highlighted compartment-specific patterns of injury, confirming innate and adaptive organization specifically localized to arteries. Our findings suggest that endothelial cells function not only as targets of the immune response but also as active contributors to ongoing alloimmune activation within the graft. Since the alloantigenic stimulus persists, the immune response cannot resolve. Continuous endothelial activation and injury likely promote maladaptive repair processes, further resulting in perivascular fibrosis. This remodeling extends into adjacent parenchymal, pleural and airway compartments, providing a mechanistic link between early vascular injury and later graft dysfunction. Collectively, these observations position the vasculature as a central orchestrator of both the inflammatory and fibrotic phases of chronic lung allograft injury.

How this concept of a vessel-centered rejection process translates to the human clinical setting with CLAD (both RAS

10.3389/ti.2026.16293

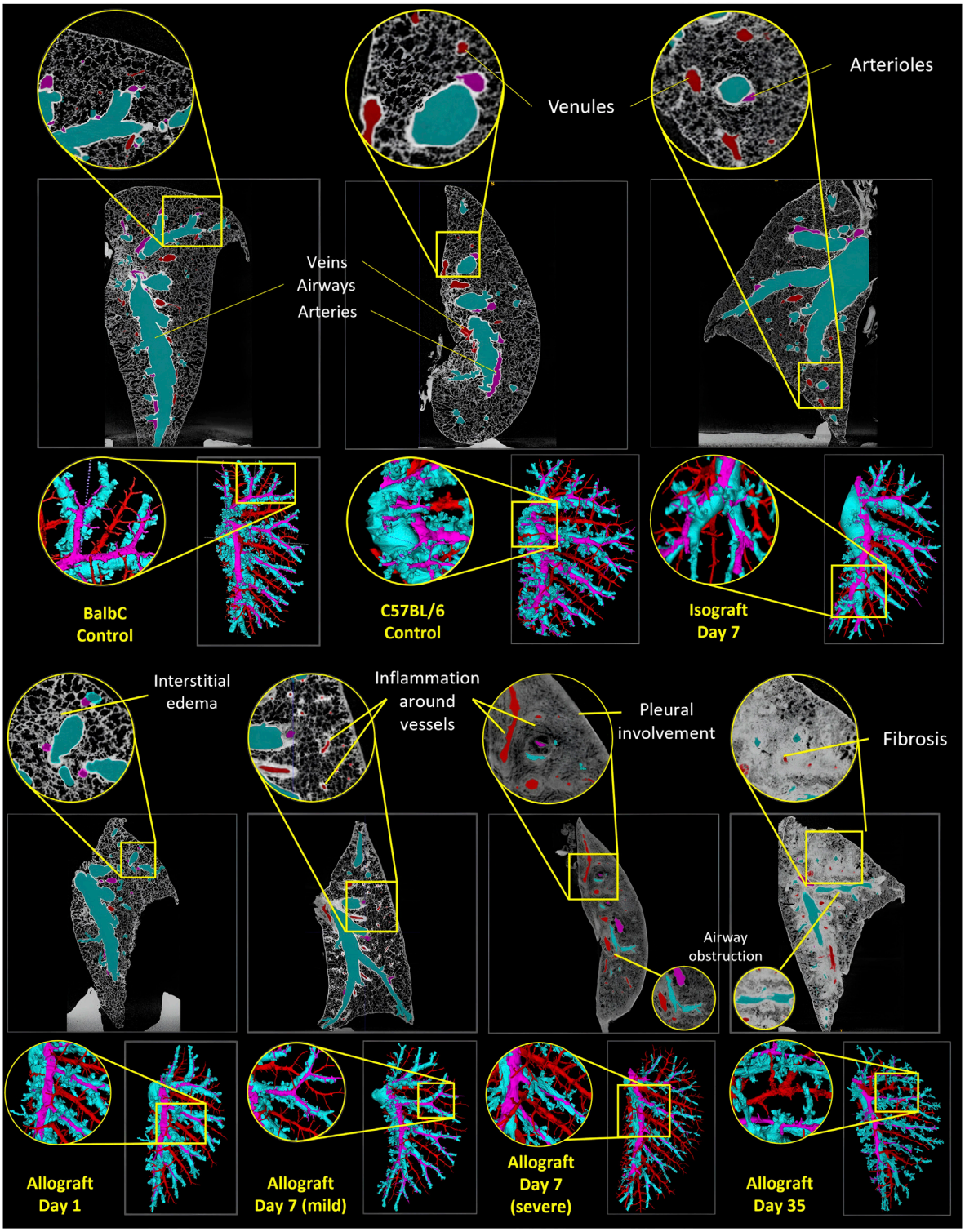


FIGURE 5
Representative *ex vivo* high resolution μCT cross-sections of the left (transplanted) lung with 3D segmentation. Allografts (Balb/cJRj in C57BL/6NRj) left transplanted lung at three different time points after murine single lung transplantation. Left lung of a non-transplant BalbC mouse for comparison, showing healthy parenchyma with open airways, lined by an artery. Allograft on day 1 showing interstitial edema. On day 7, an increased density was noticed around the blood vessels, this might indicate perivascular inflammation. Allograft on day 35 after transplantation showed intense increased density in the whole lung, which could be pulmonary fibrosis. 3D segmentation shows a prominent decrease in blood vessel density and branching in transplanted mice compared to control. Blue indicates airways, purple indicates arteries and red shows the veins.

and BOS) is highly relevant. Acute rejection is histologically confirmed by the presence of lymphocytic perivascular infiltrates in the clinic, which is in parallel with the acute rejection observed on day 7 in the mice. In addition, some human studies highlighted the vascular contribution to CLAD, with reduced VEGF levels in bronchoalveolar lavage fluid of patients with RAS [9], and vascular remodeling, including pulmonary arteriopathy and venopathy, has been described in both BOS and RAS [7, 33].

To extend our molecular and histological observations to the macrostructural level, a high-resolution *ex vivo* microCT was used enabling segmentation of the airway tree and pulmonary vascular compartments. Consistent with our molecular findings, vascular structures in allografts showed progressive narrowing, pruning, and remodeling by day 35, while airway architecture remained largely preserved, providing 3D confirmation that chronic graft injury in this mouse model primarily affects the vasculature rather than the airway compartment. This vascular involvement suggests that vascular injury precedes or drives subsequent parenchymal or airway remodeling which ultimately leads to loss of lung function. From a translational perspective, this also implies that, potentially, *in vivo* imaging approaches focusing on vascular alterations could serve as sensitive tools to detect CLAD progression in clinical lung transplantation at earlier stages, prior to the decrease in lung function. Advanced imaging modalities capable of assessing pulmonary perfusion or vascular integrity may therefore hold diagnostic value in identifying patients at risk for CLAD. Moreover, therapeutic strategies aimed at preserving endothelial integrity or modulating vascular inflammation might complement current immunosuppressive regimens and offer a new avenue to improve long-term graft survival.

The limitations of this study are the nature of the model, being a highly controlled setting to dissect alloimmune mechanisms, which cannot fully replicate the complexity of human lung transplantation. Immunosuppressive regimens also differ between species; we used cyclosporine A to moderate the immune response, whereas tacrolimus-based therapy is standard in clinical practice, which may affect the kinetics and nature of rejection. Only male mice were included, and potential sex-specific immune differences therefore remain unexplored. Furthermore, the number of isograft controls was limited, which may reduce statistical power for some comparisons. Mechanistic pathways underlying endothelial cell loss and its direct effects on fibroblast activation and fibrosis were not addressed here but represent an important direction for future work. Finally, this is a murine model of rejection, not CLAD. Modeling CLAD requires graft-specific functional measurements, and their absence is a limitation of this study. Despite these limitations, this model and study offered a unique opportunity to study rejection processes under reproducible and isolated conditions, minimizing confounding factors that are difficult to control in human transplantation.

In conclusion, the current study reveals that chronic vascular injury is a central feature of rejection also in the lung, preceding and potentially driving fibrotic remodeling. By identifying the endothelium as an active participant rather than a passive target, this study redefines lung rejection as a vessel-centered process. Targeting vascular inflammation and preserving endothelial integrity may thus hold the key to improving long-term lung allograft survival. This study invites to investigate how vascular rejection fits into the concept of CLAD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was approved by Ethical Committee for Animal Experimentation (ECD) of KU Leuven (Katholieke Universiteit Leuven) (P194/2019). The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

Conceptualization: JK, CH, PEVdS, RV, and BMV; Transplant procedure: JK, CH, XJ, TH, HL, JVS, MM, MZ-O, CV, AOY, AB, LJC, and BMV; µCT imaging and visualization: JK, CH, XJ, AV, MM, MZ-O, YM, BT, and BMV; Flow cytometry: JK, CH, XJ, EP, FP, PEVdS, and BMV; Spatial GeoMx: JK, CH, PK, JRQ, FP, BMV, BO and LV; Histology: JK, CH, XJ, AV, GA, TH, MM, VG, AV, AOY, BMV, AS, and LV; writing – original draft preparation: JK, CH, AZ, RV, and BMV; writing – review and editing: JK, CH, XJ, TH, HL, EP, FP, HB, PK, AV, JV, MM, MZ-O, AZ, GA, VG, AV, CV, YM, BT, AOY, SB, LDS, LG, AB, JRQ, FP, PEVdS, LJC, RV, BMV, LV, BO, and AS. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declared that financial support was received for this work and/or its publication. JK (1198920N), CH (1152225N), XJ (11PGT24N), PK (1120425N) and VG (11L9822N) are sponsored by a fundamental research grant from the FWO. EP is a recipient of the L'Oréal-Unesco Women for Sciences PhD fellowship. RV is supported by FWO as a senior clinical researcher (1803526N) and by a research grant (G060322N). PEVdS is funded by KU Leuven (C14/23/143) and an FWO research grant (G066723N). LJC is supported by an FWO research grant (G090922N). BMV is funded by KU Leuven (C16/19/005) and by an FWO research grant (G098025N).

Conflict of interest

The authors(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2026.16293/full#supplementary-material

References

1. Verleden GM, Glanville AR, Lease ED, Fisher AJ, Calabrese F, Corris PA, et al. Chronic lung allograft dysfunction: definition, diagnostic criteria and approaches to treatment. A consensus report from the pulmonary council of the ISHLT. *J Heart Lung Transpl* (2019) 38(5):493–503. doi:10.1016/j.healun.2019.03.009

2. Graham CN, Watson C, Barlev A, Stevenson M, Dharnidharka VR. Mean lifetime survival estimates following solid organ transplantation in the US and UK. *J Med Econ* (2022) 25(1):230–7. doi:10.1080/13696998.2022.2033050

3. Zajacova A, Dupont LJ, De Leyn P, Ceulemans LJ, Vos R, Leuven Lung Transplant Group. Characteristics and outcomes of 1500 lung transplantations in the leuven lung transplant program: turning past lessons into tomorrow's foundations. *Transpl Int* (2025) 38:15495. doi:10.3389/ti.2025.15495

4. Chambers DC, Cherikh WS, Harhay MO, Hayes D, Hsich E, Khush KK, et al. The international thoracic organ transplant registry of the international society for heart and lung transplantation: Thirty-sixth adult lung and heart–lung transplantation Report—2019; focus theme: donor and recipient size match. *J Heart Lung Transpl* (2019) 38(10):1042–55. doi:10.1016/j.healun.2019.08.001

5. Gauthier JM, Ruiz-Pérez D, Li W, Hachem RR, Puri V, Gelman AE, et al. Diagnosis, pathophysiology and experimental models of chronic lung allograft rejection. *Transplantation* (2018) 102(9):1459–66. doi:10.1097/TP.0000000000002250

6. Bos S, Vos R, Van Raemdonck DE, Verleden GM. Survival in adult lung transplantation: where are we in 2020? *Curr Opin Organ Transpl* (2020) 25(3): 268–73. doi:10.1097/MOT.0000000000000753

7. Vanstapel A, Verleden S, Verbeken E, Braubach P, Goos T, De Sadeleer L, et al. Beyond bronchiolitis obliterans: in-depth histopathologic characterization of bronchiolitis obliterans syndrome after lung transplantation. *J Clin Med* (2021) 11(1):111. doi:10.3390/jcm11010111

8. Meyer KC, Raghu G, Verleden GM, Corris PA, Aurora P, Wilson KC, et al. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis Obliterans syndrome. *Eur Respir J* (2014) 44(6):1479–503. doi:10.1183/09031936.00107514

9. Verleden SE, Vos R, Vanaudenaerde BM, Verleden GM. Chronic lung allograft dysfunction phenotypes and treatment. *J Thorac Dis* (2017) 9(8):2650–9. doi:10.21037/jtd.2017.07.81

10. Mitchell RN, Libby P. Vascular remodeling in transplant vasculopathy. *Circ Res* (2007) 100(7):967–78. doi:10.1161/01.RES.0000261982.76892.09

11. Libby P, Pober J *Chronic rejection*, 14 (2021). p. 387–97.

12. Naesens M, Roufosse C, Haas M, Lefaucheur C, Mannon RB, Adam BA, et al. The banff 2022 kidney Meeting Report: reappraisal of microvascular inflammation and the role of biopsy-based transcript diagnostics. *Am J Transpl* (2024) 24(3):338–49. doi:10.1016/j.ajt.2023.10.016

13. Kloc M, Ghobrial RM. Chronic allograft rejection: a significant hurdle to transplant success. *Burns Trauma* (2014) 2(1):2321–3868. doi:10.4103/2321-3868.121646

14. Mehra MR, Crespo-Leiro MG, Dipchand A, Ensminger SM, Hiemann NE, Kobashigawa JA, et al. International society for heart and Lung transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy—2010. *J Heart Lung Transpl* (2010) 29(7):717–27. doi:10.1016/j.healun.2010.05.017

15. Bos S, Milross L, Filby AJ, Vos R, Fisher AJ. Immune processes in the pathogenesis of chronic lung allograft dysfunction: identifying the missing pieces of the puzzle. *Eur Respir Rev* (2022) 31(165):220060. doi:10.1183/16000617.0060-2022

16. Bos S, Pradère P, Beeckmans H, Zajacova A, Vanaudenaerde BM, Fisher AJ, et al. Lymphocyte depleting and modulating therapies for chronic lung allograft dysfunction. *Pharmacol Rev* (2023) 75(6):1200–17. doi:10.1124/pharmrev.123.000834

17. Auner S, Hillebrand C, Boehm PM, Boecker J, Koren D, Schwarz S, et al. Impact of transient and persistent donor-specific antibodies in lung transplantation. *Transpl Int* (2024) 37:12774. doi:10.3389/ti.2024.12774

18. Loupy A, Lefaucheur C. Antibody-mediated rejection of solid-organ allografts. *N Engl J Med* (2018) 379(12):1150–60. doi:10.1056/NEJMra1802677

19. Bery AI, Hachem RR. Antibody-mediated rejection after lung transplantation. *Ann Transl Med* (2020) 8(6):411. doi:10.21037/atm.2019.11.86

20. Beeckmans H, Bos S, Vos R, Glanville AR. Acute rejection and chronic lung allograft dysfunction. *Clin Chest Med* (2023) 44(1):137–57. doi:10.1016/j.ccm.2022.10.011

21. Lama VN, Belperio JA, Christie JD, El-Chemaly S, Fishbein MC, Gelman AE, et al. Models of lung transplant research: a consensus statement from the national heart, lung, and blood institute workshop. *JCI Insight* (2017) 2(9), e93121. doi:10.1172/jci.insight.93121

22. Heigl T, Kaes J, Aelbrecht C, Serré J, Yamada Y, Geudens V, et al. The nature of chronic rejection after lung transplantation: a murine orthotopic lung transplant study. *Front Immunol* (2024) 15:1369536. doi:10.3389/fimmu.2024.1369536

23. Chiang CF, Chao TT, Su YF, Hsu CC, Chien CY, Chiu KC, et al. Metformin-treated cancer cells modulate macrophage polarization through AMPK-NF-κB signaling. *Oncotarget* (2017) 8(13):20706–18. doi:10.18632/oncotarget.14982

24. Jungraithmayr W, Draenert A, Marquardt K, Weder W. Ultrastructural changes in acute lung allograft rejection: novel insights from an animal study. *The J Heart Lung Transplantation: The Official Publication Int Soc Heart Transplant* (2012) 31(1):94–100. doi:10.1016/j.healun.2011.10.003

25. Kaes J, Pollenus E, Hooft C, Liu H, Aelbrecht C, Cambier S, et al. The immunopathology of pulmonary rejection after murine lung transplantation. *Cells* (2024) 13(3):241. doi:10.3390/cells13030241

26. Jin X, Kaes J, Van Slambrouck J, Inci I, Arni S, Geudens V, et al. A comprehensive review on the surgical aspect of lung transplant models in mice and rats. *Cells* (2022) 11(3):480. doi:10.3390/cells11030480

27. Pollenus E, Pham TT, Vandermosten L, Possemiers H, Knoops S, Opdenakker G, et al. CCR2 is dispensable for disease resolution but required for the restoration of leukocyte homeostasis upon experimental malaria-associated acute respiratory distress syndrome. *Front Immunol* (2021) 11:628643. doi:10.3389/fimmu.2020.628643

28. Berghen N, Dekoster K, Marien E, Dabin J, Hillen A, Wouters J, et al. Radiosafe micro-computed tomography for longitudinal evaluation of murine disease models. *Sci Rep* (2019) 9(1):1–10. doi:10.1038/s41598-019-53876-x

29. Vande Velde G, Poelmans J, De Langhe E, Hillen A, Vanoirbeek J, Himmelreich U, et al. Longitudinal micro-CT provides biomarkers of lung disease that can be used to assess the effect of therapy in preclinical mouse models, and reveal compensatory changes in lung volume. *Dis Model Mech* (2016) 9(1):91–8. doi:10.1242/dmm.020321

30. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *NeuroImage* (2006) 31(3):1116–28. doi:10.1016/j.neuroimage.2006.01.015

31. Jambusaria A, Hong Z, Zhang L, Srivastava S, Jana A, Toth PT, et al. Endothelial heterogeneity across distinct vascular beds during homeostasis and inflammation. *eLife* (2020) 9:e51413. doi:10.7554/eLife.51413

32. Amersfoort J, Eelen G, Carmeliet P. Immunomodulation by endothelial cells — partnering up with the immune system? *Nat Rev Immunol* (2022) 22(9): 576–88. doi:10.1038/s41577-022-00694-4

33. Vanstapel A, Goldschmeding R, Broekhuizen R, Nguyen T, Sacreas A, Kaes J, et al. Connective tissue growth factor is overexpressed in explant lung tissue and bronchoalveolar lavage in transplant-related pulmonary fibrosis. *Front Immunol* (2021) 12: 661761. doi:10.3389/fimmu.2021.661761

ESOT | Transplant International

TYPE Original Research
PUBLISHED 04 May 2026
DOI 10.3389/ti.2026.15985

Check for updates

OPEN ACCESS

*CORRESPONDENCE
K. Semash,
doctorsemash@gmail.com

RECEIVED 02 December 2025
REVISED 06 April 2026
ACCEPTED 17 April 2026
PUBLISHED 04 May 2026

CITATION
Semash K, Dzhanbekov T, Nasirov M, Subanov A and Umarov B (2026) Venous reconstruction in living donor liver transplantation: lessons learned from a new national program in a resource-limited setting.
Transpl. Int. 39:15985.
doi: 10.3389/ti.2026.15985

COPYRIGHT
© 2026 Semash, Dzhanbekov, Nasirov, Subanov and Umarov. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Venous reconstruction in living donor liver transplantation: lessons learned from a new national program in a resource-limited setting

K. Semash *, T. Dzhanbekov , M. Nasirov , A. Subanov and B. Umarov

Department of Minimally Invasive Surgery and Transplantation, National Children's Medical Center, Tashkent, Uzbekistan

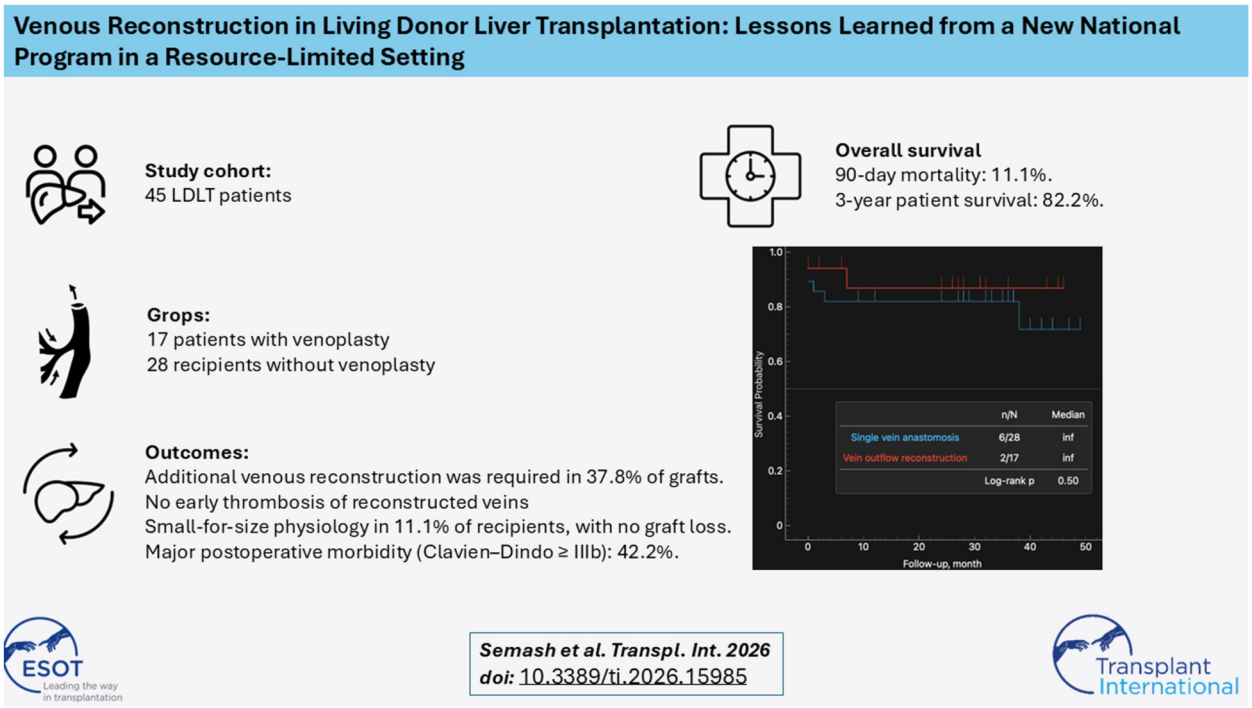
Complex venous outflow reconstruction in living donor liver transplantation (LDLT) is technically demanding, particularly in resource-limited settings lacking consistent access to synthetic or cryopreserved grafts. We retrospectively analyzed 45 consecutive LDLTs performed during the initiation of a national program. Venous anatomy was evaluated using preoperative CT volumetry and intraoperative findings. Reconstruction strategies included direct anastomosis, unification venoplasty, PTFE grafts, and autologous conduits (falciform ligament, umbilical vein). Outcomes were compared between patients with (n = 17) and without (n = 28) venoplasty. Additional venous reconstruction was required in 37.8% of cases. In 6.7%, anatomically indicated veins could not be reconstructed due to lack of suitable conduits. No early venous thrombosis occurred, and all autologous conduits remained patent during follow-up. Small-for-size physiology developed in 11.1% of recipients, resolved conservatively, and was not associated with unreconstructed major veins. Major morbidity (Clavien–Dindo ≥ IIIb) occurred in 42.2%. The 90-day mortality rate was 11.1%, and 3-year survival was 82.2%, without significant differences between groups. In a newly established program within a resource-limited setting, predominantly autologous venoplasty was feasible and provided satisfactory early and mid-term outcomes.

KEYWORDS
hepatic veins, liver transplantation, living donors, resource-limited settings, venous reconstruction

Introduction

Living donor liver transplantation (LDLT) has become an essential strategy for addressing the persistent shortage of deceased donor organs in many regions of the world. The success of LDLT depends critically on the restoration of adequate venous outflow. Unlike deceased donor liver transplantation that uses a whole organ with relatively uniform venous anatomy, LDLT relies on partial grafts with substantial anatomical variability. This variability creates significant technical challenges during reconstruction of the hepatic veins [1, 2].

Insufficient venous drainage is one of the major determinants of early graft dysfunction. Impaired outflow may result in congestion of the graft, reduction in microvascular perfusion, cholestasis, ischemic injury, and in severe cases complete graft loss [3]. The



GRAPHICAL ABSTRACT

venous system of the liver demonstrates extensive variation. It includes the right hepatic vein, the middle hepatic vein, the left hepatic vein, and the inferior right hepatic veins. The number, diameter, and drainage patterns of these veins differ markedly among donors. These anatomical factors directly influence the choice of surgical technique required for reconstruction [4–6]. Restoration of tributaries of the middle hepatic vein, accessory veins of segments five and eight, and inferior right hepatic veins becomes especially important when these vessels drain a considerable portion of the graft or when the risk of small for size physiology is anticipated [7–12].

Advances in preoperative imaging, including multidetector computed tomography with three dimensional reconstruction and intraoperative Doppler ultrasonography, provide precise visualization of venous anatomy and allow surgeons to anticipate technical difficulties in advance [13, 14]. These imaging modalities help guide the selection of individualized reconstruction strategies. Depending on the specific configuration of the graft, options may include direct anastomoses, unification venoplasty, extended venoplasty, and the use of autologous, homologous, or synthetic venous conduits [7–11].

Most innovations in venous outflow reconstruction have been developed in the context of right lobe LDLT, where the drainage of segments five and eight presents a particular challenge because the middle hepatic vein is usually retained in the donor to preserve function of the remnant liver. However, left lobe grafts, left lateral sector grafts, and monosegmental grafts also require precise venous reconstruction. In pediatric recipients, and especially in neonates and infants in whom vascular diameters are extremely small, these procedures are frequently performed using microsurgical techniques that reduce the risk of early venous thrombosis [4, 15–18].

Despite considerable progress, there remains no universally accepted standard for venous outflow reconstruction in LDLT. Publications from high volume centers in Japan, the Republic of Korea, China, Taiwan, Singapore, India, and Europe demonstrate substantial variation in surgical approaches [7, 10, 11, 16, 19, 20]. Differences include the criteria for reconstruction of segment five and segment eight tributaries, the preferred type of venous conduit, the method of forming a common venous channel, and the strategies used to maintain patency of reconstructed veins. This variability underlines the need for comprehensive reviews that integrate current evidence with actual clinical experience.

This study incorporates clinical data from our national LDLT program. At present, Uzbekistan has no deceased-donor organ procurement program [21], and all liver transplantations rely exclusively on living related donors, which further restricts the availability of vascular conduits for complex reconstructions. Working within a setting where we had limited availability of prosthetic graft materials and biological conduits, these cases provide important insight into the practical challenges of venous outflow reconstruction. To the best of our knowledge, this study represents the first comprehensive report of venous outflow reconstruction in a newly established national LDLT program operating without a deceased-donor vascular bank and with only intermittent availability of synthetic grafts. This series offers a practical, reproducible framework for other resource-constrained programs worldwide.

Materials and methods

This study was reviewed and approved by the Institutional Review Board (protocols No 11-17-98/2025 and No 77-77/2025).

All procedures were conducted in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments.

This study was designed as a single-center retrospective observational cohort study and included 45 consecutive living-related donor liver transplantations performed between October 2021 and December 2024. The institutional cases were conducted by the same surgical team and represent the initial phase of program development in a resource limited setting. Overall, 42 cases involved related donorship. The relationships of donors to recipients were as follows: 11 sons, 10 brothers, nine sisters, five cousins, two fathers, two mothers, two aunts, and one nephew. Additionally, under the laws of the Republic of Uzbekistan, spouses are eligible to be organ donors if they have been married for over 3 years [21]. In this study, three wives were approved as donors.

All donors underwent high resolution multiphase computed tomography using a GE Revolution HD 256 slice scanner. A uniform protocol was employed for arterial, portal venous, and hepatic venous phases [21]. The hepatic venous phase served as the primary dataset for evaluation of venous anatomy. Three dimensional reconstruction and volumetric assessment were performed on a GE Advantage Workstation equipped with the Hepatic VCAR application and OsiriX software. In two cases, 3D virtual modeling was used to access vascular anatomy of the donor's liver (Supplementary video S1) [22].

The venous anatomy was assessed in detail. The right hepatic vein, middle hepatic vein, left hepatic vein, and inferior right hepatic veins were evaluated for number, diameter, distance between their orifices, and drainage territories. Tributaries of segments five and eight were specifically analyzed to determine diameter, length of extrahepatic course, and the angle of entry into the middle hepatic vein. The expected drainage volume of each tributary was estimated using three dimensional volumetry. Reconstruction of S5 and S8 tributaries was planned when at least one of the following objective criteria was met: (1) venous diameter ≥5 mm on preoperative CT or intraoperative measurement; (2) estimated drainage territory ≥20–30% of the anterior sector volume based on three-dimensional volumetry; or (3) graft-to-recipient weight ratio (GRWR) ≤1.0%, indicating increased risk of small-for-size physiology.

Left sided grafts were evaluated as a separate anatomical category. Particular attention was given to the configuration of the left hepatic vein trunk, the drainage patterns of segments two and three, and the relationship between the left hepatic vein and the middle hepatic vein. Left lobe grafts commonly demonstrated separate entry of the middle and left hepatic veins into the inferior vena cava, which necessitated systematic preoperative planning of venous reconstruction. For left lateral segment grafts, venous drainage was reassessed when the segment two and segment three veins entered the inferior vena cava as independent openings. This classification of right sided and left sided drainage patterns guided the selection of unification venoplasty, patch augmentation, or other reconstructive techniques to ensure adequate venous outflow for each graft (Table 1).

The surgical technique for donors and recipients has been described previously in our previous publications [23]. Intraoperatively, the diameters of the S5, S8, and inferior right hepatic veins were assessed, and veins measuring greater than 5 mm were classified as significant; in addition, back-table evaluation included assessment of preservative solution outflow through individual venous branches, and veins measuring 5 mm or less were also considered for reconstruction when they demonstrated substantial efflux of preservative solution. Reconstruction of inferior right hepatic veins was performed by direct end-to-side anastomosis to the recipient inferior vena cava. Each significant iRHV was implanted separately when anatomically feasible to ensure adequate venous drainage and prevent segmental congestion. In cases where an isolated significant segment V (S5) or segment VIII (S8) tributary was identified, the respective vein was reconstructed using an interposition conduit and anastomosed to the recipient middle hepatic vein to restore anterior sector outflow. When both S5 and S8 tributaries were deemed significant, reconstruction of middle hepatic vein performed on the graft, which was then reconstructed toward the recipient IVC. If necessary, Unification plasty was performed using a continuous 6/0 polydioxanone suture. When autologous conduits (falciform ligament or recipient umbilical vein) were utilized, reconstruction of the corresponding venous branches was carried out on the back table. The conduit was tailored to the required diameter, anastomosed to the segmental veins under magnification, and tested for watertight integrity using preservation solution before implantation. After graft implantation, venous outflow patency was monitored with Doppler ultrasonography immediately after reperfusion, at twenty-four hours, and at regular intervals during the postoperative period. Computed tomography was obtained in cases where ultrasonographic evaluation suggested impaired venous flow. Laboratory markers and clinical parameters of graft congestion were correlated with imaging findings. We also evaluated postoperative criteria for small for size syndrome. Clinical and laboratory indicators were monitored in accordance with established definitions of small for size physiology, including early hyperbilirubinemia, coagulopathy that persisted despite correction, excessive ascites production, and characteristic trajectories of aminotransferase levels [24]. Hemodynamic parameters such as portal venous flow and pressure were assessed when clinically indicated. These variables were analyzed to identify early signs of graft dysfunction related to insufficient graft size or compromised venous outflow.

Follow-up was conducted from the date of transplantation until the last available clinical assessment. The duration of follow-up varied among patients due to the ongoing nature of the program.

Continuous variables were reported as mean ± standard deviation or median [interquartile range], according to their distribution, which was assessed using the Shapiro–Wilk test. Categorical variables were summarized as absolute and relative frequencies. Group comparisons (venoplasty vs. no venoplasty) were performed using Fisher's exact test or the chi-square test for categorical variables and Student's t-test or the Mann–Whitney U test for continuous variables, selected based on data distribution and variance homogeneity. Potential confounders were evaluated through univariable analyses, and variables with clinical relevance or $p < 0.10$ were entered into a multivariable logistic regression model to identify independent predictors of early biliary leakage. Adjusted odds ratios with 95% confidence intervals were calculated, and model fit was assessed using standard goodness-of-fit diagnostics. Survival outcomes were estimated using the Kaplan–Meier method with right-censoring at

TABLE 1 Classification of hepatic venous drainage patterns and their implications for reconstruction.

Anatomical group	Key venous features	Diagnostic criteria	Reconstructive implications
Right hepatic vein dominant drainage	Single large RHV draining the majority of the right hemiliver	RHV with sufficient diameter and long extrahepatic cuff	Usually suitable for direct anastomosis. Patch enlargement used when cuff is short
Inferior right hepatic vein dependent drainage	Presence of one or more IRHVs with significant drainage territory	IRHV diameter large enough to require preservation. Visible on CT and confirmed intraoperatively	Often requires separate anastomosis or interposition graft. Failure to reconstruct may lead to segmental congestion
Segment five tributaries (S5)	One or more veins draining segment five toward the MHV	Diameter and drainage area significant on CT	Options include direct anastomosis, unification venoplasty, or patch augmentation depending on number and size
Segment eight tributaries (S8)	Major or minor veins draining segment eight into the MHV	Preoperative CT shows significant S8 venous branch	Frequently requires venoplasty or use of conduits. Combined reconstruction with S5 when orifices are adjacent
Left lobe venous drainage	Separate drainage of MHV and LHV into the inferior vena cava	Consistent finding in majority of left lobe donors. Assessed with three dimensional reconstruction	Venous reconstruction always planned preoperatively due to mandatory restoration of outflow for segments two, three, and four
Left lateral segment drainage (segments two and three)	Segment two and segment three veins draining into IVC through separate openings	Identified on CT and confirmed with 3D reconstruction	Requires unification venoplasty or patch reconstruction to create a common outflow channel and prevent stenosis
Combined right sided and left sided anatomical variants	Complex or mixed drainage patterns involving multiple venous territories	Variability confirmed by preoperative CT + 3D reconstruction	Reconstruction individualized using a combination of direct anastomosis, unification venoplasty, patch augmentation, or conduits

Abbreviations: RHV, right hepatic vein; MHV, middle hepatic vein; LHV, left hepatic vein; IRHV, inferior right hepatic vein; S5, segment five; S8, segment eight; S2, segment two; S3, segment three; IVC, inferior vena cava.

the date of last follow-up. A *post hoc* exploratory subgroup analysis was performed comparing the first 30 cases with the last 15 cases to assess the potential influence of program maturation and learning curve on outcomes. A two-sided p-value <0.05 was considered statistically significant. All analyses were conducted using IBM SPSS Statistics, version 26.0 (IBM Corp., USA).

Results

A total of forty-five grafts were analyzed, including forty-two right lobe grafts, one left lobe grafts, and two left lateral segment grafts. Variants of hepatic venous anatomy and the corresponding reconstructive strategies are summarized in Table 2. Median GRWR was 1.1% (0.7-2.7). The median GRWR was 1.05% (range 0.7%–2.0%) in the venoplasty group and 1.1% (range 0.85%–2.7%) in the no-venoplasty group.

Right liver grafts

The majority of right liver grafts demonstrated a single dominant right hepatic vein. In twenty eight cases, a single right hepatic vein with no significant accessory branches was present, which allowed for a single caval anastomosis without the need for venoplasty. When a hepatic vein that required reconstruction was left unreconstructed, post-reperfusion inspection consistently revealed an area of congested graft parenchyma with a darker, bluish discoloration (Figure 1).

An additional inferior right hepatic vein was identified in three grafts. In these cases, two separate caval anastomoses were performed, and no venoplasty was required because the diameter and venous territory of the inferior right hepatic vein permitted direct implantation.

Two grafts demonstrated three independent right hepatic venous trunks, two of which corresponded to inferior right hepatic veins with significant drainage territories. These cases required unification venoplasty of the inferior right hepatic veins followed by two separate caval anastomoses.

Reconstruction of segmental veins from segments five and eight was required in several grafts. PTFE interposition grafts were used in five grafts. In two cases a PTFE conduit was used for outflow reconstruction of a segment five vein, and in one of these cases conduit was anastomosed to the recipient's middle hepatic vein draining into the inferior vena cava (Figure 2). One graft required PTFE reconstruction for a segment eight vein. In one graft a single PTFE conduit was used to unify and drain both segment five and segment eight veins into the inferior vena cava. Additionally, in one case PTFE conduits were used to reconstruct the separate S5 and S8 hepatic veins, resulting in three distinct outflow channels that were anastomosed individually to the IVC (Figures 3A–C).

Autologous tissue was used for venous reconstruction in three cases. Two grafts required unification of the segment five and segment eight veins using a conduit fashioned from the falciform ligament (Figures 4A–C). In one case the umbilical vein of the

TABLE 2 Venous Outflow Anatomy and Reconstruction Techniques (n = 45 grafts).

Graft type	Venous structure/configuration	Number of grafts	Reconstruction/anastomosis technique
RL	Single RHV, no significant accessory veins or there was no possibility of reconstruction	28	Single caval anastomosis; no venoplasty
RL	One additional iRHV	3	Two caval anastomoses; no venoplasty
RL	Three RHVs (two iRHV accessory veins)	3	Unification plasty of iRHVs + two caval anastomoses
RL	PTFE graft to S5 vein	2	PTFE conduit anastomosed to IVC
RL	PTFE graft to S8 vein	1	PTFE conduit anastomosed to IVC
RL	PTFE graft connecting S5 + S8 and separate iRHV	1	PTFE conduit of separate S5 and S8 → three anastomoses with IVC
RL	S5+S8 reconstruction using falciform ligament graft	2	Autologous FL conduit for unification, anastomosed to IVC
RL	S5+S8 reconstruction using umbilical vein of recipient	1	Umbilical vein conduit obtained from recipient for unification, anastomosed to IVC
RL	S8 was close to the RHV	1	Unification plasty of RHV and S8
LL	Three separate veins (MHV, S2, S3)	1	Unification plasty
LLS	Single LHV	1	Single caval anastomosis; no venoplasty
LLS	Separate S2 and S3 veins	1	Unification plasty

Abbreviations: RL, right lobe; LL, left lobe; LLS, left lateral section; RHV, right hepatic vein; MHV, middle hepatic vein; LHV, left hepatic vein; iRHV, inferior right hepatic vein. S2, S3, S5, S8, hepatic segmental veins corresponding to Couinaud segments two, three, five, and eight; IVC, inferior vena cava; PTFE, polytetrafluoroethylene; FL, falciform ligament.

recipient was harvested and used as an interposition conduit to reconstruct the outflow of both segment five and segment eight veins (Figures 4D–F).

One graft demonstrated a segment eight tributary running very close to the right hepatic vein. In this case, unification venoplasty was performed without the use of interpositional material.

Left liver grafts

During harvesting LL graft, we faced an unusual and technically challenging venous configuration that resulted directly from an intraoperative mechanical complication. During donor left hepatectomy, the stapling device malfunctioned, causing the venous structures to be transected lower than the planned level. As a result, the middle hepatic vein, the segment two vein, and the segment three vein were obtained as three separate orifices located at a considerable distance from one another. The distance-spaced venous openings required an extensive and complex unification venoplasty to create a single, adequate outflow channel suitable for implantation into the inferior vena cava (Figure 3D).

Also, two left lateral section grafts were included. One graft contained a single left hepatic vein and required only one caval anastomosis without the need for additional venoplasty. The second graft demonstrated separate venous orifices from segment two and segment three. These veins were reconstructed using unification venoplasty.

Postoperative outcomes

Early and late postoperative complications were compared between recipients who underwent a single hepatic vein anastomosis (no venoplasty, n = 28) and those who received venous outflow reconstruction (venoplasty, n = 17) (Table 3). Overall, most vascular complication rates were low and did not differ significantly between the groups.

Hepatic artery thrombosis occurred only in the single-vein group (3.6%) and was not observed in venous reconstruction group (p = 1.000). Hepatic artery stenosis was comparable between cohorts (10.7% vs. 5.9%, p = 1.000), with a non-significant trend toward a lower risk in the venoplasty group (OR 0.58, 95% CI 0.06–6.06). Clinical features consistent with splenic artery steal syndrome (SASS) were observed only in patients without venoplasty (10.3% vs. 0%, p = 0.542). SASS was defined clinically as a combination of persistently reduced hepatic arterial flow on Doppler ultrasound in the absence of hepatic artery thrombosis or stenosis, associated with a disproportionately increased splenic artery flow, and improvement after splenic artery–directed intervention or conservative management. Angiography was performed selectively when clinically indicated.

Portal vein thrombosis developed more frequently among patients who underwent venous reconstruction (11.8% vs. 3.6%), although the difference did not reach statistical significance (p = 0.287; OR 4.00, 95% CI 0.34–47.4).

Early biliary leakage occurred in 13 of 45 patients (28.9%). The incidence was significantly higher in the venoplasty group (58.8% vs. 10.7%, p = 0.001). This difference was most pronounced during the first 30 cases (64.3% vs. 18.8%, p = 0.023) and decreased in the last 15 consecutive cases after introduction of an ultrasonic cavitation aspirator (CUSA), improved liver retraction systems, and stricter donor selection (8.3% vs. 0%, p = 1.000). Multivariable logistic regression showed that venoplasty was not an independent predictor of early biliary leak (adjusted OR 2.8, 95% CI 0.6–13.2, p = 0.19). The

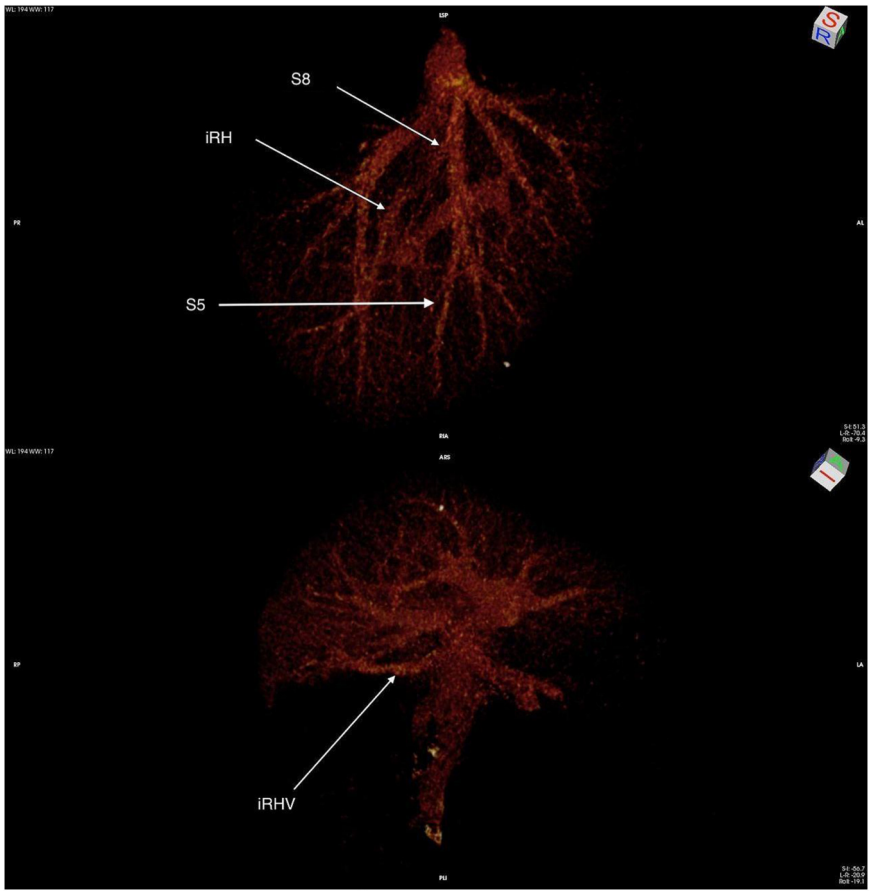


FIGURE 1
Three-dimensional CT reconstruction of the donor's venous outflow. Arrows indicate the significant venous branches of segments 5 and 8, as well as the inferior right hepatic vein (IRHV).

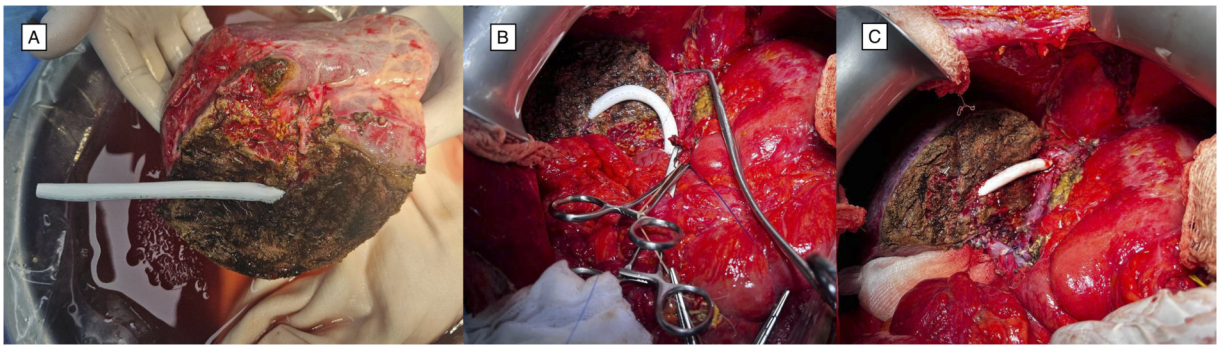


FIGURE 2
Reconstruction of segment five vein in right lobe liver graft using PTFE graft. **(A)** Back-table stage. A PTFE conduit was anastomosed with significant S5 vein on the liver graft. **(B)** A veno-caval anastomosis was performed. Preparation for PTFE graft anastomosis. **(C)** The PTFE conduit was anastomosed to the recipient's middle hepatic vein. Appearance after venous reperfusion. Abbreviations: PTFE, polytetrafluoroethylene; S5, segment V of the Couinaud liver segmentation system.

only independent risk factors were the number of bile duct orifices (OR 4.7 per additional orifice, 95% CI 1.6–13.8, p = 0.005) and the early phase of the program (first 30 vs. last 15 cases: OR 22.4, 95% CI 2.5–201, p = 0.005). Late biliary strictures occurred in two patients (4.4%), one in each group, and were successfully managed surgically.

Postoperative bleeding requiring relaparotomy was noted only in the no-venoplasty cohort (6.9% vs. 0%, p = 0.531). The overall burden of severe complications (Clavien–Dindo ≥ IIIb) was higher among patients who underwent venous reconstruction (50.0% vs. 34.5%), although this difference was not statistically significant (p =

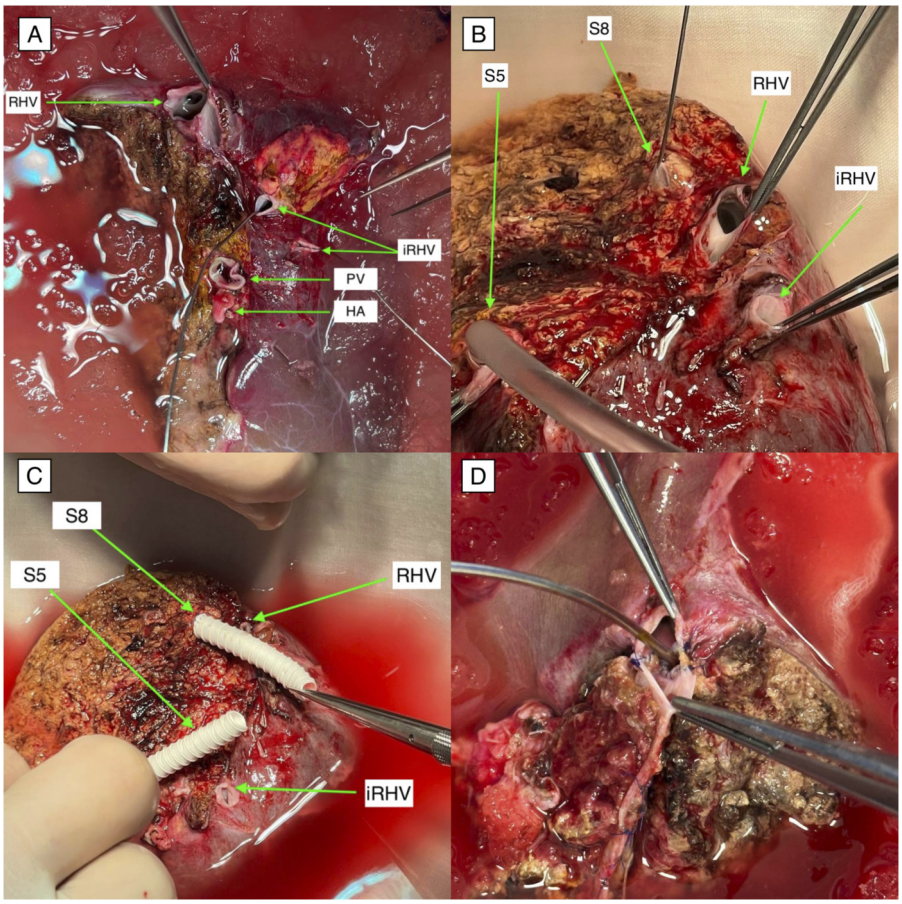


FIGURE 3
Variations of venous anatomy in liver grafts **(A)** A right-lobe liver graft with two separate inferior right hepatic veins required unification venoplasty of the inferior veins and construction of two distinct veno-caval anastomoses. **(B)** A right-lobe liver graft with significant venous branches from segments 5 and 8, as well as an additional inferior right hepatic vein. S5 vein canulated for conservant solution outflow assession. **(C)** A venous reconstruction approach for segments 5 and 8 using separate PTFE conduits; additionally, this graft contained an accessory inferior right hepatic vein that required an independent anastomosis to the inferior vena cava. **(D)** A left-lobe liver graft in which unification venoplasty was performed to combine the S2 and S3 venous branches with the middle hepatic vein; the probe is positioned within the lumen of the S3 vein. Abbreviations: PTFE, polytetrafluoroethylene; S2, S3, S5, S8, segments II, III, V, and VIII of the Couinaud liver segmentation system.

0.360; OR 1.90, 95% CI 0.56–6.45). 90-day mortality (Clavien–Dindo grade V) was similar between groups (12.5% vs. 10.3%, p = 1.000). The Comprehensive Complication Index (CCI) demonstrated a significantly higher cumulative morbidity in the venoplasty group, with a median of 39.8 (IQR 26.2–66.3) compared with 20.9 (IQR 0–39.8) in the single-vein cohort (p = 0.047), indicating a greater severity and overall burden of complications in patients requiring venous reconstruction.

Clinical features consistent with small-for-size syndrome were observed in five recipients (11.1%). Three cases occurred in the no-venoplasty group (3/28, 10.7%) and two in the venoplasty group (2/17, 11.8%), with no statistically significant difference between groups (p = 1.000). SFSS was defined clinically based on persistent hyperbilirubinemia, refractory ascites, and/or prolonged coagulopathy in the absence of mechanical outflow obstruction or other identifiable causes. Management was performed according to standard recommendations and included optimization of hemodynamics, albumin supplementation, diuretic therapy, careful fluid balance control, and close Doppler surveillance. All cases were managed conservatively without graft loss attributable to SFSS.

There was no venous outflow–related complications in the study cohort. No cases of early thrombosis of reconstructed venous outflow were observed. Refractory ascites was observed in 3 patients (6.7%) and was attributed to small-for-size syndrome, as there was no objective evidence of impaired venous outflow in these patients, in conjunction with a low graft-to-recipient weight ratio.

The median follow-up duration was 32.5 months for patients without venoplasty and 27 months for those who underwent venoplasty. Across the entire cohort, the median follow-up time was 29 months. Overall patient survival did not differ significantly between recipients who underwent venoplasty and those with a single vein anastomosis (log-rank p = 0.62; Figure 5). The actuarial 1-year and 3-year patient survival rates estimated by Kaplan–Meier analysis were were 86.8% and 82.8%, in the single-anastomosis group and 87.5% and 81.2% in the reconstruction group, respectively. Median survival was not reached in either group during the maximum follow-up of 50 months. Hospital mortality

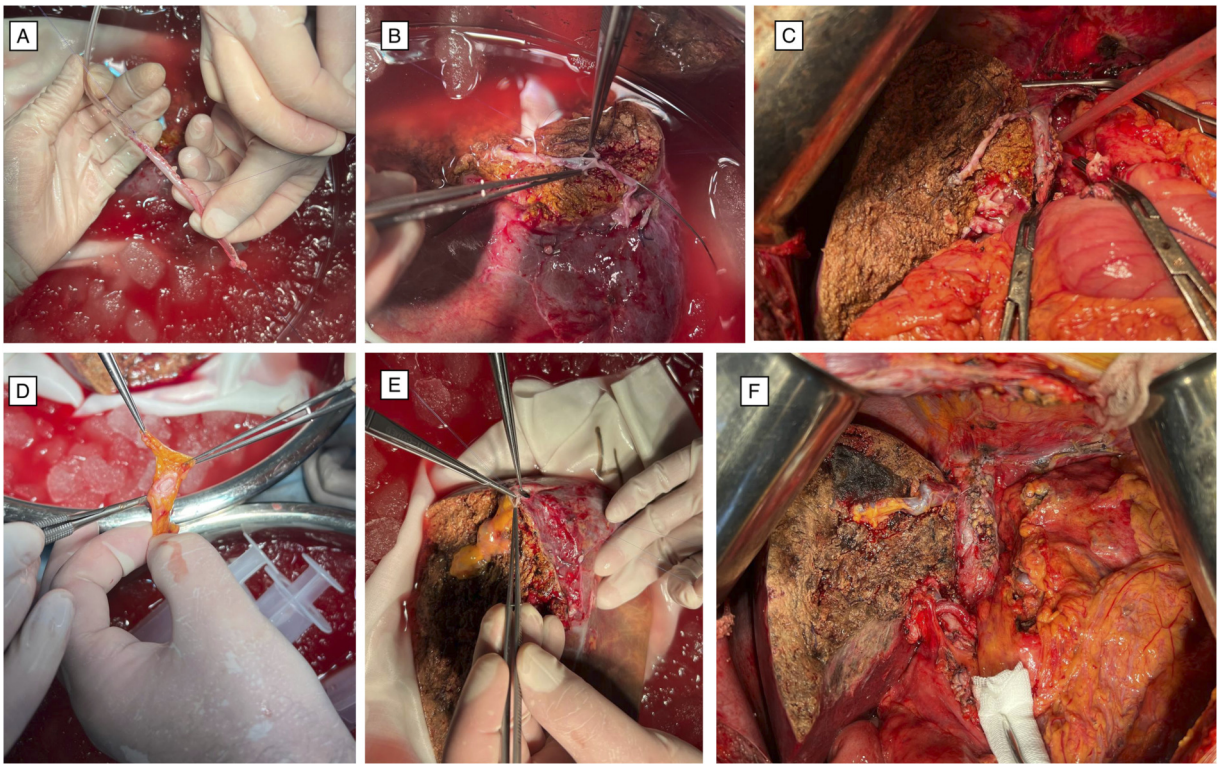


FIGURE 4
(A) A conduit was fashioned on the back table from the donor's falciform ligament, which was wrapped around a sterile 14-F tube to create a tubular graft. **(B)** Anastomosis of the falciform-ligament conduit to the venous branches of segments 5 and 8 was performed and unified with the right hepatic vein on the graft. **(C)** Appearance of the graft prior to venous reperfusion. **(D)** The recipient's umbilical vein shunt was harvested, and openings were created to enable anastomosis with the significant venous branches of segments 5 and 8. **(E)** The umbilical vein conduit was anastomosed to the S5 and S8 branches and unified with the right hepatic vein on the graft. **(F)** Appearance of the graft following venous reperfusion. Abbreviations: PTFE, polytetrafluoroethylene; S5, S8, segments V, and VIII of the Couinaud liver segmentation system.

in the cohort was 11.1% (5 of 45 patients). Two patients died from severe acute rejection, two from sepsis, and one from complications related to portal vein thrombosis. During long-term follow-up, three additional deaths occurred: one due to COVID-19 associated pneumonia, one due to nonadherence to immunosuppressive therapy, and one due to aspiration. No death in the entire series was attributable to venous outflow compromise.

Discussion

Venous outflow reconstruction remains one of the principal determinants of graft function in living donor liver transplantation [11]. The present series illustrates not only the anatomical complexity of partial liver grafts but also the considerable constraints imposed by a resource-limited environment. The absence of a deceased donor program, the restricted availability of vascular prostheses, and the inability to perform graft biopsy for differential diagnosis significantly influenced surgical decision-making and postoperative management. These conditions differentiate our experience from that of high-volume centers in East Asia and Europe, where venous reconstruction techniques have evolved in settings with broad access to vascular materials and advanced diagnostic infrastructure.

At the initial stage of the program, donor selection was intentionally conservative: we prioritized donors with straightforward hepatic anatomy and grafts with a favorable graft-to-recipient weight ratio. As surgical experience accumulated, we gradually expanded the range of acceptable anatomical variations and began to undertake more complex venous outflow reconstructions. International experience consistently supports an assertive strategy for reconstruction of segment V and segment VIII tributaries when these veins exceed four or 5 mm in diameter or drain a substantial portion of the anterior sector [11, 25]. This approach is grounded in extensive evidence from different transplant centers, where centers routinely employ autologous, homologous, and synthetic conduits and where vascular banking is standard practice. Studies by Sakamoto, Jeng, Thorat, Taha, Pamecha, Park, and others demonstrate that restoration of middle hepatic vein tributaries improves parenchymal perfusion, reduces venous congestion, enhances early graft regeneration, and mitigates the risk of small-for-size physiology [7, 8, 12, 20, 25–27]. Work by Mizuno et al has shown that regeneration of the anterior sector is significantly greater in grafts with reconstructed venous outflow [28].

The application of these principles in our program was necessarily selective. Although preoperative imaging and intraoperative assessment in several cases demonstrated clear indications for venous reconstruction, the unavailability of PTFE

10.3389/ti.2026.15985

TABLE 3 Postoperative outcomes.

Parameter	No venoplasty (n = 28)	Venoplasty (n = 17)	p-value
Hepatic artery thrombosis	1 (3.6%)	0	1.000
Hepatic artery stenosis	3 (10.7%)	1 (5.9%)	1.000
Splenic artery steal syndrome	3 (10.7%)	0	0.290
Portal vein thrombosis	1 (3.6%)	2 (11.8%)	0.546
Postoperative bleeding requiring relaparotomy	2 (7.1%)	0	0.525
Clinical features for small-for-size syndrome	3 (10.7%)	2 (11.8%)	1.000
Early biliary leak — overall	3 (10.7%)	10 (58.8%)	0.001
Early biliary leak — first 30 cases (1–30)	3/16 (18.8%)	9/14 (64.3%)	0.023
Early biliary leak — last 15 cases (31–45)	1/12 (8.3%)	0/3	1.000
Late biliary stricture	1 (3.6%)	1 (5.9%)	1.000
Number of bile duct orifices — mean ± SD	1.8 ± 0.8	2.4 ± 0.7	0.018
Number of biliary anastomoses — mean ± SD	1.7 ± 0.7	2.4 ± 0.6	0.006
Clavien–Dindo ≥ IIIb	10 (35.7%)	9 (52.9%)	0.360
90-day mortality	3 (10.7%)	2 (11.8%)	1.000
Comprehensive complication index, median [IQR]	20.9 [0–39.8]	42.6 [26.2–66.3]	0.032
Patient actuarial survival 1/3 years	86.8%/82.8%	87.5%/81.2%	0.78

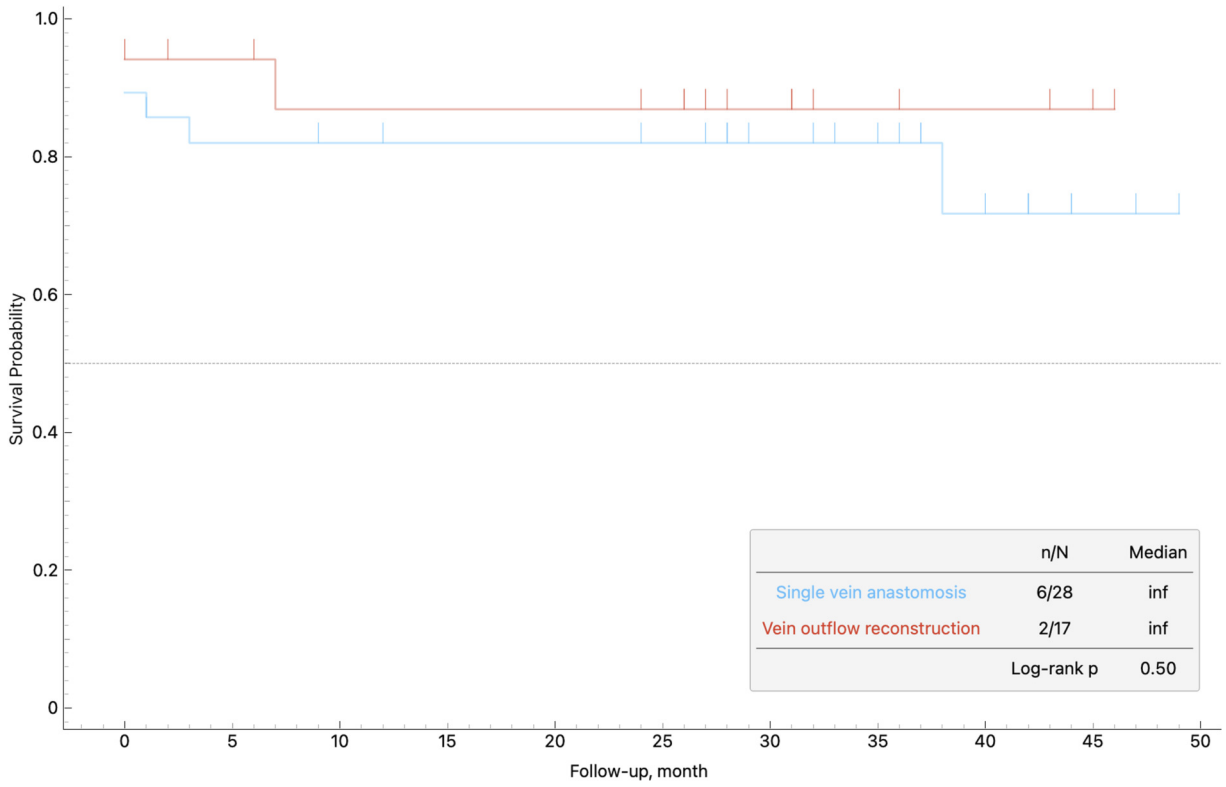


FIGURE 5
The actuarial Kaplan–Meier overall patient survival curves stratified by performance of venoplasty.

grafts in these cases made standard reconstruction technically impossible. Decisions were therefore individualized. Reconstruction was prioritized when volumetric analysis indicated a substantial drainage territory, when diameters exceeded 5 mm, and when the graft-to-recipient weight ratio approached the lower acceptable threshold. When prosthetic material was unavailable, alternative methods were employed. These included reconstruction with the falciform ligament, the recipient's umbilical vein, or spontaneously developed portosystemic shunts. Such solutions reflect the adaptive strategies described in early LDLT program development and demonstrate that acceptable venous outflow can be achieved even in the absence of dedicated vascular grafts.

An additional aspect that deserves consideration is the use of venous patch augmentation, which is frequently employed in high-volume transplant centers to facilitate creation of a wide and congruent anastomotic surface. Patch reconstruction enlarges the venous orifice, reduces the risk of anastomotic stenosis, and improves the geometric alignment between the graft vein and the recipient inferior vena cava. In many programs, homologous venous patches obtained from deceased donors or synthetic prosthetic patches are routinely applied [29]. In our series, patch venoplasty was not performed because no deceased-donor venous patches were available in our setting.

The most notable difference between the groups was the higher crude incidence of early biliary leaks in patients who underwent venoplasty (58.8% vs. 10.7%, p = 0.001). However, this association was almost entirely confined to the initial phase of the program and disappeared completely after technical maturation. Of the 13 early biliary leaks, 12 (92.3%) occurred within the first 30 cases (64.3% vs. 18.8% in the venoplasty and no-venoplasty groups, respectively). In the most recent 15 consecutive LDLTs (cases 31–45), performed after introduction of an ultrasonic cavitation aspirator (CUSA), advanced liver retraction systems, and stricter donor selection, only one early biliary leak was recorded in the entire cohort (6.7%), and it occurred in the no-venoplasty group (0% vs. 8.3%, p = 1.000). Multivariable logistic regression confirmed that venoplasty was not an independent risk factor for biliary leakage (adjusted OR 3.1, 95% CI 0.6–15.4, p = 0.17). The only independent predictors were multiple bile duct orifices (OR 4.9 per additional orifice, 95% CI 1.6–15.0, p = 0.005) which were significantly more common in grafts requiring venous reconstruction and the early program period (first 30 vs. last 15 cases: OR 24.8, 95% CI 2.7–227, p = 0.004). These findings strongly indicate that the observed association was driven by selection of anatomically complex donors and the institutional learning curve rather than by the venous reconstruction itself. In the mature phase of the program, venoplasty was not associated with increased biliary morbidity. Collectively, these factors, together with the influence of the institutional learning curve [30], likely affected the outcomes observed during the early development of our program. Our biliary leak rates align with reported ranges in emerging LDLT programs [31], and the rapid decline demonstrates the impact of technical evolution.

A further challenge of the resource-limited setting was the absence of liver biopsy, which prevented histological differentiation of early postoperative dysfunction. Biopsy remains the most reliable method to distinguish small-for-size syndrome from acute rejection and sepsis-associated cholestasis [32, 33]. In our series, clinical assessment depended on biochemical trends, Doppler ultrasound, and advanced imaging. Clinical suspicion of small for size syndrome was documented in five recipients. Three of these patients presented exclusively with high volume ascitic output during the first ten postoperative days. Daily drainage volumes reached up to four thousand milliliters and required replacement with crystalloid solutions, albumin infusion, and prolonged maintenance of abdominal drains. Two of these three patients had a single venous anastomosis and relatively small grafts with GRWRs of 0.7 and 1.1. The third patient with the same clinical pattern had two venous anastomoses, specifically the right hepatic vein and an inferior right hepatic vein, and a GRWR 1.1. The clinical pattern was consistent with the diagnostic framework proposed by the ILTS consensus group [34, 35]. In another patient, uncontrolled hyperbilirubinemia initially raised concern for outflow impairment, but the clinical course ultimately revealed reactivation of autoimmune hepatitis, which responded favorably to bortezomib [36]. This case underscores the diagnostic uncertainty inherent in the absence of histological confirmation. One female recipient with a GRWR of 0.9 and a single venous outflow presented with uncontrolled postoperative hyperbilirubinemia. Mechanical obstruction was excluded by magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography. The clinical picture was interpreted as a combination of sepsis and acute rejection. Due to limited resources, graft biopsy could not be performed. On postoperative day five, the patient developed ovarian apoplexy which required surgical intervention. Postoperative infectious complications progressed, and the patient ultimately died from sepsis.

The observation that clinical features suggestive of splenic artery steal syndrome occurred only in grafts without venoplasty should be interpreted cautiously. Given the retrospective design and limited number of events, this finding is hypothesis-generating and does not imply a causal protective effect of venous reconstruction.

Donor morbidity was analyzed according to the Clavien–Dindo classification. Overall, complications were predominantly minor and managed conservatively. Wound seroma developed in two donors and was treated with local measures. One donor developed hospital-acquired pneumonia (Clavien–Dindo grade II), which resolved with appropriate medical treatment. One donor developed acute renal dysfunction during antibacterial prophylaxis with sulperazone, presenting with oliguria, proteinuria, hematuria, peripheral edema, and pleural effusion. Sulperazone was discontinued, and diuretic therapy was initiated, resulting in complete recovery of renal function. Pleural effusion occurred in two donors and required therapeutic thoracentesis. Two donors developed postoperative bilomas that were successfully managed with percutaneous drainage. In two additional cases of bile leakage, surgical revision was necessary. One donor experienced postoperative bleeding due to slippage of a clip from the inferior vena cava, necessitating urgent reoperation. No donor mortality occurred in this series.

Comparison of our findings with the international literature reveals considerable alignment. The functional importance of anterior sector drainage, the necessity for detailed preoperative three-dimensional venous mapping, and the contribution of reconstructed middle hepatic vein tributaries to early graft performance are all consistent with established evidence [17, 34]. Our results also emphasize that acceptable outcomes can be achieved in a resource-constrained program when surgical planning is meticulous and techniques are adapted to the available materials. In cases with a high GRWR, the physiological reserve of the graft may compensate for small unreconstructed venous branches, and reconstruction is not always necessary or feasible. The frequent need to substitute autologous or unconventional conduits for synthetic or homologous grafts highlights the divergence between theoretically optimal strategies and the realities of clinical practice in a developing transplantation system.

Several limitations of the present study stem directly from the context in which the program operates. The absence of a deceased donor program precludes procurement and cryopreservation of vascular conduits. The intermittent unavailability and high cost of PTFE grafts restrict their use and limit uniformity of surgical technique. The lack of biopsy capability complicates postoperative diagnostic accuracy. In addition, the proportion of left lobe and left lateral segment grafts was small. Also, donor selection during the initial period was intentionally conservative, favoring anatomically straightforward grafts with favorable GRWR, which may introduce selection bias. In addition, the progressive accumulation of surgical experience and technical refinements over time represent potential confounding factors that may have influenced complication rates independently of venous reconstruction strategy. Therefore, subgroup comparisons should be interpreted cautiously. Despite these limitations, this series represents the early developmental phase of a national LDLT program and illustrates the feasibility of venous outflow reconstruction under resource-constrained conditions, while underscoring the importance of structured program maturation and cautious interpretation of outcomes.

Conclusion

This study demonstrates that venous outflow reconstruction in living donor liver transplantation can be successfully implemented in a resource-limited setting during the early phase of program development. In this cohort, autologous reconstruction techniques provided satisfactory early and mid-term patency without evidence of venous outflow–related graft loss.

Importantly, our experience indicates that clinical outcomes were influenced not only by the reconstructive strategy itself but also by progressive institutional learning, refinement of surgical technique, and more selective donor assessment. The marked reduction in biliary complications over time highlights the critical role of programmatic maturation in determining results.

These findings suggest that, in emerging transplant programs, structured technical standardization and accumulation of surgical experience may be as important as the choice of venous reconstruction method in achieving safe and reproducible outcomes. Further studies with larger cohorts and longer follow-up are required to confirm long-term durability.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by IRB of National Children's Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

Conceptualization: KS and TD; Methodology: KS; Project administration: KS; Supervision: KS; Visualization: KS, TD, and AS, Resources: BU, Data curation: KS, TD, and MN; Statistical analysis: KS; Writing – original draft: KS and TD; Writing – review and editing: All authors. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The authors(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2026.15985/full#supplementary-material

SUPPLEMENTARY VIDEO S1
Three-dimensional reconstruction of the hepatic vasculature in a living donor using SurgiPrint software. The use of 3D imaging enables a detailed assessment of vascular anatomy and spatial relationships between vessels, thereby facilitating precise preoperative surgical planning.

References

1. Balci D, Kirimker EO. Hepatic vein in living donor liver transplantation. *HBPD Int* (2020) 19(4):318–23. doi:10.1016/j.hbpd.2020.07.002

2. Voskanyan SE, Kolyshev IY, Bashkov AN, Artemiev AI, Rudakov VS, Shabalin MV, et al. Efferent blood supply to the right hepatic lobe regarding its transplantation from a living donor: variant anatomy, classification. Part 1. *Ann HPB Surg* (2023) 28(1):10–24. doi:10.16931/1995-5464.2023-1-10-24

3. Kow AWC, Liu J, Patel MS, De Martin E, Reddy MS, Soejima Y, et al. Post living donor liver transplantation small-for-size syndrome: definitions, timelines, biochemical, and clinical factors for diagnosis: guidelines from the ILTS-iLDLT-LTSI consensus conference. *Transplantation* (2023) 107(10):2226–37. doi:10.1097/TP.0000000000004770

4. Radulova-Mauersberger O, Weitz J, Riediger C. Vascular surgery in liver resection. *Langenbecks Arch Surg* (2021) 406(7):2217–48. doi:10.1007/s00423-021-02310-w

5. Catalano OA, Singh AH, Uppot RN, Hahn PF, Ferrone CR, Sahani DV. Vascular and biliary variants in the liver: implications for liver surgery. *Radiographics* (2008) 28(2): 359–78. doi:10.1148/rg.282075099

6. Voskanyan SE, Artemiev AI, Naidenov EV, Iyu K, Shabalin MV, Bashkov AN, et al. Vascular reconstructions and transplant technologies in liver surgery (part I). *Khirurgiia (Mosk)* (2023) 1:46–55. doi:10.17116/hirurgia202301146

7. Sakamoto K, Ogawa K, Tamura K, Ito C, Iwata M, Sakamoto A, et al. Importance of reconstruction of middle hepatic vein tributaries of right-lobe grafts in living donor liver transplantation: demonstration of the reconstruction technique. *Langenbecks Arch Surg* (2022) 407(4):1585–94. doi:10.1007/s00423-021-02398-0

8. Thorat A, Jeng LB, Yang HR, Li PC, Li ML, Yeh CC, et al. Outflow reconstruction for right liver allograft with multiple hepatic veins: "V-Plasty" of hepatic veins to form a common outflow channel versus 2 or more hepatic vein-to-inferior vena cava anastomoses in limited retrohepatic space. *Liver Transpl* (2016) 22(2):192–200. doi:10.1002/lt.24342

9. de Villa VH, Chen CL, Chen YS, Wang CC, Lin CC, Cheng YF, et al. Right lobe living donor liver transplantation-addressing the middle hepatic vein controversy. *Ann Surg* (2003) 238(2):275–82. doi:10.1097/01.SLA.0000081093.73347.28

10. Kasahara M, Takada Y, Fujimoto Y, Ogura Y, Ogawa K, Uryuhara K, et al. Impact of right lobe with middle hepatic vein graft in living-donor liver transplantation. *Am J Transpl* (2005) 5(6):1339–46. doi:10.1111/j.1600-6143.2005.00817.x

11. Wehrle CJ, Fujiki M, Satish S, Iuppa G, Campos L, Aucejo F, et al. Mechanisms and management of graft inflow and outflow in liver transplantation. *J Hepatol* (2025) 83(6): 1427–42. doi:10.1016/j.jhep.2025.06.024

12. Taha AMI, Abdalla AM, Hassan RA, Elkhateb AI, Ali AM. Outflow reconstruction in right lobe living donor liver transplant: middle hepatic vein reconstruction versus separate tributaries to inferior vena cava anastomosis. *Exp Clin Transpl* (2023) 21(3): 245–50. doi:10.6002/ect.2022.0417

13. Tan CHN, Hwang S, Bonney GK, Ganpathi IS, Madhavan K, Kow WCA. The influence of the middle hepatic vein and its impact on outcomes in right lobe living donor liver transplantation. *HPB (Oxford)* (2019) 21(5):547–56. doi:10.1016/j.hpb.2018.09.003

14. Cavicchioli M, Moglia A, Garret G, Puglia M, Vacavant A, Pugliese G, et al. D^2-RD-UNet: a dual-stage dual-class framework with connectivity correction for hepatic vessels segmentation. *Comput Biol Med* (2025) 195:110530. doi:10.1016/j.compbiomed.2025.110530

15. Dulundu E, Coşkun M, Aral RC, Akın Mİ, Gunal O, Yegen C, et al. Outflow reconstruction techniques in living donor liver transplantation (single center experience). *Int J Surg* (2020) 75:S30. doi:10.1016/j.ijsu.2020.01.119

16. Gautier SV, Tsiroulnikova OM, Moysyuk YG, Akhaladze DG, Tsiroulnikova IE, Silina OV, et al. Liver transplantation in children: six-year experience analysis. *Russ J Transpl Artif Organs* (2014) 16(3):54–62. doi:10.15825/1995-1191-2014-3-54-62

17. Makuuchi M, Sugawara Y. Living-donor liver transplantation using the left liver, with special reference to vein reconstruction. *Transplantation* (2003) 75(3 Suppl. l): S23–S24. doi:10.1097/01.TP.0000046617.21019.17

18. Karakaya E, Akdur A, Ayvazoğlu Soy EH, Boyvat F, Moray G, Haberal M. Vascular complications in pediatric liver transplants and their management. *Exp Clin Transpl* (2022) 20(Suppl. 3):72–5. doi:10.6002/ect.PediatricSymp2022.O23

19. Lin Z, Feng F, Yu Q, Ye Y, Yang Y, Zhu H, et al. Comparison of combined versus separate reconstruction of middle hepatic vein tributaries in the right lobe split liver transplantation. *Langenbecks Arch Surg* (2025) 410:181. doi:10.1007/s00423-025-03758-w

20. Pamecha V, Pattnaik B, Sinha PK, Patil NS, Mohapatra N, Sasturkar SV, et al. Single orifice outflow reconstruction: refining the venous outflow in modified right lobe live donor liver transplantation. *J Gastrointest Surg* (2021) 25(8):1962–72. doi:10.1007/s11605-020-04776-3

21. Semash K. Evaluation and management of living donors in the setting of living donor liver transplant program in the Republic of Uzbekistan. *Exp Clin Transpl* (2024) 22(9): 664–74. doi:10.6002/ect.2024.0148

22. Salavracos M, Danse E, Michoux N, de Hemptinne A, De Poortere T, Coubeau L. Contribution of 3D virtual modeling in locating hepatic metastases, particularly "vanishing tumors": a pilot study. *Artif Intell Surg* (2024) 4:331–47. doi:10.20517/ais.2024.23

23. Semash K, Dzhanbekov T, Akbarov M, Mirolimov M, Usmonov A, Razzokov N, et al. Implementation of a living donor liver transplantation program in the Republic of Uzbekistan: a report of the first 40 cases. *Clin Transpl Res* (2024) 38(2):116–27. doi:10.4285/ctr.24.0013

24. Del PL, Quintini C, Diago UT. The small-for-size syndrome in living donor liver transplantation: current management. *Updates Surg* (2025) 77(6):1797–806. doi:10.1007/s13304-024-01964-7

25. Kilercik H, Akbulut S, Elsarawy A, Aktas S, Alkara U, Sevmis S. Effect of complex venous outflow drainage reconstruction on postoperative graft function in right-lobe living donor liver transplantation. *J Clin Med* (2025) 14(6):2005. doi:10.3390/jcm14062005

26. Jeng LB, Thorat A, Yang HR, Li PC. Venous outflow reconstruction in living donor liver transplantation: dealing with venous anomalies. *World J Transpl* (2015) 5(4): 145–53. doi:10.5500/wjt.v5.i4.145

27. Park GC, Hwang S, Ha TY, Song GW, Jung DH, Ahn CS, et al. Hemashield vascular graft is a preferable prosthetic graft for middle hepatic vein reconstruction in living donor liver transplantation. *Ann Transpl* (2019) 24:639–46. doi:10.12659/AOT.919780

28. Mizuno S, Iida T, Yagi S, Usui M, Sakurai H, Isaji S, et al. Impact of venous drainage on regeneration of the anterior segment of right living-related liver grafts. *Clin Transpl* (2006) 20(4):509–16. doi:10.1111/j.1399-0012.2006.00515.x

29. Hata K, Hatano E. Optimizing venous outflow reconstruction for V5 and V8 in right-lobe living-donor liver transplantation: "half-circumferential anastomosis" using autologous vein grafts. *Hepatobiliary Surg Nutr* (2025) 14(5):817–23. doi:10.21037/hbsn-2025-244

30. Miller CM, Quintini C, Dhawan A, Durand F, Heimbach JK, Kim-Schluger HL, et al. The international liver transplantation society living donor liver transplant recipient guideline. *Transplantation* (2017) 101(5):938–44. doi:10.1097/TP.0000000000001571

31. Fasullo M, Patel M, Khanna L, Shah T. Post-transplant biliary complications: advances in pathophysiology, diagnosis, and treatment. *BMJ Open Gastroenterol* (2022) 9(1):e000778. doi:10.1136/bmjgast-2021-000778

32. Hakeem AR, Mathew JS, Aunés CV, Mazzola A, Alconchel F, Yoon YI, et al. Preventing small-for-size syndrome in living donor liver transplantation: guidelines from the ILTS-iLDLT-LTSI consensus conference. *Transplantation* (2023) 107(10): 2203–15. doi:10.1097/TP.0000000000004769

33. Charlton M, Levitsky J, Aqel B, O'Grady J, Hemibach J, Rinella M, et al. International liver transplantation society consensus statement on immunosuppression in liver transplant recipients. *Transplantation* (2018) 102(5): 727–43. doi:10.1097/TP.0000000000002147

34. Durairaj MS, Shaji Mathew J, Mallick S, Nair K, Manikandan K, Titus Varghese C, et al. Middle hepatic vein reconstruction in adult living donor liver transplantation: a randomized clinical trial. *Br J Surg* (2021) 108(12):1426–32. doi:10.1093/bjs/znab346

35. Kirchner VA, Shankar S, Victor DW, 3rd, Tanaka T, Goldaracena N, Troisi RI, et al. Management of established small-for-size syndrome in post living donor liver transplantation: medical, radiological, and surgical interventions: guidelines from the ILTS-iLDLT-LTSI consensus conference. *Transplantation* (2023) 107(10):2238–46. doi:10.1097/TP.0000000000004771

36. Semash K, Dzhanbekov T, Nasirov M, Monakhov A, Gadzhieva P. Bortezomib as a potential treatment for recurrent autoimmune hepatitis following pediatric liver transplantation. *Pediatr Transpl* (2025) 29(4):e70082. doi:10.1111/petr.70082

ESOT | Transplant International

TYPE Original Research
PUBLISHED 26 May 2026
DOI 10.3389/ti.2026.16059

Check for updates

OPEN ACCESS

*CORRESPONDENCE
Sophie Caillard,
sophie.caillard@chru-strasbourg.fr

†These authors share first authorship

‡These authors share last authorship

RECEIVED 13 December 2025
REVISED 22 April 2026
ACCEPTED 01 May 2026
PUBLISHED 26 May 2026

CITATION
Mangin M, Lucas J, Taton B, Anglicheau D, Blancho G, Bertrand D, Leon J, Apithy M-J, Benotmane I, Couzi L and Caillard S (2026) ABO-incompatible kidney transplantation: impact of apheresis on graft and patient survival in recipients with low isoagglutinin titer. *Transpl. Int.* 39:16059. doi: 10.3389/ti.2026.16059

COPYRIGHT
© 2026 Mangin, Lucas, Taton, Anglicheau, Blancho, Bertrand, Leon, Apithy, Benotmane, Couzi and Caillard. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

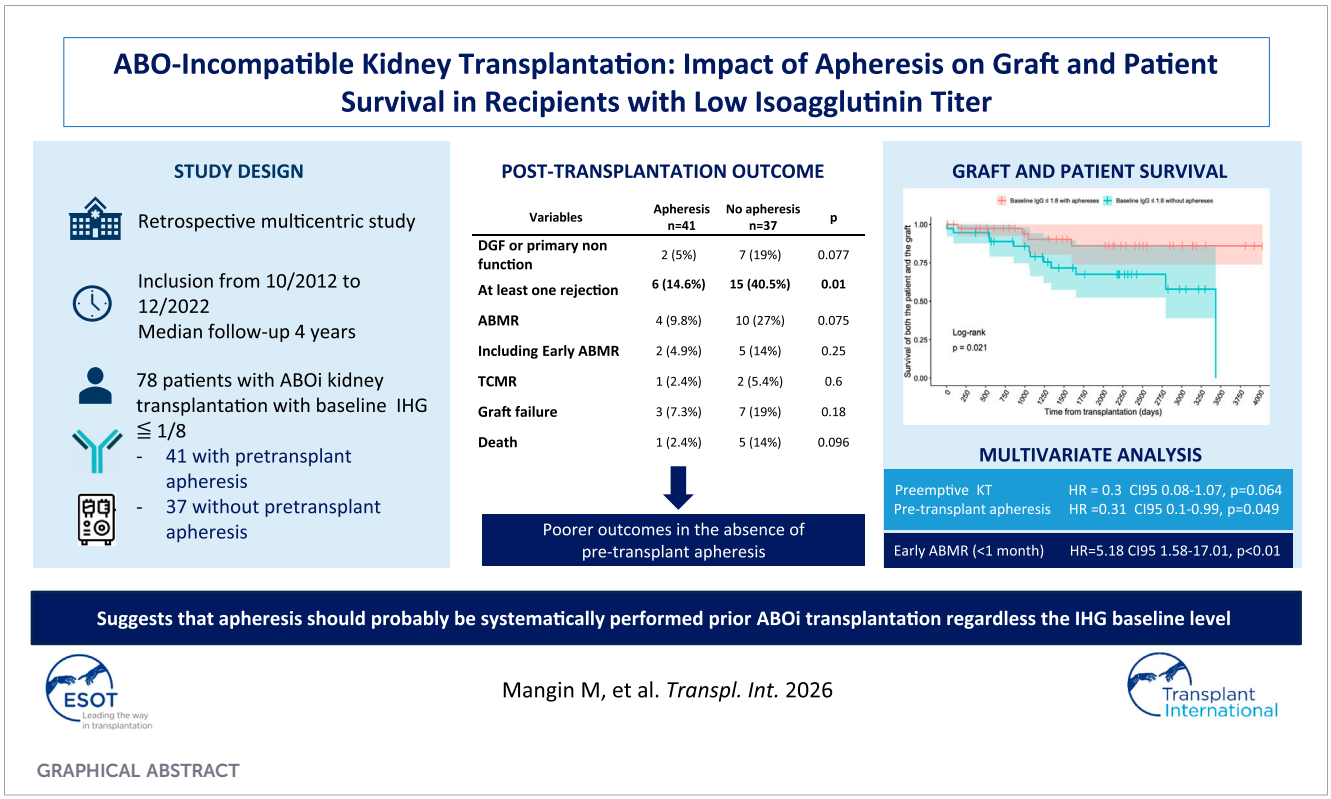
ABO-incompatible kidney transplantation: impact of apheresis on graft and patient survival in recipients with low isoagglutinin titer

Marion Mangin[1†], Juliette Lucas[2†], Benjamin Taton[2,3], Dany Anglicheau[4], Gilles Blancho[5], Dominique Bertrand[6], Juliette Leon[4], Marie-Joëlle Apithy[7], Ilies Benotmane[1,8], Lionel Couzi[2,9‡] and Sophie Caillard[1,8*‡]

[1]Department of Nephrology Dialysis and Transplantation, Strasbourg University Hospital, Strasbourg, France, [2]Department of Nephrology, Transplantation, Dialysis and Apheresis, Bordeaux University Hospital, Bordeaux, France, [3]INSERM U1219 Bordeaux Population Health, Equipe LEHA, Bordeaux University, Bordeaux, France, [4]Department of Kidney and Metabolic Diseases, Transplantation and Clinical Immunology, Necker Hospital, Assistance Publique - Hôpitaux de Paris, Université Paris Cité, Paris, France, [5]CHU Nantes, Nantes Université, Service de Néphrologie - Immunologie Clinique, ITUN, INSERM, Center for Research in Transplantation and Translational Immunology, UMR 1064, Nantes, France, [6]Nephrology and Transplantation Department, Rouen University Hospital, Rouen, France, [7]Etablissement Francais du Sang Grand Est, Strasbourg, France, [8]Molecular ImmunoRhumatology, INSERM UMR_S1109, Strasbourg University, Strasbourg, France, [9]CNRS-UMR 5164 ImmunoConcEpT, Bordeaux University, Bordeaux, France

ABO-incompatible (ABOi) kidney transplantation carries a high risk of acute antibody-mediated rejection due to the presence of isoagglutinins. To mitigate this risk, current protocols recommend performing apheresis before transplantation. Our objective was to evaluate outcomes in ABOi recipients with low isoagglutinin titers, comparing those who did and did not undergo pre-transplant apheresis. We conducted a multicenter study including recipients of ABOi kidney transplants between 2012 and 2022. A total of 78 patients with baseline isoagglutinin titers ≤1:8 were included; 41 received pre-transplant apheresis, 37 did not. Patients who did not undergo apheresis had more rejection episodes (p = 0.01), and a trend toward higher rates of delayed graft function and antibody mediated rejection, which adversely impacted patient and graft survival. At 3 years, event-free survival (death or graft loss) was 90% in the apheresis versus 79% in the no-apheresis group (p = 0.02). In multivariable analysis, factors associated with improved event-free survival included pre-transplant apheresis (HR = 0.31, p = 0.049) while ABMR within the first month was associated with poorer outcome (HR = 5.18, p = 0.0007). No differences emerged regarding the occurrence of overall infections. These findings suggest that apheresis should be systematically performed prior to ABOi transplantation, regardless of baseline isoagglutinin titer.

KEYWORDS
ABO incompatible, antibody mediated rejection, apheresis, delayed graft function, infections



GRAPHICAL ABSTRACT

Introduction

ABO-incompatible (ABOi) kidney transplantation has expanded the living donor pool by overcoming the traditional limitations imposed by ABO blood group compatibility. This strategy has become increasingly relevant in the context of organ shortage and prolonged waiting times, particularly for recipients with less common blood types. In addition to increasing access to transplantation, ABOi kidney transplantation retains the inherent advantages of living donation: elective surgery scheduling, better immunological matching through donor selection, and shorter cold ischemia times. Thanks to advances in immunosuppressive strategies, ABOi transplantation is now routinely performed in many centers. Protocols typically include pre-transplant rituximab administration, and extracorporeal antibody removal—via plasma exchange (PE) or immunoadsorption (IA)—in patients with elevated isoagglutinin titers. Several studies have documented favorable outcomes following ABO-incompatible kidney transplantation, supporting the efficacy of contemporary desensitization strategies [1, 2]. Nonetheless, these findings remain debated, as two meta-analyses reported inferior graft survival in ABOi recipients compared with ABO-compatible controls [3, 4]. ABOi transplantation continues to represent a procedure with substantial immunologic risk, primarily due to the potential for early antibody-mediated rejection (ABMR) driven by anti-A and/or anti-B antibodies, with a relative risk approaching four [4], and occasionally manifesting as severe thrombotic microangiopathy [5]. The relationship between pre-transplant isoagglutinin titers and rejection risk remains controversial: while several investigations have demonstrated a positive correlation between higher titers and increased incidence or severity of rejection [5], others have found no such association [6, 7].

Although a target titer of ≤1:8 on the day of transplantation is frequently used, this threshold varies across institutions. Moreover, in patients with low baseline isoagglutinin levels, the role of apheresis remains controversial. Indeed, despite their potential immunological benefits, apheresis procedures are associated with significant logistical, financial, and clinical burdens. These include the need for central venous access, increased bleeding risk due to coagulation factor depletion, and heightened infection risk. Some studies have also reported higher 1-year mortality and infection rates in ABOi recipients, likely linked to intensified immunosuppressive protocols [1, 4]. Over the past decade, some centers have adopted protocols that omit apheresis when pre-transplant isoagglutinin titers are already below the target threshold, typically ≤1:8. In this context, Masterson [8] reported the outcomes of 20 ABO-incompatible kidney transplants performed at the Royal Melbourne Hospital using a standard immunosuppressive regimen with basiliximab induction but without rituximab nor pre-transplant

Abbreviations: ABMR, antibody mediated rejection; APKD, autosomal polycystic kidney disease; ATG, Anti Thymoglobulin; CTIN, chronic tubulo interstitial nephropathy; DGF, Delayed Graft Function; DFPP, double filtration plasmapheresis; DSA, donor specific antibody; eGFR, estimated glomerular filtration rate; IA, immunoadsorption; IHG, Isohemagglutinin; MFI, mean fluorescence intensity; PE, plasma exchange; TCMR, T cell mediated rejection.

apheresis, in patients with baseline anti-A and/or anti-B IgG titers ≤1:16 confirmed by three independent techniques. Graft survival at 3 years was 100%, with no significant impairment of graft function. The incidence of ABMR was 5%, comparable to rates reported in studies where isoagglutinin depletion protocols were used.

The aim of our study was to evaluate patient outcome as well as graft and patient survival following ABOi kidney transplantation in a French cohort, in patients with initial low isoagglutinin titers (≤1:8) according to whether or not pre-transplant apheresis was performed. We also assessed the incidence of immunological and infectious complications, to determine whether apheresis conferred any benefit in this low-risk population.

Patients and methods

For this purpose, we conducted a multicenter retrospective study involving recipients of ABO-incompatible (ABOi) living donor kidney transplants. Participating centers included Necker Hospital (Paris), Strasbourg University hospital, Rouen University hospital, Nantes University hospital, and Bordeaux University hospital. Ethical approval was granted from Bordeaux institutional review board (CER-BDX 2025-338).

Study population

Eligible patients were all adults who underwent ABO incompatible living donor kidney transplantation with a baseline anti-A and/or anti-B IgG isoagglutinin titer ≤1:8. Transplants were performed between October 2012 and December 2022. Follow-up was completed until October 31, 2023.

Study design and objectives

Our objectives were to compare: i) graft and patient survival -defined as survival free from graft loss or death-according to the use or absence of pre-transplant apheresis in patients with low baseline IgG isoagglutinin titers (≤1:8); ii) the incidence of immunological complications - ABMR, T cell-mediated rejection [TCMR], borderline rejection- and iii) the occurrence of infectious complications between groups. We also aimed to identify risk factors associated with graft and patient survival.

Data collection

Clinical data were retrospectively extracted from medical records—both paper and electronic—using local hospital systems: Sined and DxCare (Strasbourg), Orbis (Necker), Sined (Rouen), Millenium and DIVAT database (Nantes), DxCare and R@N (Bordeaux). Isoagglutinin titers were provided by the French Blood Establishment (EFS). We recorded rituximab administration (date and dose), induction therapy (anti-thymocyte globulin (ATG) or basiliximab), and maintenance immunosuppression at hospital discharge (tacrolimus, cyclosporine, mycophenolate mofetil [MMF], corticosteroids). The number and type of apheresis sessions (PE, IA, or double filtration plasmapheresis [DFPP]) performed pre- and post-transplant were documented. The use of intravenous immunoglobulin (IVIg) in the post-transplant period was also recorded. Presence of preformed or *de novo* donor specific antibodies (DSA) was recorded considering a MFI threshold of 1000 (Luminex assay, Lab. One lambda, in all centers).

Isoagglutinin titers

Anti-A and/or anti-B IgG and IgM titers were measured at baseline (prior to desensitization), on the day before or the day of transplantation (pre-transplant titer), and post-transplant at week 1, month 1, month 3, and month 12, as well as at the time of any suspected rejection. For final analysis, only IgG titers were considered. Techniques used for isoagglutinin measurement varied by center: tube hemagglutination at Necker, gel hemagglutination at Rouen, Strasbourg, Bordeaux and Nantes.

Pre-transplant desensitization

Rituximab (a single dose of 375 mg/m^2) was administered before transplantation (day −30) in all but four patients, according to local protocols. Apheresis sessions were performed according to local procedures. It was systematically applied in Strasbourg (9 patients, treated with 3 sessions) and in the majority of patients in Necker (24/28 patients treated with 1–13 sessions; mean 3.3 sessions). In contrast, apheresis was generally not used in Rouen (6/9 patients without apheresis), Bordeaux (9/11 patients without apheresis), or Nantes (15/18 patients without apheresis).

The apheresis techniques used were as follows: Glycorex immunoadsorption (n = 5) and plasma exchange (n = 4) in Strasbourg; plasma exchange in Necker (n = 23), except for one patient with preformed DSA treated with immunoadsorption (IA); plasma exchange in Bordeaux (n = 2) and Nantes (n = 3); and immunoadsorption (IA, Globaffin®) in Rouen (n = 3). Additional details regarding local procedures are provided in Supplementary Table S1.

Post-transplant follow-up

Delayed graft function (DGF) was defined as the need for at least one dialysis session during the first post-transplant week. Follow-up variables included serum creatinine and glomerular filtration rate according to CKD EPI formula at 3, 12, and 36 months, graft function status at end of follow-up, date of return to dialysis (if applicable), patient death (date and cause: cardiovascular, oncologic, or infectious), and biopsy-proven rejection episodes (classified according to Banff criteria). The presence of *de novo* DSA, including MFI and class, and isoagglutinin titer at the time of rejection, were also recorded. ABMR was defined as follows: immediate cortical necrosis consistent with hyperacute rejection occurring within hours after transplantation, early thrombotic microangiopathy, or histological findings consistent with ABMR according to the Banff classification on graft biopsy performed later post-transplant. Early ABMR was defined as ABMR rejection occurring during the first post-transplant month.

For infectious complications, the type and date of each event were collected. In cases of recurrent infections of the same type, only

the first occurrence was dated. Events occurring after graft loss were not included in the analysis.

Statistical analysis

All statistical analyses were performed using R software (version 4.3.2) and appropriate packages. Quantitative variables with a symmetrical distribution were summarized as mean ± standard deviation (SD), while non-normally distributed quantitative variables and ordinal data were presented as median [first quartile; third quartile]. Categorical variables were expressed as counts (percentage). A p-value <0.05 was considered statistically significant. Group comparisons were conducted using Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables. Survival analyses were performed using a composite endpoint defined as "graft loss or patient death." Event-free survival was estimated using Kaplan–Meier curves, and differences between groups were assessed with the log-rank test. For the analysis of rejection events, cumulative incidence functions were estimated using the Aalen-Johansen estimator, accounting for graft loss or death as competing events. Between-group comparisons were performed using Gray's test. Risk factors associated with ABMR, biopsy-proved rejection episodes (BPAR: ABMR + TCMR), and a composite endpoint of graft loss or death were investigated using Cox proportional hazards models. Cox regression results are reported as hazard ratios (HR) with 95% confidence intervals (95% CI). Comparisons of HRs to the null value (HR = 1) were assessed using Wald tests. Explanatory variables were first assessed in univariate analyses including all patients with available data. A multivariable Cox model was then constructed, incorporating variables that were statistically associated with the outcome in univariate analysis and those considered clinically relevant ($p \leq 0.2$). In addition, we performed a LASSO-Cox regression to assess the association of the covariables with death and graft failure. The regularization coefficient was selected using 5-fold cross-validation as the one that optimized the C-statistics [REF glmnet]. Stability of variable selection was assessed by bootstrapping the whole procedure (1000 samples) then computing the proportion of samples for which each variable was selected by the LASSO-Cox regression.

Results

Patient characteristics

A total of 78 patients with baseline anti-A and/or anti-B IgG isoagglutinin titers ≤1:8 were included (see characteristics in Table 1). The cohort was predominantly male (69%). Preemptive transplantation was performed in 45% of cases. Prior to transplantation, 58% of patients (n = 45) were sensitized and 6 (7.7%) had also preformed DSA with a median sum of MFI of 1400 (range 1000–6500). Blood group O was the most common among recipients (46%). Donors were predominantly female (71%), with blood group A being the most frequent (63%), followed by group B (26%) and AB (12%). The most common donor-recipient combination was from a group A donor to a group O recipient, accounting for 36% of cases. Most patients (94%) received anti-CD20 monoclonal antibody therapy prior to transplantation.

Among the 41 patients (53%) who did undergo apheresis, PE alone was most commonly used (n = 31), followed by IA (n = 6), and a combination of PE and IA (n = 3). One patient received a combination of PE and DFPP. On average, patients who underwent apheresis received 3 sessions (range: 2–5). In contrast, pre-transplant apheresis was not performed in 37 patients (47%).

The main baseline differences between patients who did and did not undergo pre-transplant apheresis are summarized in Table 1. Of note, one of the 37 patients with a baseline IgG ≤1:8 who did not undergo apheresis showed an increase in IgG titer to 1:16 on the day of transplantation. Briefly, patients in the no-apheresis group were less often treated with IVIG and MMF ($p < 0.01$ and 0.046 respectively).

Post transplant outcome

In the whole cohort, patient survival after transplantation was 99.5% at 1 year, 97% at 3 years, and 95.5% at 5 years and graft survival was 94.3% at 1 year, 90% at 3 years, and 86% at 5 years.

A total of eight patients experienced delayed graft function and one patient displayed primary non-function (Table 2). Only 4 patients showed a IHG rebound (defined as a post-transplant IgG titer ≥1:16) in the first post-transplant month. During follow-up, we recorded 22 rejection episodes which occurred in 21 patients, including 14 ABMR, 3 TCMR, and 5 borderline rejections. Among them, 7 patients developed early acute ABMR, most cases occurring immediately after transplantation. Their characteristics are described in Supplementary Table S2. During follow up, 11 patients developed *de novo* DSA, after a median delay of 15.3 months (range 0.5–83 months). Cumulative incidence of ABMR was 12% at 1 year, and 19% at 3 and 5 years (Figure 1A). Ten patients lost their graft (see Supplementary Table S3) and 6 died. Median follow-up time after transplantation was 4.29 years [2.22, 6.72].

Comparison of outcomes according to pre-transplant apheresis status is shown in Table 2. In the group without apheresis, one patient experienced graft loss due to cortical necrosis at the time of transplantation, and four patients developed hyperacute rejection with thrombotic microangiopathy. Consistent with these findings, there was a trend toward a higher incidence of DGF in patients who did not receive apheresis compared to those who did (19% vs. 5%, p = 0.077). In 5 out of 8 patients with DGF (four in the no-apheresis group and one in the apheresis group), DGF was attributed to thrombotic microangiopathy and/or hyperacute rejection. The evolution of isoagglutinin titers during the first post-transplantation year according to the groups is depicted in Supplementary Figure S1 and showed a rebound in 3 patients of the apheresis group and 1 in the no-apheresis group. Post transplant apheresis were performed in 5 patients of each group, according to local center procedures, due to isoagglutinin rebound (n = 3) and/or rejection episodes (n = 7).

Rejections episodes were more frequent in the no-apheresis group (40.5% vs. 14.6%, p = 0.01). Early ABMR episodes were also more frequent in the no-apheresis group (14% vs. 4.9%), although the difference did not reach statistical significance (p = 0.25). Of

10.3389/ti.2026.16059

TABLE 1 Baseline characteristics of 78 kidney transplantation recipients with a baseline isoagglutinin titers ≤1:8 and comparison between groups according to pre-transplant apheresis sessions. Mean ± SD, median [IQR], number (%).

Variables	Total cohort n = 78	Patients with apheresis n = 41	Patients without apheresis n = 37	P*
Recipient age (year)	50.37 ± 13.8	50.04 ± 13.81	50.73 ± 13.98	0.83
Recipient sex (M/F)	54 (69%)/24(31%)	29 (71%)/12 (29%)	25 (68%)/12 (32%)	0.81
Nephropathy				0.45
CTIN	30 (38%)	17 (41%)	13 (35%)	
Glomerulopathy	22 (28%)	10 (24%)	12 (32%)	
APKD	14 (18%)	8 (20%)	6 (16%)	
Vascular nephropathy	7 (9%)	2 (5%)	5 (14%)	
Other	5 (6.4%)	4 (10%)	1 (3%)	
Preemptive transplantation (yes/no)	35 (45%)/43(55%)	17 (41%)/24 (59%)	18 (49%)/19 (51%)	0.65
Graft rank				0.22
1	65 (83%)	35 (85%)	30 (81%)	
2 or more	13 (16.6%)	6 (15%)	7 (19%)	
Preformed DSA (yes/no)	6 (7.7%)/72(92.3)	4 (9.7%)/37 (90.3%)	2 (5.4%)/35 (94.6%)	0.68
Blood type incompatibility				0.76
A > B	21 (27%)	12 (29%)	9 (24%)	
A > O	28 (36%)	17 (41%)	11 (30%)	
AB > A	6 (7.7%)	3 (7%)	3 (8%)	
AB > B	3 (3.8%)	1 (2%)	2 (5%)	
B > A	12 (15%)	5 (12%)	7 (19%)	
B > O	8 (10%)	3 (7%)	5 (14%)	
Rituximab (yes/no)	73 (94%)/5(6.4%)	40 (98%)/1 (2.4%)	33 (89%)/4 (11%)	0.18
Baseline IHG titer				0.18
0 or 1:1	20 (25.6%)	7 (17%)	13 (35.1%)	
1:2 or 1:4	37 (47.4%)	21 (51.2%)	16 (43.2%)	
1:8	21 (26.9%)	13 (31.7%)	8 (21.6%)	
Pre transplant apheresis				
PE	31 (40%)	31 (40%)	—	
IA	6 (7.7%)	6 (7.7%)	—	
IA + PE	3 (3.8%)	3 (3.8%)	—	
PE + DFPP	1 (1.3%)	1 (1.3%)	—	
Pre transplant apheresis number	3 [2, 5]	3 [2, 5]	—	
Pre transplant IA number (n = 9)	3 [2, 5]	3 [2, 5]	—	
Pre transplant PE number (n = 35)	3 [1, 5]	3 [1, 5]	—	
IHG titer at time of transplantation				0.19
0 or 1:1	34 (43.5%)	22 (53.6%)	12 (32.4%)	
1:2 or 1:4	29 (31.2%)	12 (29.3%)	17 (45.9%)	
1:8	13 (17%)	6 (14.6%)	7 (18.9%)	
1:16	1 (1.3%)	0 (0%)	1 (3%)	
Missing data	1 (1.3%)	1 (2.4%)	—	
Donor sex (M/F)	23 (29%)/55(71%)	12 (29%)/29 (71%)	11(30%)/26 (70%)	1

(*Continued*)

TABLE 1 Continued

Variables	Total cohort n = 78	Patients with apheresis n = 41	Patients without apheresis n = 37	P*
Donor age (year)	53.95 ± 12.23	54.2 ± 11.51	53.68 ± 13.14	0.85
Donor GFR (mL/min)	94.68 ± 13.31	92.79 ± 13.28	96.76 ± 13.21	0.19
Induction: basiliximab/ATG	34 (44%)/44(56%)	27 (66%)/14 (34%)	17 (46%)/20 (54%)	0.11
CNI: Tacrolimus/Cyclosporine	76 (97%)/2(2.6%)	39 (95%)/2 (5%)	37 (100%)/0 (0%)	0.49
MMF (yes/no)	74 (95%)/4(5.1%)	41 (100%)/0 (0%)	33 (89%)/4 (11%)	0.046
IVIg (yes/no)	26 (33%)/52(67%)	21 (51%)/20 (49%)	5 (14%)/32 (86%)	0.00062

CTIN, chronic tubulo interstitial nephropathy; APKD, autosomal Polycystic Kidney Disease; DSA, donor specific antibodies; PE, plasma exchange; IA: immunoadsorption; DFPP, double filtration plasmapheresis; GFR, glomerular filtration rate; IHG, Isohemagglutinin (IgG only); ATG, Anti-Thymocyte Globulin; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; IVIg, Intravenous Immunoglobulin.
*comparisons between groups with or without apheresis.

TABLE 2 Post transplantation outcome of the whole population, and in the 2 groups of patients, according to pretransplant apheresis sessions. Median [IQR], number (%).

Variables	Total Cohort, n = 78	Patients with apheresis, n = 41	Patients without apheresis, n = 37	P*
DGF or primary non function				0.077
No	69 (88%)	39 (95%)	30 (81%)	
Yes	9 (12%)$	2 (5%)	7 (19%)$	
Post transplant apheresis				0.24
none	65 (83.3%)	33 (80.5%)	32 (86%)	
PE	10 (16.7%)	5 (12.2%)	5 (14%)	
Missing data	3 (3.9%)	3 (7.3%)	0	
Number of post-transplant PE sessions	5 [3; 5]	5 [3; 5]	4 [2; 5]	0.67
IHG titer ≥1:16 during the first month post-transplant (%)	4/68 (5.9%)	3/37 (8.1%)	1/31 (3.2%)	0.39
De novo donor-specific antibody	11 (14.1%)	6 (14.6%)	5 (13.5%)	0.88
At least one rejection (yes/no)	21(26.9%)/57(73.1%)	6(14.6%)/35 (85.4%)	15(40.5%)/22(59.5)	0.01
ABMR (yes/no)	14 (17%)/65(83%)	4 (9.8%)/37 (90%)	10 (27%)/27 (73%)	0.075
Including early ABMR (Yes/No)	7 (9%)/71 (91%)	2 (4.9%)/39 (95%)	5 (14%)/32 (86%)	0.25
TCMR (yes/no)	3 (3.8%)/75(96%)	1 (2.4%)/40 (98%)	2 (5.4%)/35 (95%)	0.6
Borderline rejection (yes/no)	5 (6.4%)/73(94%)	1 ((2.4%)/40 (97.6%)	4 (10.8%)/33 (89.2%)	0.18
Graft failure (yes/no)	10 (13%)/68(87%)	3 (7.3%)/38 (93%)	7 (19%)/30 (81%)	0.18
Death (yes/no)	6 (7.7%)/72(92%)	1** (2.4%)/40 (98%)	5*** (14%)/32 (86%)	0.096

DGF, delayed graft function; PE, plasma exchange; ABMR, Antibody Mediated Rejection; Early ABMR, ABMR, rejection occurring during the first post-transplant month; TCMR, T-cell Mediated Rejection.
$1 patient with primary non function.
*comparisons between groups with or without apheresis.
**from neoplasia.
***1 from cardiovascular cause (heart rhythm disorder), 1 from infectious cause (pneumocystis) and 3 due to neoplasia.

note, one of the two early ABMR episodes in the apheresis group occurred in a patient with high preformed donor-specific antibodies (DSA) with a cumulated MFI >6000. Kaplan–Meier analysis similarly demonstrated a trend toward a higher incidence of ABMR episodes in patients who did not receive apheresis (p = 0.073, Figure 1B). Evolution of glomerular filtration rate in both group during the study is depicted in Figure 2 and was not different between groups.

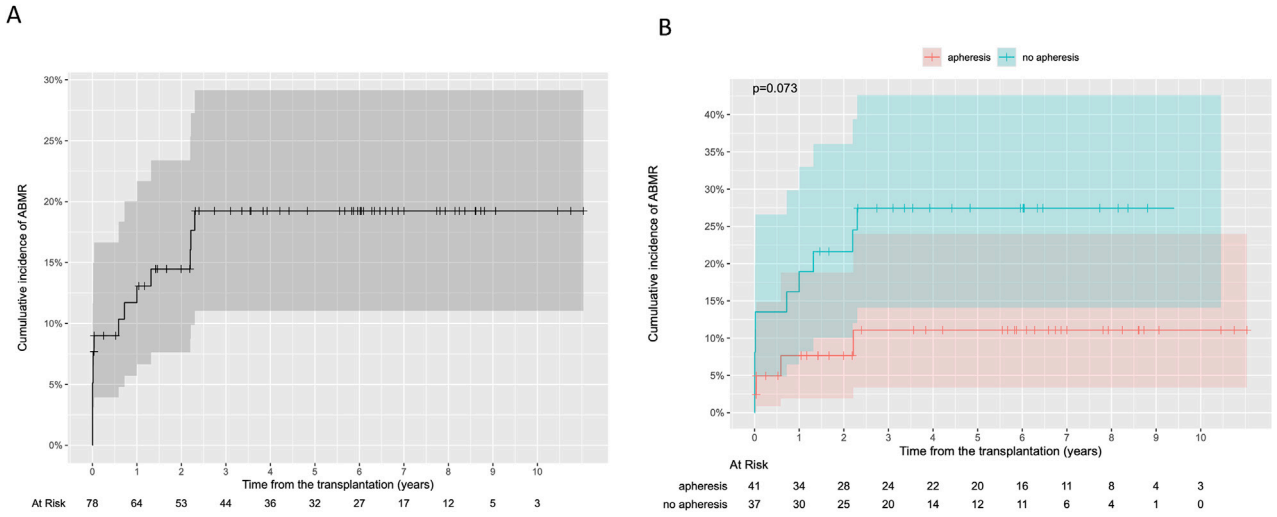


FIGURE 1
(A) Cumulative incidence of ABMR in the whole cohort (n = 71) **(B)** Antibody mediated rejection cumulative incidence according to pre-transplant apheresis status. Patients who did not undergo apheresis had a trend toward more ABMR episodes (p = 0.073, log-rank test). Patients with apheresis, n = 41, red curve and patients without pretransplant apheresis, n = 37, blue curve.

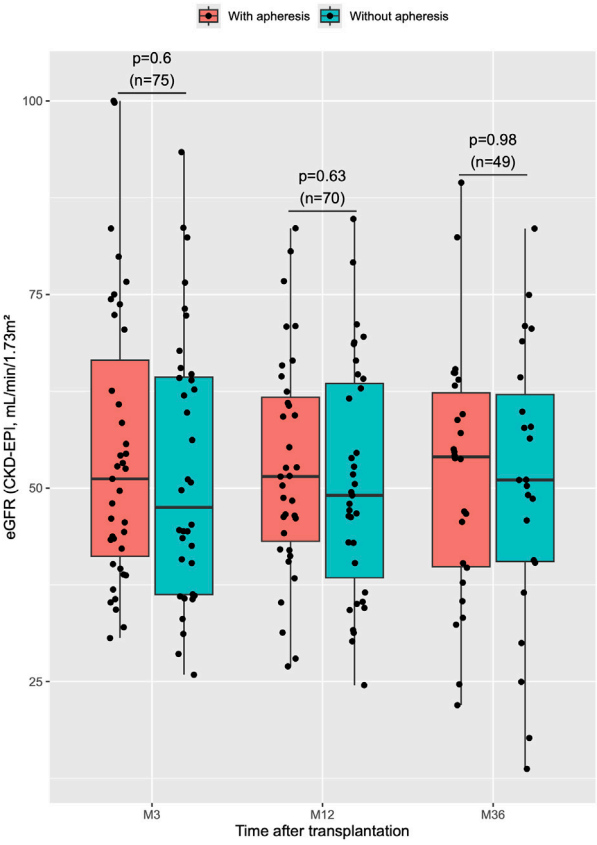


FIGURE 2
Evolution of eDFG (CKD EPI formula) in the 3 post-transplant years, in patients with a functioning graft, in apheresis group (red plots) compared to the no-apheresis group (blue plots).

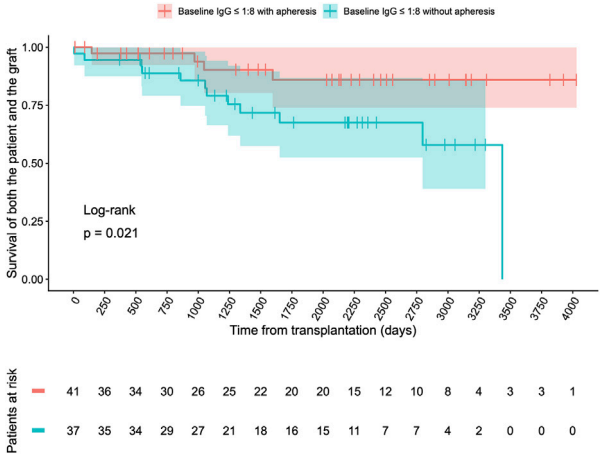


FIGURE 3
Event-free survival (graft survival and patient survival) according to pre-transplant apheresis status. Patients who did not undergo apheresis had significantly lower event-free survival (p = 0.021, log-rank test). Patients with apheresis, n = 41, red curve and patients without pretransplant apheresis, n = 37, blue curve.

Patient and graft survival

A significant difference in event-free survival—defined as survival free from graft loss or all-cause mortality—was observed comparing patients who underwent pre-transplant apheresis and those who did not (p = 0.021), with inferior outcomes in the no-apheresis group (Figure 3). At 3 years, event-free survival (death or graft loss) was 90% in the apheresis group and 79% in the no-apheresis group. At 5 years, it was 86% in the apheresis group and

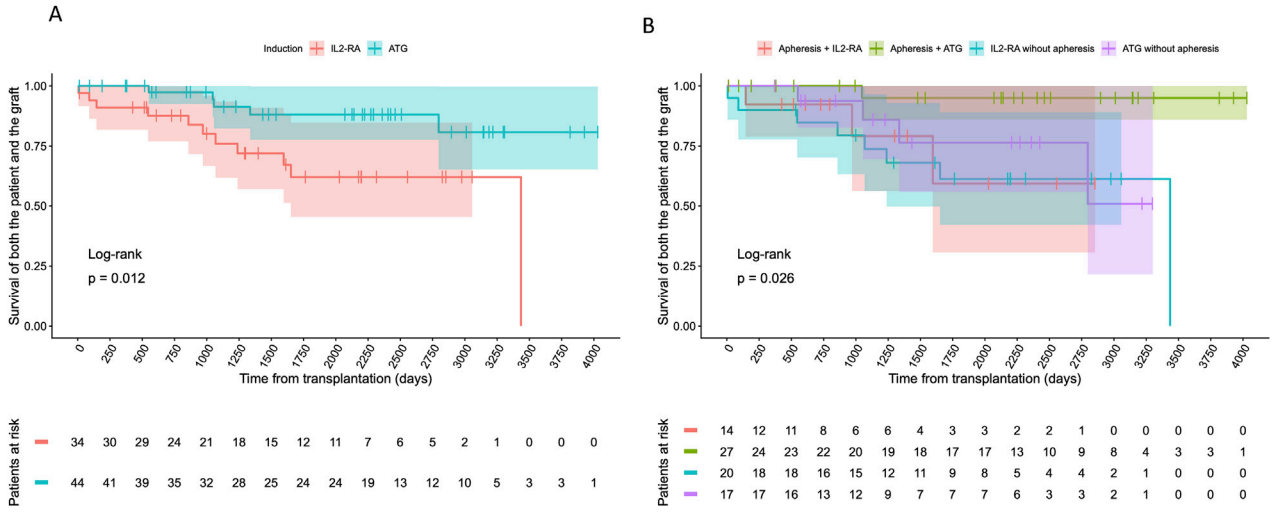


FIGURE 4
(A) Event-free survival stratified by induction therapy. Thymoglobulin was associated with significantly better outcomes compared to Basiliximab; Basiliximab, n = 34, red curve and ATG, n = 44, blue curve. **(B)** Event-free survival by combined stratification of pre-transplant apheresis and induction regimen. The subgroup receiving both apheresis and thymoglobulin induction showed the highest survival rates (p = 0.026, log-rank test): ATG + apheresis, n = 27 green curve; ATG without apheresis, n = 17, purple curve; Basiliximab + apheresis, n = 14, red curve; and Basiliximab without apheresis, n = 20, blue curve.

68% in the no-apheresis group. When event-free survival was analyzed according to baseline IHG titer strata, no significant differences were observed between groups (Supplementary Figure S2). Subsequent analysis based on the induction regimen revealed that patients receiving thymoglobulin (n = 44) demonstrated superior event-free survival compared to those treated with Basiliximab (n = 34) (Figure 4A). When stratifying both apheresis status and induction therapy, the subgroup receiving pre-transplant apheresis in combination with thymoglobulin induction exhibited the most favorable outcome (p = 0.026) (Figure 4B).

When death and graft loss were analyzed separately, a higher number of events was observed in the group that did not undergo pre-transplant apheresis, but these differences did not reach statistical significance (p = 0.07 for mortality and p = 0.19 for graft loss, Supplementary Figure S3). Precise causes of graft loss are provided in Supplementary Table S3. When comparing outcomes based on induction therapy, graft loss was significantly less frequent among patients who received thymoglobulin compared to those who received basiliximab (p = 0.012, Supplementary Figure S4), while no significant difference was observed in mortality between the two groups (p = 0.61, data not shown).

Factors associated with patient and graft survival and rejection episodes (AMR and BPAR)

Factors significantly associated with improved patient and graft survival in univariate analysis were the use of pre-transplant apheresis (HR = 0.28, 95% CI 0.091–0.89, p = 0.03) and thymoglobulin induction therapy (HR = 0.28, 95% CI 0.096–0.81, p = 0.019). Conversely, delayed graft function and early ABMR were linked to an increased risk of graft loss and patient death (HR = 3.3, 95% CI 1.1–10, p = 0.041 and HR = 6.9, 95% CI 2.1–22, p = 0.0012, respectively). The presence of preformed donor-specific antibodies was not statistically associated with outcomes in this cohort. These findings are summarized in Table 3. In multivariable Cox regression analysis, pre-transplant apheresis was independently associated with improved patient and graft survival (HR = 0.31, 95% CI 0.10–0.99, p = 0.049). Conversely, the occurrence of early ABMR (within the first month post-transplant) was significantly associated with an increased risk of patient death and graft loss (HR = 5.18 95% CI 1.58–17.01, p = 0.0007). These results are summarized in Table 4. The variables selected by the LASSO model corroborate those identified in the multivariate Cox model (Supplementary Figure S5).

Regarding rejection episodes, we observed a trend toward an association between pre-transplant apheresis and ABMR or BPAR (p = 0.08 and 0.09, respectively), in both univariate and multivariate analyses (Supplementary Tables S4, S5).

Infections

No differences were observed between groups with or without pre-transplant apheresis considering occurrence of all infections. The probability of viral, bacterial and fungal infections at 1- and 3-year post-transplantation according to apheresis group are described in Table 5. There were more fungal or parasitic infections in the no apheresis group (p = 0.047) –1 microsporidiosis *vs.* 2 pneumocystis pneumonia, 2 candidiases and 3 cryptosporidioses-, and a trend toward a higher incidence of CMV infection among patients who underwent apheresis (p = 0.056; Supplementary Figure S6). Presumed BKV nephropathy incidence was not different between the two groups.

10.3389/ti.2026.16059

TABLE 3 Factors associated with event free survival (graft survival and patient survival) in 78 kidney transplant recipients with low (≤1:8) IHG in univariate analysis.

Variables	HR	CI95	p
Recipient age	1	[0.97; 1]	0.81
Recipient sex (F vs. M)	0.47	[0.13; 1.6]	0.24
Preemptive transplantation (yes vs. no)	0.35	[0.099; 1.2]	0.10
First graft (yes vs. no)	1.87	[0.42; 8.3]	0.41
A to O transplantation (vs. other incompatibilities)	1.56	[0.58; 4.2]	0.38
Sensitized (yes vs. no)	0.64	[0.23; 1.8]	0.40
Preformed DSA (yes vs. no)	2.49	[0.56; 11.09]	0.23
Rituximab (yes vs. no)	0.36	[0.08; 1.6]	0.18
Pre transplant apheresis (yes vs. no)	**0.28**	**[0.091; 0.89]**	**0.03**
Donor age	1	[0.96; 1]	0.93
Donor sex (F vs. M)	3	[0.69; 13]	0.14
Donor eGFR	1.02	[0.99; 1.1]	0.18
IgG at D0			
<1:8	ref.	-	-
≥1:8	0.63	[0.14; 2.8]	0.54
Induction (ATG vs. basiliximab)	**0.28**	**[0.096; 0.81]**	**0.019**
DGF (Yes vs. No)	**3.3**	**[1.1; 10]**	**0.041**
Early ABMR (yes vs. no)	**6.9**	**[2.1; 22]**	**0.0012**

CTIN: chronic tubulo-interstitial nephropathy; APKD, autosomal polycystic Kidney Disease; eGFR, estimated Glomerular Filtration Rate; ATG, anti thymoglobulin; DGF, delayed graft function; PNF, primary non function; ABMR, antibody mediated rejection; DSA, donor specific antibodies; D0, day of kidney transplantation.

TABLE 4 Multivariate analysis of factors associated with event free survival (graft survival and patient survival) in 78 kidney transplant recipients with low IHG (IgG≤1:8).

Covariable	HR	CI95	p
Preemptive transplantation	0.30	[0.08; 1.07]	0.064
Pre transplant apheresis	0.31	[0.10; 0.99]	0.049
Early ABMR	5.18	[1.58; 17.01]	0.0007

Early ABMR , antibody mediated rejection in the first post transplant month.

Discussion

This multicenter French study examined the outcomes of 78 ABO-incompatible kidney transplant recipients with baseline anti-A and/or anti-B IgG titers ≤1:8, over a median follow-up of 4 years. In this cohort, both patient and graft survival rates were excellent, with patient survival at 99.5% at 1 year, 97% at 3 years, and 95.5% at 5 years, and graft survival at 94.3% at 1 year, 90% at 3 years, and 86% at 5 years. However, patients who did not undergo pre-transplant apheresis had poorer outcomes, with lower event-free survival (defined as survival free from graft loss or death), a higher rate of rejection, and a trend toward higher rates of DGF and ABMR.

Overall, patient and graft survival in our cohort appears higher than that reported in studies including ABO-incompatible transplant recipients regardless of baseline isoagglutinin titers. In the study by Montgomery et al. [9], patient survival was 93.7% at 3 years and 88.3% at 5 years, while in the cohort reported by Barnett et al. [10], 1- and 3-year survival rates were 94.5% and 91.9%, respectively. In contrast, our results align with a single-center study from Spain [11], which included 57 patients with low baseline isoagglutinin titers (<1:16), of whom 50% did not undergo pre-transplant apheresis. In that study, patient survival was 100% at both 1 and 5 years, and graft survival was 90% at both time points. However, patients in that cohort were younger and less sensitized than those in our study.

In our cohort, patients who did not undergo pre-transplant apheresis had poorer outcomes compared to those who did, with reduced event-free survival and a marked trend toward higher ABMR incidence. We observed one case of primary non-function due to cortical necrosis in the no-apheresis group, and six additional early ABMR episodes with thrombotic microangiopathy (TMA) within the first month, of which four occurred in the no-apheresis group. It should also be emphasized that the two groups were not fully comparable, as patients in the no-apheresis group generally received less intensive immunosuppression, including lower use of rituximab, MMF, and ATG induction therapy.

Studies investigating ABO-incompatible kidney transplantation without pre-transplant apheresis in patients with low isoagglutinin titers have also reported cases of hyperacute rejection. Shinoda et al. [12] described one episode of hyperacute rejection with TMA and thrombosis among 35 patients without apheresis. In the study by

10.3389/ti.2026.16059

TABLE 5 Probability of infections occurrence at 1- and 3-year post-transplantation according to pre transplant apheresis or not.

Infection	Time	Apheresis group (n = 41)	No apheresis group (n = 37)	p
Any infection				0.58
	1 year	42 [26, 57]	32 [18, 48]	
	3 years	59 [40, 74]	53 [35, 68]	
Any viral infection				0.12
	1 year	24 [11, 38]	14 [4.8, 27]	
	3 years	37 [21, 53]	23 [10, 38]	
Presumptive BKV nephropathy				0.39
	1 year	16 [6.3, 29]	11 [3.4, 23]	
	3 years	19 [8.2, 33]	11 [3.4, 23]	
CMV disease				0.17
	1 year	0	0	
	3 years	0	5.7 [0.99, 17]	
CMV infection				0.056
	1 year	21 [9.5, 35]	2.7 [0.2, 12]	
	3 years	23 [11, 38]	8.2 [2.1, 20]	
Viral pneumonia				0.086
	1 year	5.2 [0.9, 15]	2.7 [0.2, 12]	
	3 years	12 [3.5, 25]	5.9 [1, 17]	
Norovirus				0.52
	1 year	2.6 [0.2, 12]	0	
	3 years	5.7 [0.98, 17]	3.2 [0.22, 14]	
Any bacterial infection				0.83
	1 year	23 [11, 38]	22 [10, 36]	
	3 years	37 [21, 53]	39 [23, 55]	
Bacterial pneumonia				0.72
	1 year	2.4 [0.18, 11]	2.7 [0.2, 12]	
	3 years	8.6 [2.1, 21]	8.6 [2.1, 21]	
Pyelonephritis				0.89
	1 year	18 [7.9, 32]	19 [8.2, 33]	
	3 years	18 [7.9, 32]	31 [16, 46]	
Bacteriemia				0.14
	1 year	7.8 [2, 19]	2.7 [0.2, 12]	
	3 years	15 [5.1, 29]	5.5 [0.96, 16]	
Any fungal or parasitic infection				0.047
	1 year	0	5.4 [0.94, 16]	

(*Continued*)

10.3389/ti.2026.16059

TABLE 5 Continued

Infection	Time	Apheresis group (n = 41)	No apheresis group (n = 37)	p
	3 years	0	11 [3.5, 24]	
Invasive fungal infection (excluding pneumocystosis)				0.15
	1 year	0	2.7 [0.2, 12]	
	3 years	0	2.7 [0.2, 12]	
Parasitic infection				0.31
	1 year	0	0	
	3 years	3 [0.22, 14]	5.9 [1.17]	
Pneumocystis infection				0.32
	1 year	0	2.7 [0.2, 12]	
	3 years	0	2.7 [0.2, 12]	

[Confidence interval 95%].
Between-group comparisons were performed using Gray's test.

Masterson [8], one hyperacute rejection with TMA was reported among 20 ABOi transplantations performed without apheresis, although the graft was successfully salvaged by post-transplant apheresis. Nevertheless, these rare events did not result in statistically significant differences in graft survival across most studies. For instance, the Japanese study by Kawamura [13] compared ABOi transplants without apheresis to historical ABO-compatible transplants in a pediatric population with baseline isoagglutinin titers ≤1:64. Rituximab was administered at 100 mg twice, and induction therapy was done with basiliximab. No differences in patient survival, graft survival, or rejection rates were observed.

In these studies, basiliximab induction was used, and the potential benefit of depleting induction therapy in reducing the risk of rejection was not evaluated. In our cohort, the subgroup of patients who received both pre-transplant apheresis and ATG induction had the most favorable outcomes and the lowest incidence of graft loss. The benefit of a depletant induction in this context was also underlined in a recent study from Netherlands [14]. Of course, this must be weighed against the theoretical increased risk of infectious and neoplastic complications associated with such intensive immunosuppression.

In our cohort, univariate analysis identified depleting induction therapy and pre-transplant apheresis as factors associated with improved patient and graft survival, while the occurrence of hyperacute or acute ABMR was, as expected, associated with poorer outcomes. The association between DGF and worse prognosis is likely explained by the high frequency of ABMR with thrombotic microangiopathy, which contributed to DGF in most cases. In multivariable analysis, pre-transplant apheresis and early rejection remained independently associated with event-free survival, supporting the potential role of pre-transplant apheresis in reducing the risk of very early immunologic or thrombotic events.

The "protective" role of apheresis in reducing the risk of acute ABMR and improving graft survival in patients with low baseline isoagglutinin titers remains a matter of debate. One hypothesis is that hemagglutination-based assays, commonly used to measure antibody levels, may lack sufficient sensitivity or specificity to accurately reflect the true antibody burden. In the UK, centers showed up to a five-dilution titer difference in National External Quality Assessment Scheme data comparing in-house techniques across laboratories. This finding highlights significant variability, where a single titer result could be interpreted as low in some centers and high in others [15]. Moreover, blood groups A and B are classified into six ABH subtypes. Using an ABH-glycan microarray, studies have reported a poor correlation between haemagglutination IgG titers against A red blood cells and IgG binding to individual subtypes I through VI. Since the subtype II antigen is predominantly expressed on renal vascular endothelium, identifying IgG binding specifically to subtype II may be more clinically relevant [16]. Finally, the respective roles of immune (IgG) and non-immune (IgM) isoagglutinin in the pathogenesis of rejection are not clearly defined [6], and only IgG titers were used in our final analysis. Interestingly, in our cohort, 39 out of 46 patients with available baseline IgM data also had titers ≤1:8, and six of the seven patients with IgM titers >1:8 received pre-transplant apheresis. Notably, the single patient with an IgM titer of 1:32 who did not receive apheresis developed cortical necrosis and primary non-function, likely due to hyperacute rejection.

Regarding infectious risk, we did not observe major differences in the overall incidence of infections between the groups, although there was more fungal or parasitic infections in the no apheresis group and a clear trend toward higher CMV viremia rates in the apheresis group. No differences were observed in the occurrence of BK virus nephropathy. Theoretically, apheresis may contribute to immunosuppression by inducing hypogammaglobulinemia and hypocomplementemia, due to the non-selective nature of the technique. In a French retrospective study, 72.7% of ABO-incompatible kidney transplant recipients experienced infectious complications compared to 47.7% of ABO-compatible recipients [17]. Such differences were also reported in the literature with an

increased incidence of wound infection, pneumonia, and urinary tract infection [18], and an increased rate of BK virus and CMV viremia in ABO-incompatible transplant recipients [19, 20]. Importantly, some of these infectious risks can be effectively managed with antiviral or antibiotic therapies and should not constitute a contraindication to apheresis.

Our study has several limitations. It is a retrospective analysis, and each transplant center applied its own protocol, with immunosuppressive regimens varying at the discretion of clinicians. Unfortunately, donor blood group A subtyping was not available in our centers, as this test was not part of standard clinical practice in France during the study period. Graft biopsies were interpreted according to the Banff classification in use at the time they were performed and were not centrally reviewed, introducing potential observer-related interpretation bias. Furthermore, isoagglutinin measurement techniques differed across centers. In the study by Zhou et al. [21], tube hemagglutination (used in one center in our cohort) consistently yielded lower dilution titers than gel hemagglutination, which was used in the other centers. Finally, despite the multicenter design, the sample size remains limited, and the number of events of interest was low, which may explain the lack of statistical significance in patient and graft survival outcomes when analyzed independently.

Whether outcomes in low-titer recipients differ from those observed in higher-titer ABOi patients undergoing standard desensitization remains uncertain, and the respective contributions of baseline isoagglutinin levels and pre-transplant conditioning cannot be disentangled in our study. As data on high-titer recipients were not available in our dataset, dedicated comparative studies are needed to address this question.

Conclusion

In this multicenter French cohort of ABO-incompatible kidney transplant recipients with low baseline anti-A and/or anti-B IgG titers (≤1:8), we observed excellent overall patient and graft survival rates, highlighting the feasibility of ABO-incompatible transplantation in this selected population. However, the absence of pre-transplant apheresis was associated with lower event-free survival, and a trend toward a higher incidence of early ABMR.

Our findings suggest that even in patients with low baseline isoagglutinin titers, pre-transplant apheresis may provide additional immunological protection, potentially mitigating the risk of hyperacute or early ABMR. Nevertheless, this potential benefit must be weighed against the risk of infectious and neoplastic complications associated with intensified immunosuppression, particularly in patients also receiving depleting induction therapy. Until more sensitive and reliable assays for isoagglutinin measurement are available, it should be reasonable to consider apheresis in all ABO-incompatible recipients, regardless of baseline titer, to ensure optimal graft outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Bordeaux Hospital ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

Participated in research design: MM, JL, BT, M-JA, LC, and SC. Participated in the data collection: all authors Participated in the writing of the paper: MM, SC, LC, and BT. Participated in data analysis: BT, SC, and LC. Participated in critical revision of the manuscript: all authors. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

SC participated to advisory boards for Pierre Fabre, Astra Zeneca and Sobi and received travel grants from Chiesi, Astellas, Alexion, Novartis and Sanofi. IB received speaker fees from AstraZeneca, MSD and Biotest, was on advisory boards for Chiesi, Takeda, and MSD and received travel grants from Chiesi, MSD, AstraZeneca and Biotest.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2026.16059/full#supplementary-material

References

1. Opelz G, Morath C, Süsal C, Tran TH, Zeier M, Döhler B. Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed ayer ABO antibody reduction: results from 101 centers. *Transplantation* (2015) 99(2): 400–4. doi:10.1097/TP.0000000000000312

2. Koo TY, Lee J, Lee Y, Kim HW, Kim BS, Huh KH, et al. Outcomes of ABO-incompatible living donor kidney transplantation compared to waiting or deceased donor kidney transplantation. *Am J Nephrol* (2024) 55(2):235–44. doi:10.1159/000535583

3. Scurt FG, Ewert L, Mertens PR, Haller H, Schmidt BMW, Chatzikyrkou C. Clinical outcomes ayer ABO-Incompatible renal transplantation: a systematic review and meta-analysis. *The Lancet* (2019) 393(10185):2059–72. doi:10.1016/S0140-6736(18)32091-9

4. De Weerd AE, Betjes MGH. ABO-incompatible kidney transplant outcomes: a meta-analysis. *Clin J Am Soc Nephrol* (2018) 13(8):1234–43. doi:10.2215/CJN.00540118

5. Bertrand D, Del Bello A, Sberro Soussan R, Caillard S, Claisse G, Couzi L, et al. Early thrombotic microangiopathy after ABO-incompatible living donor kidney transplantation. *Kidney Int Rep* (2024) 10(3):828–37. doi:10.1016/j.ekir.2024.12.031

6. Shimmura H, Tanabe K, Ishida H, Tokumoto T, Ishikawa N, Miyamoto N, et al. Lack of correlation between results of ABO-incompatible living kidney transplantation and Anti-ABO blood type antibody titers under our current immunosuppression. *Transplantation* (2005) 80(7):985–8. doi:10.1097/01.tp.0000173647.43616.78

7. Kim H, Choe W, Shin S, Kim YH, Han D, Park S, et al. ABO-incompatible kidney transplantation can be successfully conducted by monitoring IGM isoagglutinin titers during desensibilisation. *Transfusion* (2020) 60(3):598–606. doi:10.1111/trf.15672

8. Masterson R, Hughes P, Walker RG, Hogan C, Haeusler M, Robertson AR, et al. ABO incompatible renal transplantation without antibody removal using conventional immunosuppression alone. *Am J Transplant* (2014) 14(12):2807–13. doi:10.1111/ajt.12920

9. Montgomery JR, Berger JC, Warren DS, James NT, Montgomery RA, Segev DL. Outcomes of ABO-incompatible kidney transplantation in the United States. *Transplantation* (2012) 93(6):603–9. doi:10.1097/TP.0b013e318245b2af

10. Barnett ANR, Manook M, Nagendran M, Kenchayikoppad S, Vaughan R, Dorling A, et al. Tailored desensitization strategies in ABO blood group antibody incompatible renal transplantation. *Transpl Int* (2014) 27(2):187–96. doi:10.1111/tri.12234

11. Gelpi R, Cid J, Lozano M, Revuelta I, Sanchez-Escuredo A, Blasco M, et al. Desensitization in ABO-incompatible kidney transplantation with low ABO isoagglutinin titers. *Transplant Proc* (2015) 47(8):2340–3. doi:10.1016/j.transproceed.2015.08.021

12. Shinoda K, Hyodo Y, Oguchi H, Mikami T, Nishikawa K, Sakurabayashi K, et al. Outcome of ABO-Incompatible kidney transplantation using a modified desensibilisation protocol without plasmapheresis. *Int J Urol Sept* (2022) 29(9): 1017–25. doi:10.1111/iju.14944

13. Kawamura T, Hamasaki Y, Takahashi Y, Hashimoto J, Kubota M, Muramatu M, et al. ABO-incompatible pediatric kidney transplantation without antibody removal. *Pediatr Nephrol* (2020) 35(1):95–102. doi:10.1007/s00467-019-04376-7

14. De Weerd AE, van den Brand JAJG, Bouwsma H, de Vries APJ, Dooper IPMM, Sanders JF, et al. ABO-incompatible kidney transplantation in perspective of deceased donor transplantation and induction strategies: a propensity-matched analysis. *Transpl Int* (2021) 34(12):2706–19. doi:10.1111/tri.14145

15. Bentall A, Regan F, White J, Milkins C, Rowley M, Ball S, et al. No progress in ABO titer measurement: time to aim for a reference? *Transplantation* (2014) 97(3):e19–21. doi:10.1097/01.TP.0000438210.27218.9e

16. Bentall A, Jeyakanthan M, Braitch M, Cairo CW, Lowary TL, Maier S, et al. Characterization of ABH-subtype donor-specific antibodies in ABO-A-incompatible kidney transplantation. *Am J Transpl* (2021) 21(11):3649–62. doi:10.1111/ajt.16712

17. Naciri BH, Abdulrahman Z, Allal A, Sallusto F, Delarche A, Game X, et al. Early post-transplant complications following ABO-incompatible kidney transplantation. *J Nephropathol* (2016) 5:19–27. doi:10.15171/jnp.2016.04

18. Lentine KL, Axelrod D, Klein C, Simpkins C, Xiao H, Schnitzler MA, et al. Early clinical complications after ABO-incompatible live-donor kidney transplantation: a national study of Medicare-insured recipients. *Transplantation* (2014) 98(1):54–65. doi:10.1097/TP.0000000000000029

19. Habicht A, Bröker V, Blume C, Lorenzen J, Schiffer M, Richter N, et al. Increase of infectious complications in ABO-incompatible kidney transplant recipients – a single centre experience. *Nephrol Dial Transpl* (2011) 26:4124–31. doi:10.1093/ndt/gfr215

20. Wilpert J, Fischer KG, Pisarski P, Wiech T, Daskalakis M, Ziegler A, et al. Longterm outcome of ABO-incompatible living donor kidney transplantation based on antigen-specific desensitization. An observational comparative analysis. *Nephrol Dial Transpl* (2010) 25:3778–86. doi:10.1093/ndt/gfq229

21. Zhou S, Liu Q, Fang M, Shen S, Wang R, Jing Y, et al. Evaluation of different methods for antibody titre determination in ABO-incompatible kidney transplantation. *Transl Androl Urol* (2025) 14(3):540–52. doi:10.21037/tau-24-617

ESOT | Transplant International

TYPE Original Research
PUBLISHED 28 May 2026
DOI 10.3389/ti.2026.16189

Check for updates

OPEN ACCESS

*CORRESPONDENCE
Nassim Kakavand,
nassim.kakavand@uksh.de

†These authors share senior authorship

RECEIVED 04 January 2026
REVISED 26 April 2026
ACCEPTED 07 May 2026
PUBLISHED 28 May 2026
CORRECTED 23 June 2026

CITATION
Kakavand N, Coemans M, de Ferrante HC, Kolbrink B, Ziemann M, Radke DI, Lindner M, Naesens M, Schmitt R, Schulte K and von Samson-Himmelstjerna FA (2026) A discrete time simulation model for kidney allocation in Germany. *Transpl. Int.* 39:16189. doi: 10.3389/ti.2026.16189

COPYRIGHT
© 2026 Kakavand, Coemans, de Ferrante, Kolbrink, Ziemann, Radke, Lindner, Naesens, Schmitt, Schulte and von Samson-Himmelstjerna. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

A discrete time simulation model for kidney allocation in Germany

Nassim Kakavand[1]*, Maarten Coemans[2], Hans C. de Ferrante[3,4], Benedikt Kolbrink[5], Malte Ziemann[6], David I. Radke[1], Matthias Lindner[1], Maarten Naesens[2], Roland Schmitt[5], Kevin Schulte[5†] and Friedrich A. von Samson-Himmelstjerna[5†]

[1]Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Christian-Albrechts-University, Kiel, Germany, [2]Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium, [3]Department of Mathematics and Computer Science, Eindhoven University of Technology, Eindhoven, Netherlands, [4]Eurotransplant International Foundation, Leiden, Netherlands, [5]Department of Nephrology and Hypertension, University Medical Center Schleswig-Holstein, Christian-Albrechts-University, Kiel, Germany, [6]Institute for Transfusion Medicine, University Medical Center Schleswig-Holstein, Universität zu Lübeck, Lübeck, Germany

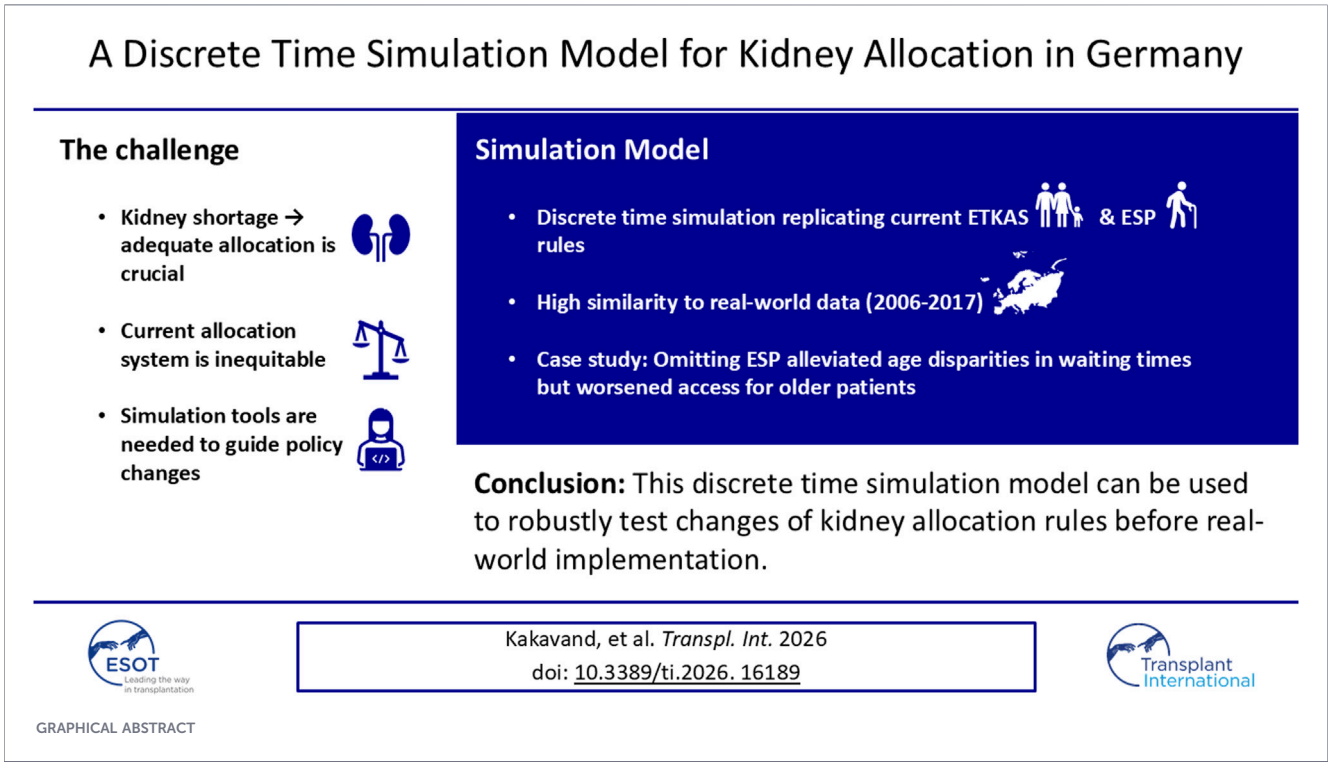
The ongoing shortage of kidney donations increases pressure to optimize utility and equity in kidney allocation; simulation models allow evaluation of policy changes before implementation. Using data from the German national transplant registry (19,517 kidney transplants), human leukocyte antigen (HLA) information from the German bone marrow donor registry, and the Eurotransplant database, we developed a discrete time simulation model that reconstructs the current German kidney allocation process. To validate the model, we simulated the period from 2006 to 2017 and compared simulated and historical outputs. Waiting list size, numbers of removals and transplants, age distributions, HLA mismatch counts, and predicted long-term survival were highly similar to historic data, indicating solid calibration. As an exemplary application for the allocation model, we explored the effects of omitting the European Senior Program (ESP) from Eurotransplant kidney allocation. This alleviated disparities in waiting time for younger adults and slightly improved overall transplant survival rates, but it worsened access to transplantation for older patients. In conclusion, this discrete time simulation model provides a tool for assessing policy trade-offs on a variety of outcomes before clinical implementation. Further work is needed to generalize the model to the full Eurotransplant area.

KEYWORDS
discrete time simulation, Eurotransplant, Germany, kidney allocation, simulated allocation models

Introduction

Patients with kidney failure face long waiting times for deceased donor kidneys. In Germany, waiting times in the Eurotransplant (ET) Kidney Allocation System (ETKAS) have increased since 2006 [1], currently reaching a median of around 9 years [2]. Despite kidney transplantation being the most effective treatment in terms of patient mortality and quality of life [3], the persistent scarcity of organs poses a major challenge for allocation.

The ET allocation program for deceased donor kidneys consists primarily of two distinct sub-programs: the ETKAS and the European Senior Program (ESP). In ETKAS, kidneys are allocated between donors and recipients younger than 65 years. Allocation is based on a scoring system, according to the following attributes: pediatric status, medical urgency, mismatch probability, human leukocyte antigen (HLA)-A, -B, -DR mismatches, waiting



time, distance between donor- and transplant center, and national kidney exchange balance [4]. In case of imminent lack of access for dialysis a high urgency status can be requested. Pediatric patients till the age of 18 receive bonus points [4]. Organs from donors aged 65 or older are primarily allocated to recipients aged 65 years or older through the ESP. It aims to minimize cold ischemia time by prioritizing local and regional allocation. Ranking is based on urgency and waiting time, without considering HLA mismatches (except for unacceptable antigens) [4].

Within the ET network—one of the world's largest organ exchange organizations [5]—balancing equity and utility remains of utmost importance [1]. Among other challenges, the rigid age thresholds for the ESP and pediatric bonus in Germany have led to age-related disparities in waiting times [1, 6]. Additionally, various proposals have been made to modify the HLA mismatching policy [7–12].

The current allocation algorithm was largely shaped by simulations conducted by Wujciak and Opelz in 1993 [13, 14]. An article published by ET in 1998 stated that "[. . .] any introduction of a change must be preceded by a computer simulation study [. . .]" [15]. Since then, however, simulation efforts and changes to the allocation system within the ET area have been rare. With the exception of the model of Niemann et al., which focused exclusively on the feasibility of epitope matching within ETKAS [10], existing models fail to account for the evolving dynamics of transplant activity and waiting lists [16], or are tailored to targeted regional allocation programs [17]. In other regions, simulation models have been used more frequently and have facilitated changes to the allocation system. Examples can be found in France [18] and particularly in the United States with the "Kidney-pancreas simulated allocation model" (KPSAM) [19] and its predecessor the United Network for Organ Sharing Kidney Allocation Model (UKAM) [20]. All these models are tailored to specific regional policies and cannot easily be transferred to other allocation systems [16, 17].

The unavailability of simulation models tailored to the ET region has impeded changes to the allocation rules.

While a simulation model for kidney allocation within the ET area is currently under development [21], different modelling approaches help ensure that conclusions about allocation strategies are robust and not overly dependent on a single method or dataset. Our study addresses this gap by developing an independent, dynamic simulation model for ET-based kidney transplant allocation. The model is calibrated using German registry data and offers an adaptable tool for evaluating allocation strategies.

Materials and methods

Data

The model was developed using several complementary data sources. The German national transplant registry served as the primary source [22]. Data derived from the registry were cross-validated against annual reports published by ET and the German Organ Procurement Organization (Deutsche Stiftung Organspende, DSO) [23, 24]. Data on HLA allele and haplotype

Abbreviations: AM, Acceptable Mismatch; DSO, German Organ Procurement Organization (Deutsche Stiftung Organspende); DKMS, German bone marrow donor registry; ESP, European Senior Program; ET, Eurotransplant; ETKAS, Eurotransplant Kidney Allocation System; HLA, Human Leukocyte Antigen; IQR, Interquartile Range; vPRA, virtual Panel Reactive Antibodies.

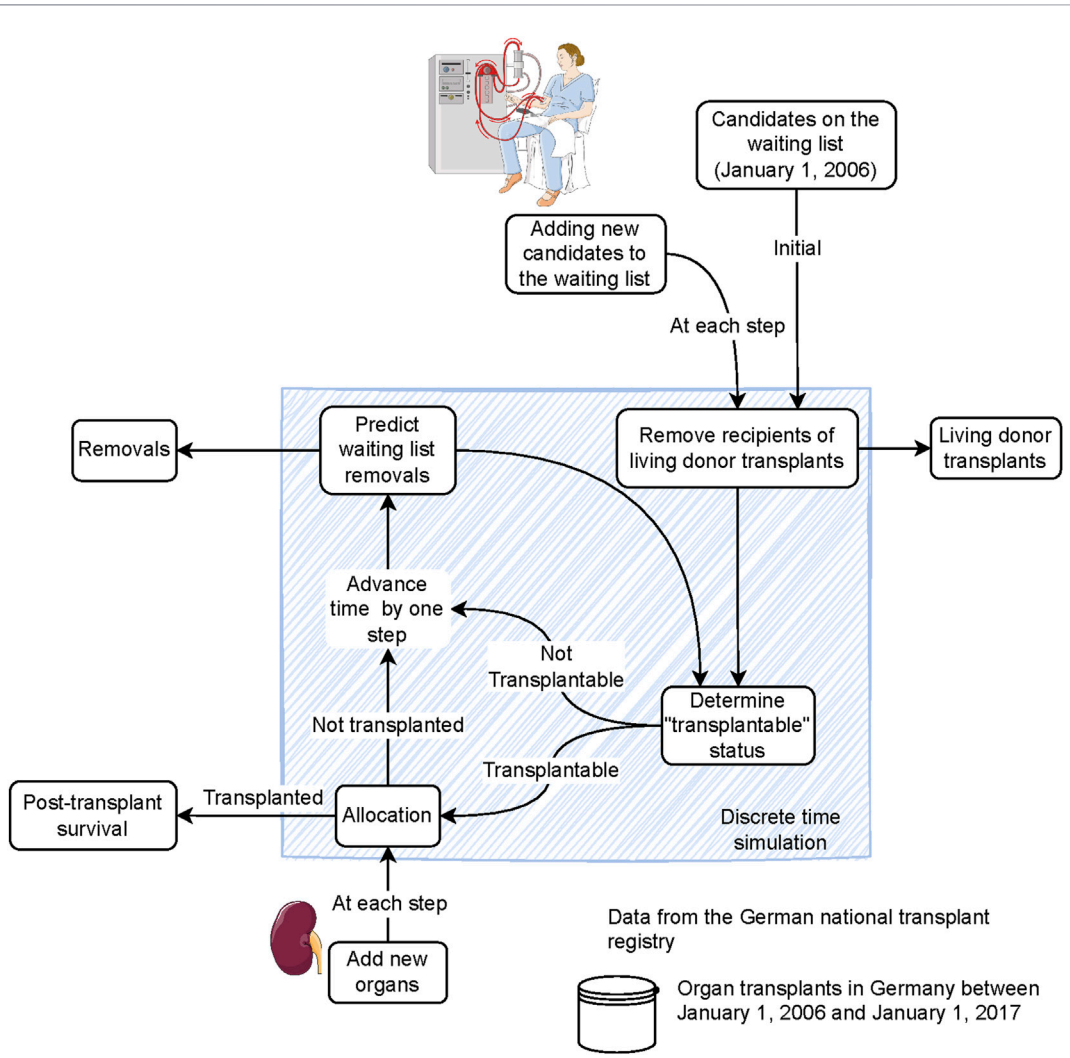


FIGURE 1
Simplified overview of the discrete time simulation model. Initially, newly added candidates are evaluated for the possibility of living donor transplantation. Next, each candidate's transplantable status is determined. If deemed transplantable, they may be matched to one of the available organs, which are added at each time step of the simulation. For candidates who receive a transplant, post-transplant graft and patient survival are predicted. Candidates who are not transplantable or not transplanted during the current time step remain in the model, and time is advanced. At each new time point, candidates may be removed from the waiting list due to death or becoming permanently unfit for transplantation. New candidates are also added to the waiting list at every step. The simulation is run until the specified number of time steps is reached. Images provided by Servier Medical Art (https://smart.servier.com/), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

frequencies were derived from published sources based on data from the German bone marrow donor registry (DKMS) [25, 26]. The kidney offer acceptance behavior of transplant centers was modeled on ET data.

The German national transplant registry [22] is an anonymized, retrospective dataset on more than 52,000 solid organ transplantations performed in Germany from January 1, 2006, to January 1, 2017. After this, the registry has been maintained prospectively; however, the quality of the reported data completeness has concomitantly declined significantly [1, 27]. Given these limitations, we chose to use only the retrospective portion of the dataset. The registry includes information sourced from transplant centers, ET, and the DSO.

Patients transplanted with other organs than kidneys were excluded (6%, n = 1.688). For the waiting list, all patients co-listed on the pancreas waiting or liver waiting list were also excluded from the analysis (8%, n = 3.425). *En-bloc* kidney transplantations–approximately 1% of annual kidney transplants–were counted as a single transplanted kidney.

Discrete time simulation

We modeled allocation using a discrete time simulation, where time advances in fixed increments rather than in response to events (as opposed to discrete event simulation).

Step sizes of 1/365, 1/36, 1/12 of a year, and 1 year were explored. No single increment size optimized all outcomes simultaneously. Smaller step sizes increased computational time, while larger ones reduced temporal precision. A step size of 1/36 of a year (≈10 days) provided a robust overall balance. The qualitative behavior of the model remained consistent across all step sizes, indicating that the simulation is not very sensitive to this choice.

The general model workflow is presented in Figure 1 (and in more detail in Supplementary Figure S1). Rare or highly complex processes were simplified to balance model stability and to focus on the core allocation dynamics.

Initialization

The simulation begins with a predefined waiting list, encompassing all kidney transplant candidates listed in the German national transplant registry as of January 1, 2006.

Each candidate on the initial waiting list has the following attributes: age, time since waiting list registration, time since start of dialysis, blood group, HLA type, DSO region, candidate status (transplantable or not transplantable), latest percentage of virtual Panel Reactive Antibodies (vPRA) (the term utilized by Eurotransplant for calculated PRA) and latest unacceptable antigens.

Missing HLA entries are imputed by resampling from HLA haplotype frequencies (see SDC Methods, HLA Types).

Synthetic candidate generation

Newly registered candidates are periodically added to the waiting list. Their attributes are generated in two stages.

Core demographic and immunologic attributes

Age at registration, blood group, and DSO region are independently resampled from the preprocessed kidney waiting list of the German national transplant registry (see SDC Methods for details), while HLA types are sampled independently from population HLA haplotype frequencies (see SDC Methods, HLA type).

Potential correlations between age at registration, DSO region, and blood group were evaluated using chi-squared, Kruskal-Wallis, Cramér's V, and eta-squared tests; all detected associations were weak. Given the limited strength of these associations and the focus on preserving the key marginal distributions, independent resampling was considered an appropriate approach.

Conditionally generated clinical and immunological attributes

Conditional on the core attributes, the following attributes are generated:

Dialysis to registration time, using age-stratified Gaussian kernel density estimation (see SDC Methods, Dialysis to Waiting list registration time).

Unacceptable antigens and vPRAs are sampled from empirical vPRA strata and filtered to avoid inconsistency with candidate's HLA type (see SDC Methods, vPRA).

Assigned allocation relevant and dynamic attributes

Each candidate–whether part of the initial cohort or synthetically added–is assigned the following attributes: ET allocation program (ETKAS or ESP), living donor donation probability, mismatch probability points, DSO subregion (see SDC Methods for details) and predicted time for removal from the waiting list (derived from a Cox proportional hazards model; see SDC Methods, Removal Model). Candidate status within the model can take four states: transplantable, not transplantable, living donor transplanted, or removed.

Living donor donations are predicted for candidates who have been on the waiting list for less than 1 year, using age-specific probabilities derived from observed living donor donation rates in 5-year age groups (Supplementary Figure S2A; see SDC Methods, Living Donor Probability).

Whether a candidate is currently considered transplantable or not is determined using a multistate recurrent event framework, with transition probabilities estimated via the Aalen-Johansen estimator (Supplementary Figure S3; see SDC Methods, Transplant Status).

Donor attributes

Organ donors are added based on the annual number of transplanted deceased donor kidneys (Supplementary Table S1). Donor attributes include age, blood group, HLA type, DSO region, and subregion. Except for HLA types, all donor attributes are independently resampled from historical deceased donor kidney donations in the registry (see SDC Methods for details). HLA types are resampled from published estimated four loci haplotype frequencies derived from the DKMS [25] (see SDC Methods, HLA Types).

Allocation

At each discrete simulation step, newly introduced donor organs are allocated to transplantable candidates on the waiting list. Allocation follows the ET allocation rules, which were modified in parts for simplification (Supplementary Figure S4; see SDC Methods, Allocation). Organ offer acceptance is simulated by a piecewise logistic regression model incorporating key predictors of acceptance, with vPRA, recipient age, donor age, years on dialysis and the number of HLA mismatches (see SDC Methods, Organ Acceptance; Supplementary Tables S2, S3). Organs that cannot be matched within a given step are removed from the model.

Time progress and removal from waiting list

After allocation, the simulation time advances by the predefined step size. The model then checks whether a candidate should be removed from the waiting list based on his/her simulated survival time, generated from a Cox proportional hazards model with a parametric baseline hazard, estimated using natural cubic splines with four knots, placed at equally spaced time points, fitted to the German national registry data (Supplementary Figure S5). Left censoring was applied to candidates registered before January 1, 2006, and transplantation events were treated as right-censoring. Proportional hazards assumptions were evaluated using Schoenfeld residual–based tests and graphical diagnostics implemented in the *lifelines* package. Observed violations in the dialysis to registration time were addressed through square-root transformation and age effects were handled using age-stratified baseline hazards.

Removal times are simulated using inverse hazard sampling as adapted from Bender et al. [28] (see SDC Methods, Removal Model).

Relisting is approximated by reintroducing candidates as newly generated individuals, which is considered by including relisted candidates in the sampling space and the total count of new registrations.

After each time step, new synthetic candidates are added to the waiting list according to the specified annual number of new registrations (Supplementary Table S4), which were evenly distributed across time steps. The simulation continues until a pre-defined number of steps has been reached.

Verification and validation

Before building the model, we validated the registry data through consistency checks, outlier detection and comparison to annual published reports by ET and the DSO [23, 24]. For model verification, we employed trace analysis (following individual simulated cases to ensure logical progression), testing under extreme and degenerate conditions, examining input-output relationships, and reprogramming critical components to cross-check results [29]. Reprogramming was applied in particular for the removal prediction component.

For model validation, we employed face validity (assessment by clinical experts), internal validity (evaluating stability of results across repeated simulations), analysis of input-output relationships, and graphical comparisons of simulated outcomes with registry data [29].

"ESP omitted" scenario

To demonstrate how different allocation strategies could be simulated by the model, we compared the current allocation rules with an alternative model that omitted ESP. Both simulations were run five times. The simulations covered the period from January 1, 2006, to January 1, 2017. In the "ESP omitted" scenario, organ allocation was performed exclusively through ETKAS. For simulating organ acceptance from donors aged ≥65 years, we applied the odds ratios from ETKAS. This assumption reflects current ETKAS practice, in which kidneys from older donors may be allocated through rescue mechanisms. All other parameters remained unchanged.

Software

Data processing and preparation were performed in R (version 4.5.0) [30], using the packages *tidyverse* (version 2.0.0) [31] and *survival* (version 3.8-3) [32] among others (Supplementary Table S5).

The simulation model was implemented in Python (version 3.11) using *Mesa* (version 2.2.4) [33], *NumPy* (version 1.26.3) [34], *pandas* (version 2.1.4) [35], *SciPy* (version 1.11.4) [36], and *lifelines* (version 0.28.0) [37] among others (Supplementary Table S5). Parallel processing (via Python's multiprocessing module) was used to reduce the total running time.

All code for model simulation is openly available on Github (https://github.com/na55imK/kidney_dtsim).

Statistics

The model was run five times. For comparison between scenarios, the identical sequence of random numbers was used across different scenarios (common random numbers). Outcomes were reported as the median of these five runs and the minimum and maximum.

Results

Model validation

By January 1, 2017, the simulation showed 19,517 transplants [min-max; 19,516–19,517], matching the registry [19,517] (median deviation 0.00%).

The median number of candidates on the waiting list was 11,828 [11,758–11,963] at the end of the simulation period, while 11,722 were recorded in the registry (median deviation 0.90%). The number of transplantable candidates differed slightly more, with a model median of 7,948 [7,874–8,029] versus 7,502 in the registry (median deviation 5.95%). The cumulative number of candidates who left the waiting list due to death or deteriorated health status was slightly underestimated by the model, with a deviation of −3.45% (model median 7,461 [7,356–7,506]; registry 7,728). Kaplan-Meier curves for waiting list removals generated by the model closely resembled those from the registry (Supplementary Figure S6). Living donor donations showed a deviation of 0.37% (model median 7,090 [7,031–7,204]; registry 7,064) (Figure 2).

Visual inspection of dialysis-to-transplant time (Figure 3A) and waiting list-to-transplant time (Supplementary Figure S7A) showed good alignment between the combined model runs and historical data, clearly separating the following groups: pediatric, 18–64 years, and 65 years and older. The median dialysis-to-transplant time was 6.95 years [IQR 4.12–8.73] in the model and 5.81 years [IQR 3.27–7.91] in the registry (Supplementary Table S6). The model demonstrated good stability across individual runs (Supplementary Figures S7C,D).

The distribution of recipient age at transplant showed the characteristic peak [1] at around 65 years. Recipients aged 65 years and pediatric recipients were slightly overrepresented in the model, whereas recipients aged older than 65 years were slightly underrepresented (Figure 3B). The median recipient age for ETKAS was 51 years [IQR 42–59] in the model and 51 years [IQR 42–59] in the registry. For the ESP, the median recipient age was 68 years [IQR 66–71] in the model and 68 years [IQR 66–71] in the registry (Table 1). The age gap (recipient age - donor age) was aligned well between model and registry data (Table 1; Supplementary Figure S7B).

Distribution of HLA mismatches in the model showed a similar pattern to that observed in the registry for ESP and ETKAS recipients (Table 1; Figure 3C).

Validity of the sub model for post-transplant risk prediction (published by Coemans et al. [38]) was evaluated by comparing model-predicted survival with outcomes observed in the transplant registry. The registry data showed a steeper decline in the Kaplan-Meier curve for dialysis-free survival probability, particularly within the first 2.5 years after transplantation, with both curves converging

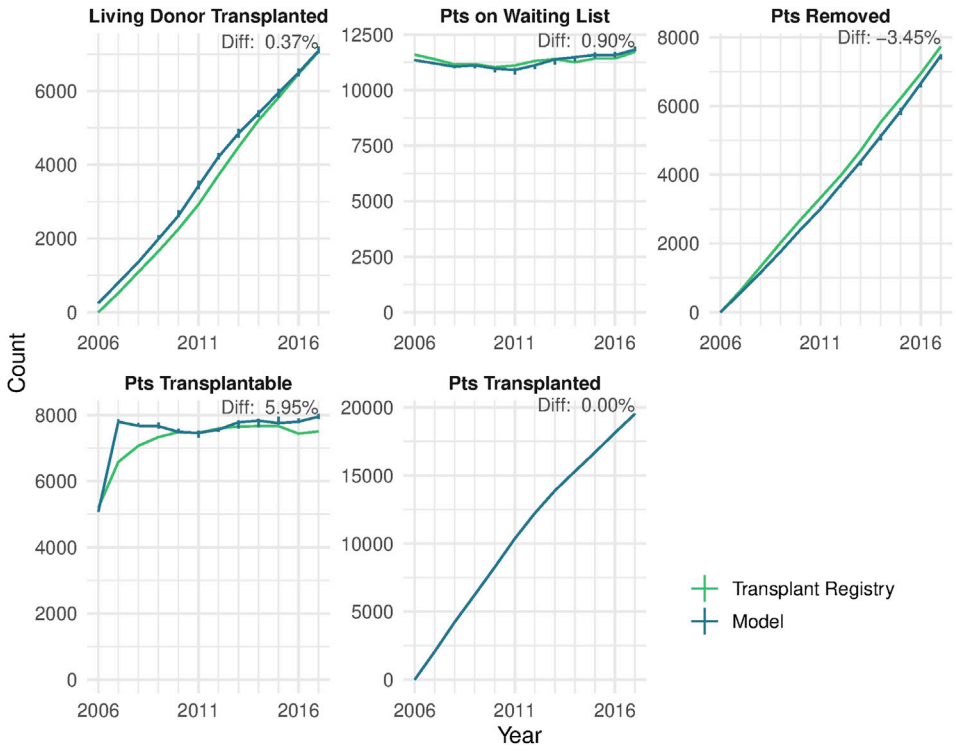


FIGURE 2
Comparison of waiting list dynamics and transplantations between the discrete time simulation and the data from the German national transplant registry. Median percentage deviation of the discrete time simulation from the German national transplant registry is shown as of January 1, 2017, with bars indicating the minimum and maximum. Living donor transplanted, removed patients, and transplanted patients show the cumulative count since January 1, 2006. Abbreviations: Pts, patients; Diff, difference.

at approximately 10 years post-transplant (Figure 3D), indicating long-term post-transplant risk profiles generated by the model were similar to those observed in the registry data. Overall survival showed a similar pattern (Supplementary Figure S8A). Graft survival probability, estimated using an Aalen-Johansen estimator, also showed an initially steeper decline followed by a slower decline (Supplementary Figure S8B).

Simulated impact of omitting ESP

At the end of the simulation period, the median number of patients on the waiting list was slightly lower in the "ESP omitted" model with 11,180 [11,040–11,214] patients compared to the "no changes" model with 11,828 [11,758–11,963] patients. Similarly, the median number of transplantable patients was lower in the "ESP omitted" model (7,400 [7,337–7,475]) than in the "no changes" model (7,948 [7,874–8,029]). These differences were driven by a higher number of candidates leaving the waiting list due to death or permanent unfitness for transplantation in the "ESP omitted" model (8,072 [8,017–8,260]) compared to the "no changes" model (7,461 [7,356–7,506]) (Figure 4A). There was little variation in the number of transplantations, as the model was constructed exclusively using the characteristics and quantities of transplanted organs.

Omitting ESP resulted in the disappearance of the spike at age 65 among organ recipients (Figure 4B). In addition, better overall minimization of HLA mismatches was observed (Figure 4C; Supplementary Table S7), e.g., zero mismatch allocation increased from 15.4% [15.0%–15.8%] to 19.4% [19.1%–19.8%] and 6/6 mismatch allocation decreased from 3.8% [3.7%–3.8%] to 0.2% [0.2%–0.3%] (Supplementary Table S7). In the "ESP omitted" model, 16.1% [16.0%–16.5%] of organs were transplanted into recipients aged 65 years and older, compared to 28.7% [28.4%–29.0%] in the "no changes" model (Supplementary Table S7). Dialysis-to-transplant time increased for recipients aged 65 years and older when ESP was omitted, with a median of 6.97 years [IQR 5.35–8.32], compared to 4.33 years [IQR 2.67–6.63] in the "no changes" model. Among recipients aged 18–64 years, the median waiting time decreased modestly ("ESP omitted": 7.17 years [IQR 5.67–8.42]; "no changes": 7.86 years [IQR 6.20–9.20]) (Figure 4D; Supplementary Figure S9A).

When ESP was omitted, recipients were on average younger relative to their donors, with a median age difference of −3 years [IQR -16–10], compared to −1 year [IQR -10–8] in the "no changes" model (Supplementary Table S7; Supplementary Figure S9B). Regional organ allocation decreased slightly in the "ESP omitted" model, with a median of 81.8% [81.5%–82.1%], compared to 85.6% [85.0%–85.6%] in the "no changes" model. Despite this shift, the distribution of organ recipients across regions remained nearly unchanged (Supplementary Table S7).

The median predicted 10-year cumulative incidence of the composite outcome of graft failure or death was 46.4% [IQR 46.4%–46.4%] in the "ESP omitted" model compared with 48.1% [IQR 47.7%–48.1%] in the "no changes" model (Figure 4E). The 10-year cumulative incidence of death with a functioning graft was likewise lower in the "ESP omitted" model, with 24.3% [IQR 24.2%–

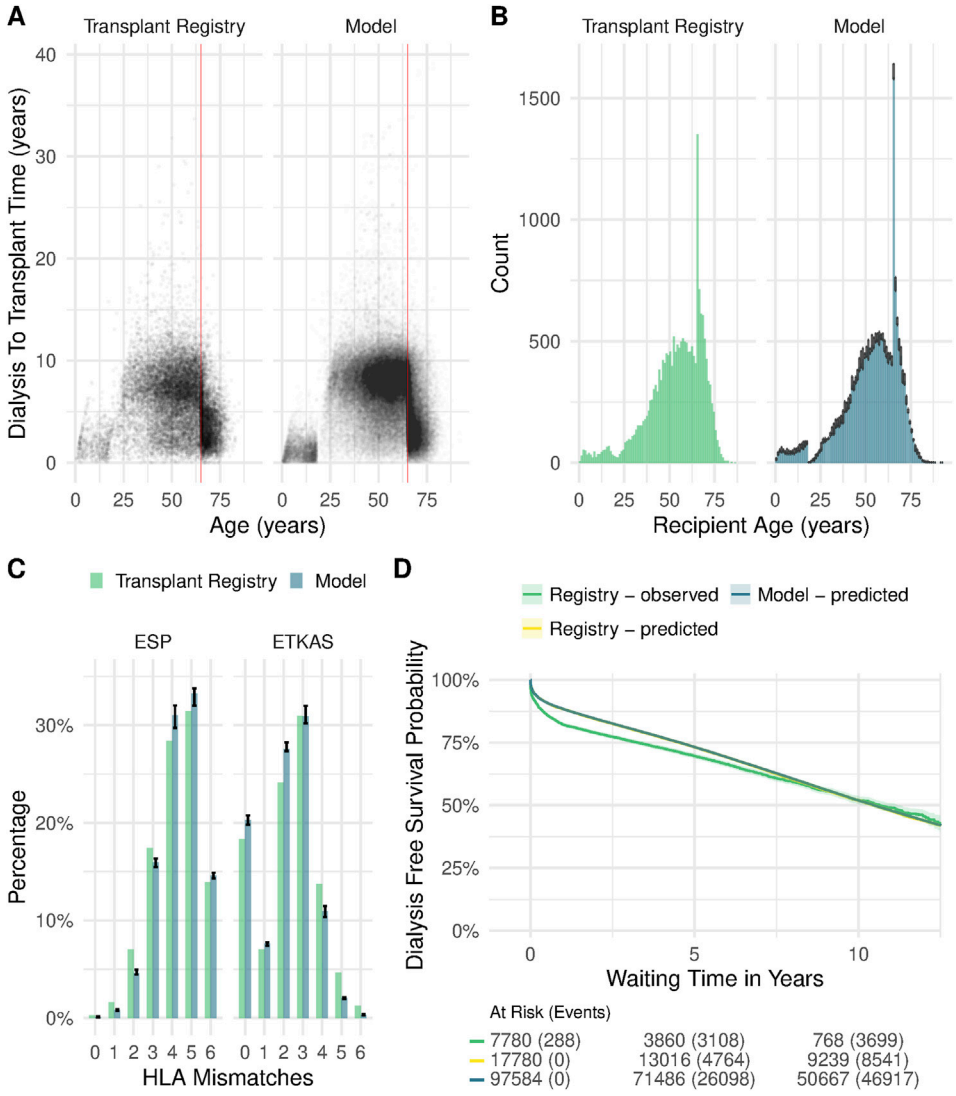


FIGURE 3
Proof of model reliability through comparison of multiple measures with historical data from the German national transplant registry **(A)** Dialysis to transplant time in years for all transplanted patients is plotted against age at transplantation in years. Every dot corresponds to one transplantation. For the discrete time simulation model, data were pooled from five independent model runs. **(B)** Recipient age at transplantation distribution grouped into one-year bins. For the simulation, the median across five model runs is shown, with black bars representing the minimum and maximum. **(C)** Distribution of HLA ABDR mismatches, shown as the percentage of transplants for each mismatch count. For the simulation, the median across five model runs is shown, with black bars indicating the minimum and maximum. Data are displayed separately for transplants in the ETKAS and the ESP. **(D)** Dialysis free survival probability is displayed. The observed dialysis free survival from the registry data is shown as a Kaplan-Meier survival curve. Predicted survival was simulated using a Royston-Parmar model published by Coemans et al., once using data from the transplant registry and once using data from the five runs of the model. Abbreviations: ESP, European Senior Program; ETKAS, Eurotransplant Kidney Allocation System; HLA, Human Leukocyte Antigen.

24.4%], compared to 28.3% [IQR 28.1%–28.3%] in the "no changes" model (Supplementary Figure S10C). In contrast, the predicted 10-year cumulative incidence of graft failure alone was slightly higher in the "ESP omitted" model with 28.2% [IQR 28.0%–28.2%], compared to 27.7% [IQR 27.5%–27.7%] (Supplementary Figure S9E).

Discussion

We developed a novel patient-level simulation model based on the ET kidney allocation algorithm. More than 35,000 patient-level entries from the German transplant registry were utilized, supplemented by data from DKMS and ET. The model incorporates multiple stochastic sub models to simulate key aspects of the transplant process, including candidate listing status, waiting list removal, organ acceptance, and post-transplant risk. Over an 11-year simulation period, the model closely reproduced observed dynamics in waiting list size, transplantation rates, and patient removals. While a brief burn-in period was observed—particularly in the number of transplantable candidates during the first two years—the model demonstrated high concordance with the observed patient, donor, and match characteristics.

We demonstrated the model's adaptability and capacity by simulating a policy scenario in which the ESP was omitted. This

10.3389/ti.2026.16189

TABLE 1 Comparison of model outcomes with data from German national transplant registry.

Characteristic	Transplant Registry			Model	
	AM N = 526	ESP N = 4,765	ETKAS N = 14,209	ESP N = 23,494	ETKAS N = 74,090
Age gap	1 (−9, 12)	−3 (−7, 1)	0 (−10, 10)	−3 (−7, 0)	0 (−11, 12)
Unknown	169	0	1,564		
Age donor	49 (40, 57)	72 (68, 75)	51 (42, 58)	71 (68, 75)	51 (42, 58)
Unknown	169	0	1,564		
Age recipient	48 (40, 56)	68 (66, 71)	51 (42, 59)	68 (66, 71)	51 (42, 59)
Recipient age group					
<18	1.5%	0.0%	5.1%		6.4% [6.1%–6.5%]
18-64	92.0%	0.0%	88.6%		87.6% [87.5%–87.7%]
≥65	6.5%	100.0%	6.3%	100.0% [100.0%–100.0%]	6.1% [5.8%–6.3%]
Donor age group					
<18	2.8%	0.0%	4.5%		4.4% [4.0%–4.5%]
18-64	96.9%	0.0%	90.0%		89.8% [89.6%–90.7%]
≥65	0.3%	100.0%	5.4%	100.0% [100.0%–100.0%]	5.8% [5.1%–6.2%]
Unknown	169	0	1,564		
Recipient blood group					
A	45.4%	44.6%	45.2%	45.4% [44.7%–46.4%]	43.5% [43.2%–43.8%]
AB	5.5%	3.8%	6.6%	2.6% [2.5%–2.9%]	5.7% [5.3%–5.9%]
B	13.9%	11.6%	12.1%	9.5% [9.1%–9.9%]	11.9% [11.7%–11.9%]
O	35.2%	40.0%	36.1%	42.2% [41.6%–43.0%]	39.1% [38.4%–39.3%]
Donor blood group					
A	30.3%	43.0%	44.8%	45.4% [44.7%–46.4%]	43.5% [43.2%–43.8%]
AB	0.0%	2.5%	6.0%	2.6% [2.5%–2.9%]	5.7% [5.3%–5.9%]
B	3.9%	10.7%	11.7%	9.5% [9.1%–9.9%]	11.9% [11.7%–11.9%]
O	65.8%	43.8%	37.6%	42.2% [41.6%–43.0%]	39.1% [38.4%–39.3%]
Unknown	169	0	1,564		
vPRA					
0%	6.1%	90.5%	82.6%	89.4% [89.1%–89.9%]	83.7% [83.5%–83.9%]
>0%-<85%	17.7%	8.7%	15.0%	9.6% [9.2%–10.1%]	12.6% [12.5%–12.9%]
≥85%	76.2%	0.8%	2.3%	1.0% [0.9%–1.1%]	3.7% [3.5%–3.7%]
HLA ABDR mismatches					
0	10.5%	0.3%	18.3%	0.1% [0.0%–0.1%]	20.3% [19.8%–20.8%]
1	21.9%	1.6%	7.0%	0.8% [0.8%–0.9%]	7.6% [7.4%–7.7%]
2	38.6%	7.0%	24.1%	4.6% [4.5%–5.0%]	27.6% [27.3%–28.2%]
3	24.8%	17.4%	30.9%	16.0% [15.5%–16.3%]	30.9% [30.2%–32.0%]
4	4.3%	28.4%	13.7%	31.0% [29.7%–32.0%]	10.9% [10.4%–11.5%]
5	0.0%	31.4%	4.6%	33.2% [32.0%–33.8%]	2.0% [2.0%–2.1%]
6	0.0%	13.9%	1.3%	14.6% [14.3%–14.9%]	0.3% [0.3%–0.4%]
Unknown	316	1,914	6,614		

(*Continued*)

TABLE 1 Continued

Characteristic	Transplant Registry			Model	
	AM N = 526	ESP N = 4,765	ETKAS N = 14,209	ESP N = 23,494	ETKAS N = 74,090
Recipient region					
Baden-Württemberg	11.8%	10.7%	10.7%	10.6% [10.2%–11.1%]	11.2% [11.1%–11.5%]
Bayern	10.2%	14.8%	15.1%	15.0% [14.5%–15.7%]	15.3% [14.9%–15.7%]
Mitte	13.4%	12.4%	13.7%	12.4% [11.5%–12.5%]	12.2% [11.8%–12.3%]
Nord	17.7%	16.5%	15.9%	16.9% [16.5%–17.4%]	16.7% [16.5%–16.8%]
Nord-Ost	11.4%	10.2%	9.1%	11.3% [10.9%–11.4%]	11.3% [10.9%–11.4%]
Nordrhein-Westfalen	23.2%	22.3%	24.2%	23.2% [23.0%–23.2%]	21.7% [21.2%–21.7%]
Ost	12.4%	13.1%	11.4%	10.6% [10.5%–11.5%]	11.9% [11.6%–12.1%]
Unknown	17	23	161		
Donor region					
Baden-Württemberg	13.4%	11.0%	11.3%	10.6% [10.2%–11.1%]	11.6% [11.4%–11.7%]
Bayern	16.5%	14.7%	15.7%	15.0% [14.5%–15.7%]	15.7% [15.4%–16.1%]
Mitte	11.6%	10.9%	12.2%	12.4% [11.5%–12.5%]	11.7% [11.3%–12.2%]
Nord	19.7%	17.1%	16.2%	16.9% [16.5%–17.4%]	16.6% [16.5%–16.8%]
Nord-Ost	10.9%	11.7%	11.2%	11.3% [10.9%–11.4%]	11.3% [11.0%–11.4%]
Nordrhein-Westfalen	18.3%	22.6%	20.8%	23.2% [23.0%–23.2%]	20.2% [19.8%–20.5%]
Ost	9.5%	12.1%	12.6%	10.6% [10.5%–11.5%]	12.8% [12.5%–13.3%]
Unknown	242	3	2,294		
Donor location relative to recipient					
Abroad	46.0%	0.1%	16.1%		
Home country	46.4%	9.8%	23.5%		19.1% [18.9%–19.7%]
Regional	7.6%	90.2%	60.5%	100.0% [100.0%–100.0%]	80.9% [80.3%–81.1%]

For the model, N equals the number of cases across all pooled simulations.
For continuous variables, the median (IQR) is calculated across all pooled simulations. For categorical variables, the percentage is first calculated within each model run, and then the median [min./max.] across model runs is reported.
Abbreviations: AM, acceptable mismatch; ESP, european senior program; ETKAS, eurotransplant kidney allocation system; HLA, human leukocyte antigen; vPRA, virtual Panel Reactive Antibodies.

scenario highlighted the ESP's role for candidates aged over 65, as its removal resulted in increased waiting times in this age group and higher waiting list removals.

Allocation simulation models are inherently system-specific, as they are designed to replicate the rules, and constraints of a given allocation system. As applied in this study, calibration using historical data and validation by comparison with observed system behavior are standard approaches in this field [10, 17, 29, 39–42].

Despite the recognized value of simulated allocation models, few exist for the ET area. Existing models show notable limitations. One model simulates the matching process at a more or less static time point [16], restricting its ability to assess changes in waiting list dynamics or transplant activity over time. Another model focuses on a small population within a kidney exchange program [17]. The model by Niemann et al. [10] explores the feasibility of epitope matching within ETKAS, offering a broader scope but excluding the ESP, which accounts for approximately one-quarter of kidney transplants in the region. Unlike the Niemann model, our simulations also incorporate living donor transplants, which were not part of their framework. In Niemann et al [10] candidate characteristics were drawn from the 2015 ET annual report, with random waiting list removals and organ acceptance fixed at a 10% probability. In contrast, our model is fitted to patient-level data and incorporates stochastic submodels for waiting list removals and organ acceptance, allowing a more dynamic and realistic simulation. Compared to the ETKidney simulator [21] - a discrete event simulation model currently under development and based directly on data from ET–our model does not require complete longitudinal datasets. It requires patient level data only for the initial waiting list, while all other inputs can be provided as summary statistics or empirical lists (e.g., list of donor ages or HLA types), facilitating flexible adjustment of model parameters and enabling exploration of future allocation dynamics through extrapolated input parameters; additionally, these inputs can be shared with minimal privacy concerns. The ETKidney Simulator [21] also does not consider living donor transplants.

Validation over more than a decade enables assessment of long-term impacts, whereas most published models cover 4 years or less

FIGURE 4
Scenario analysis of omitting the ESP. Two different scenarios were compared; simulation of the Eurotransplant allocation rules, as currently in place ("no changes"), and simulation of a scenario where only the ETKAS rules are used for allocation ("ESP omitted"). **(A)** Evolution of the waiting list and the number of transplantations over the simulated time frame. Median percentage deviation of the "ESP omitted" scenario from the "no changes" scenario is shown as of January 1, 2017. Living donor transplanted, removed patients, and transplanted patients show the cumulative count since January 1, 2006. **(B)** Age distribution of transplant recipients. Age was grouped into one-year bins. The median across five model runs per scenario is displayed, with black bars indicating the minimum and maximum. **(C)** Distribution of HLA ABDR mismatches, displayed as the percentage of transplants by mismatch count. The median across five model runs per scenario is displayed, with black bars indicating the minimum and maximum. **(D)** Boxplot of dialysis to transplant time, stratified by recipient age group across both scenarios. **(E)** Boxplot of predicted 10-year cumulative incidence of graft failure or death across both scenarios. Cumulative incidences were simulated based on a Royston-Parmar model published by Coemans et al. [38]. Abbreviations: Pts, patients; Diff, difference; ESP, European Senior Program; ETKAS, Eurotransplant Kidney Allocation System; HLA, Human Leukocyte Antigen.

[10, 40] or rely on static designs [16]. Despite operating at the patient-level, our model remains computationally efficient, completing in under an hour on a personal computer.

All simulation models require explicit assumptions about system behavior, reflecting an inherent trade-off between capturing sufficient complexity and maintaining robustness. When a model becomes too complex, the reliability of scenario analyses can be reduced, as it limits how confidently results can be generalized to different settings. Accordingly, several simplifications were made during development. The Acceptable Mismatch (AM) program was not implemented, as it accounted for only 2.7% (n = 526) of transplantations between 2006 and 2017; these candidates were instead allocated through

ETKAS and ESP. Similarly, "high urgent" status was not implemented (n = 332, 1.7% of transplants). Multiorgan transplants were also not implemented. Candidates listed for multiple organs would have different model behavior (e.g., in acceptance, waiting list survival etc.), making the model far more complex with limited benefit for the study objectives.

Model accuracy is impaired for subgroups with limited available data, such as very old or very young candidates and donors. It could be expanded, with available data, to other countries in the ET region and the time after 2016. Direct application of the model to allocation systems outside the ET region is limited, but the methodological framework is transferable and can be adapted to other regions. Improvements of the model could be made with better data regarding HLA types, vPRAs and follow-up, which are currently limited in quality in the German national transplant registry.

In conclusion, our work enables policymakers to assess both system-level and individual consequences, such as shifts in transplant rates, waiting list dynamics, or post-transplant risks, before implementing changes in practice. It also offers the opportunity to retrospectively reassess past policy decisions in the ET-area. Moreover, the simulator could estimate the impact of changing external conditions, such as an aging society, declining or rising donor rates.

Data availability statement

The datasets presented in this article are not readily available because the registry data analyzed in this study contains anonymized, patient-level information and therefore cannot be made publicly available. Access may be granted by the German national transplant registry upon reasonable request. Aggregated model input data and the simulation model are publicly available at https://github.com/na55imK/kidney_dtsim. Requests to access the datasets should be directed to https://transplantations-register.de.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

NK, FS-H, MC, HF, BK, MZ, MN, RS, KS, DR, and ML participated in research design. NK and FS-H wrote the manuscript. NK, MC, and HF performed the statistical analyses. All authors contributed to the article and approved the submitted version.

Funding

The author(s) declared that financial support was received for this work and/or its publication. FS-H and BK are supported by the Medical Faculty of the Christian-Albrechts-University Kiel. MN is supported by The Research Foundation Flanders (FWO) as senior clinical investigator (1844024N) and with a project grant (G038024N), and by a grant from the KU Leuven Research Council (C2M/24/057). MC holds an FWO fellowship grant (12D6423N).

Conflict of interest

FS-H reports receiving lecturing fees and travel support from AstraZeneca GmbH, Chiesi GmbH and Lilly Deutschland GmbH.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Correction note

A correction has been made to this article. Details can be found at: 10.3389/ti.2026.17122.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. The authors used ChatGPT 5.2 (OpenAI) for proofreading sections of the manuscript and assistance during model development (interpreting error messages, suggesting alternative code structures, and documentation). All suggestions were critically evaluated, tested, and revised by the authors.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2026.16189/full#supplementary-material

References

1. Kolbrink B, Kakavand N, Voran JC, Zacharias HU, Rahmel A, Vogelaar S, et al. Allocation rules and age-dependent waiting times for kidney transplantation. *Deutsches Ärzteblatt International* (2024) 121:559–65. doi:10.3238/arztebl.m2024.0137

2. Zecher D, Tieken I, Wadewitz J, Zeman F, Rahmel A, Banas B. Regional differences in waiting times for kidney transplantation in Germany. *Dtsch Arztebl Int* (2023) 120(23): 393–9. doi:10.3238/arztebl.m2023.0098

3. Tonelli M, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, et al. Systematic review: Kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant* (2011) 11(10):2093–109. doi:10.1111/j.1600-6143.2011.03686.x

4. Eurotransplant Manual – version 2025. 2: chapter 4 (2025). Available online at: https://www.eurotransplant.org/wp-content/uploads/2025/03/H4-Kidney-2025.2-March-2025.pdf. (Accessed April 7, 2025).

5. Eurotransplant. Annual report 2023. Available online at: https://www.eurotransplant.org/wp-content/uploads/2024/06/ETP_AR2023_LowRes.pdf (Accessed April 8, 2025).

6. Echterdiek F, Heemann U. Allokation von Nieren im Zeitalter des Organmangels in Deutschland. *Nephrologie* (2023) 18(2):72–7. doi:10.1007/s11560-022-00627-1

7. Doxiadis IIN, Smits JMA, Persijn GG, Frei U, Claas FHJ. It takes six to boogie: allocating cadaver kidneys in eurotransplant. *Transplantation* (2004) 77(4):615–7. doi:10.1097/01.TP.0000103725.72023.D7

8. Fijter J, Dreyer G, Mallat M, Budde K, Pratschke J, Klempnauer J, et al. A paired-kidney allocation study found superior survival with HLA-DR compatible kidney transplants in the eurotransplant Senior program. *Kidney Int* (2023) 104(3):552–61. doi:10.1016/j.kint.2023.05.025

9. Halleck F, Khadzhynov D, Liefeldt L, Schrezenmeier E, Lehner L, Duerr M, et al. Immunologic outcome in elderly kidney transplant recipients: is it time for HLA-DR matching? *Nephrol Dial Transplant* (2016) 31(12):2143–9. doi:10.1093/ndt/gfw248

10. Niemann M, Lachmann N, Geneugelijk K, Spierings E. Computational eurotransplant kidney allocation simulations demonstrate the feasibility and benefit of T-cell epitope matching. *PLOS Comput Biol* (2021) 17(7):e1009248. doi:10.1371/journal.pcbi.1009248

11. Duquesnoy RJ. Are we ready for epitope-based HLA matching in clinical organ transplantation? *Transplantation* (2017) 101(8):1755–65. doi:10.1097/TP.0000000000001667

12. Tambur AR, Kosmoliaptsis V, Claas FHJ, Mannon RB, Nickerson P, Naesens M. Significance of HLA-DQ in kidney transplantation: time to reevaluate human leukocyte antigen–matching priorities to improve transplant outcomes? An expert review and recommendations. *Kidney Int* (2021) 100(5):1012–22. doi:10.1016/j.kint.2021.06.026

13. Wujciak T, Opelz G. Computer analysis of cadaver kidney allocation procedures. *Transplantation* (1993) 55(3):516–21.

14. Wujciak T, Opelz G. A proposal for improved cadaver kidney allocation. *Transplantation* (1993) 56(6):1513–7. doi:10.1097/00007890-199312000-00044

15. De Meester J, Persijn GG, Wujciak T, Opelz G, Vanrenterghem Y, Foundation for the EI. The new eurotransplant kidney allocation system1: report one year after implementation. *Transplantation* (1998) 66(9):1154–9. doi:10.1097/00007890-199811150-00007

16. Lima BA, Henriques TS, Alves H. Kidney allocation rules simulator. *Transpl Immunol* (2022) 72:101578. doi:10.1016/j.trim.2022.101578

17. de Klerk M, Kal-van Gestel JA, van de Wetering J, Kho ML, Middel-de Sterke S, Betjes MGH, et al. Creating options for difficult-to-match kidney transplant candidates. *Transplantation* (2021) 105(1):240–8. doi:10.1097/TP.0000000000003203

18. Jacquelinet C, Audry B, Golbreich C, Antoine C, Rebibou JM, Claquin J, et al. Changing kidney allocation policy in France: the value of simulation. *AMIA Annu Symp Proc* (2006) 374–8.

19. Stegall MD, Stock PG, Andreoni K, Friedewald JJ, Leichtman AB. Why do we have the kidney allocation system we have today? A history of the 2014 kidney allocation system. *Hum Immunol 2017 Jan 1; The New Kidney Allocation Syst (Kas) Perspect From The Transpl Community Two Years Post-Implementation* (2017) 78(1):4–8. doi:10.1016/j.humimm.2016.08.008

20. Taranto SE, Harper AM, Edwards EB, Rosendale JD, McBride MA, Daily OP, et al. Developing a national allocation model for cadaveric kidneys. In: *2000 Winter Simulation Conference Proceedings (Cat. No.00CH37165)*, 2 (2000). p. 1971–7. doi:10.1109/WSC.2000.899194

21. Ferrante HC, Goya RL, Smeulders BML, Spieksma FCR, Tieken I. The ETKidney simulator: a discrete event simulator to assess the impact of alternative kidney allocation rules in eurotransplant. *arXiv* (2025). doi:10.48550/arXiv.2502.15001

22. Transplantationsregister. Transplantationsregister. Available online at: https://transplantations-register.de/ (Accessed March 23, 2025).

23. DSO Jahresbericht. Deutsche stiftung organtransplantation DSO jahresbericht. Available online at: https://dso.de/organspende/statistiken-berichte/jahresbericht (Accessed July 2, 2025).

24. Eurotransplant. Annual report - eurotransplant. Available online at: https://www.eurotransplant.org/statistics/annual-report/ (Accessed July 2, 2025).

25. Seitz S, Lange V, Norman PJ, Sauter J, Schmidt AH. Estimating HLA haplotype frequencies from homozygous individuals – a technical report. *Int J Immunogenet* (2021) 48(6):490–5. doi:10.1111/iji.12553

26. Allele Frequency Net Database. The allele frequency net database [germany pop 8]. Available online at: http://www.allelefrequencies.net/pop6001c.asp?pop_id=3089 (Accessed March 30, 2025).

27. Otto G, Budde K, Bara C, Gottlieb J. Unzureichende Datenqualität der Neudaten 2017–2020 des deutschen Transplantationsregisters. *Dtsch Med Wochenschr* (2024) 149(18):e76–83. doi:10.1055/a-2347-3975

28. Bender R, Augustin T, Blettner M. Generating survival times to simulate cox proportional hazards models. *Stat Med* (2005) 24(11):1713–23. doi:10.1002/sim.2059

29. Sargent RG. Verification and validation of simulation models. In: *Proceedings of the 2010 Winter Simulation Conference* (2010). p. 166–83. doi:10.1109/WSC.2010.5679166

30. R Core Team. *R: A Language and Environment for Statistical Computing [Manual]*. Vienna, Austria (2025). Available online at: https://www.R-project.org/ (Accessed October 21, 2025).

31. Wickham H, Averick M, Bryan J, Chang W, McGowan L, François R, et al. Welcome to the tidyverse. *JOSS* (2019) 4(43):1686. doi:10.21105/joss.01686

32. Therneau TM. A package for survival analysis in R (2024). Available online at: https://CRAN.R-project.org/package=survival (Accessed October 21, 2025).

33. Ter HE, Kwakkel J, Hess V, Pike T, Wang B, rht, et al. Mesa 3: agent-based modeling with python in 2025. *JOSS* (2025) 10(107):7668. doi:10.21105/joss.07668

34. Harris CR, Millman KJ, Van Der Walt SJ, Gommers R, Virtanen P, Cournapeau D, et al. Array programming with NumPy. *Nature* (2020) 585(7825):357–62. doi:10.1038/s41586-020-2649-2

35. The pandas development team. pandas-dev/pandas: pandas. *Zenodo* (2023). doi:10.5281/ZENODO.10304236

36. Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, et al. SciPy 1.0: fundamental algorithms for scientific computing in python. *Nat Methods* (2020) 17(3):261–72. doi:10.1038/s41592-019-0686-2

37. Davidson-Pilon C. Lifelines: survival analysis in python. *JOSS* (2019) 4(40):1317. doi:10.21105/joss.01317

38. Coemans M, Tran TH, Döhler B, Massie AB, Verbeke G, Segev DL, et al. A competing risks model to estimate the risk of graft failure and patient death after kidney transplantation using continuous donor-recipient age combinations. *Am J Transplant* (2024) 5:355–67. doi:10.1016/j.ajt.2024.07.029

39. Weaver T, Pyke J. Background and methodology in simulation analysis: OASim (2024). Available online at: https://srtr.org/media/1837/srtr-simulation-methodology.pdf (Accessed April 9, 2025).

40. Sandıkçı B, Tunç S, Tanrıover B. A new simulation model for kidney transplantation in the United States. In: *2019 Winter Simulation Conference (WSC)* (2019). p. 1079–90. doi:10.1109/WSC40007.2019.9004914

41. Zhang Y, Hu A, Lin Y, Cao Y, Muller S, Wong G, et al. simKAP: simulation framework for the kidney allocation process with decision making model. *Sci Rep* (2023) 13(1):1. doi:10.1038/s41598-023-41162-w

42. De Ferrante HC, De Rosner-Van Rosmalen M, Smeulders BML, Spieksma FCR, Vogelaar S. A discrete event simulator for policy evaluation in deceased-donor liver allocation in eurotransplant. *Operat Res Data Anal Logis* (2025). 45:200476 doi:10.48550/ARXIV.2410.10840

ESOT | Transplant International

TYPE Letter to the Editor
PUBLISHED 07 May 2026
DOI 10.3389/ti.2026.16365

Check for updates

OPEN ACCESS

*CORRESPONDENCE
Jorge Andrade-Sierra,
jorge.andrade@academicos.udg.mx

RECEIVED 06 February 2026
REVISED 30 March 2026
ACCEPTED 20 April 2026
PUBLISHED 07 May 2026

CITATION
Reynoso de la Torre HL, Rojas-Campos E, Cerrillos-Gutiérrez JI, Evangelista-Carrillo LA, Banda-López A, Cruz-Landino M, Aguilar-Fletes LE, González-Correa LG, Alatorre-Moreno EV, Simancas-Ruiz PE, Salazar López CB, Miranda-Díaz AG, Sutto ST, Cardona Muñoz EG, Carvallo-Venegas M, Mendoza-Cabrera S, Mendoza Cerpa CA, Romo-Álvarez C, Arellano-Arteaga KJ and Andrade-Sierra J (2026) Human leukocyte antigen-incompatible living donor kidney transplantation after desensitization: experience from a major transplant centre in Mexico.
Transpl. Int. 39:16365.
doi: 10.3389/ti.2026.16365

COPYRIGHT
© 2026 Reynoso de la Torre, Rojas-Campos, Cerrillos-Gutiérrez, Evangelista-Carrillo, Banda-López, Cruz-Landino, Aguilar-Fletes, González-Correa, Alatorre-Moreno, Simancas-Ruiz, Salazar López, Miranda-Díaz, Sutto, Cardona Muñoz, Carvallo-Venegas, Mendoza-Cabrera, Mendoza Cerpa, Romo-Álvarez, Arellano-Arteaga and Andrade-Sierra. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Human leukocyte antigen-incompatible living donor kidney transplantation after desensitization: experience from a major transplant centre in Mexico

Hugo Leonardo Reynoso de la Torre[1], Enrique Rojas-Campos[2], José I. Cerrillos-Gutiérrez[1], Luis A. Evangelista-Carrillo[1], Adriana Banda-López[1], Moises Cruz-Landino[1], Laura E. Aguilar-Fletes[1], Luis G. González-Correa[1], Edith V. Alatorre-Moreno[1], Perla E. Simancas-Ruiz[1], Cindy B. Salazar López[1], Alejandra G. Miranda-Díaz[3], Sylvia Totsuka Sutto[3], Ernesto G. Cardona Muñoz[3], Mauricio Carvallo-Venegas[1], Salvador Mendoza-Cabrera[1], Claudia A. Mendoza Cerpa[4], Carolina Romo-Álvarez[1], Kevin Javier Arellano-Arteaga[5] and Jorge Andrade-Sierra[1,3]*

[1]Department of Nephrology and Organ Transplant Unit, Specialties Hospital, National Western Medical Centre, Mexican Institute of Social Security, Guadalajara, Mexico, [2]Medical Research Unit in Renal Diseases, Specialties Hospital, National Western Medical Centre, Mexican Institute of Social Security, Jalisco, Mexico, [3]University of Guadalajara, University Health Sciences Center, Department of Physiology, Institute of Experimental and Clinical Therapeutics (INTEC), Guadalajara, Jalisco, Mexico, [4]Department of Pathology, Specialties Hospital, National Western Medical Centre, Mexican Institute of Social Security, Guadalajara, Mexico, [5]Department of Internal Medicine. Hospital Civil de Guadalajara "Dr. Juan I. Menchaca", Guadalajara, Jalisco, Mexico

KEYWORDS
antibody-mediated rejection, desensitization, donor-specific antibodies, highly sensitized recipients, HLA-incompatible transplantation

Dear editors,

Kidney transplant recipients (KTRs) sensitized against human leukocyte antigens (HLA) represent a major clinical challenge because multiple donor-specific antibodies (DSAs) often lead to positive crossmatches and a high risk of graft loss from antibody-mediated rejection (AMR) [1]. This challenge is worsened in Latin America as there are fewer kidney-exchange programs and DSA biobanks, reducing access to compatible donors. Consequently, our institution—one of the most active transplant centers in Latin America—expanded living-donor transplantation for HLA-incompatible pairs through individualized desensitization.

We performed a single-center retrospective cohort study of 65 highly sensitized living-donor KTRs (2018–2022) undergoing individualized desensitization with intravenous immunoglobulin (IVIG) alone (200 mg/kg/day ×3) or plasmapheresis (PP)-based therapy (three sessions plus IVIG and rituximab [RTX] 375 mg/m^2, 1–2 doses) with a ≥12-month follow-up (Table 1). Crossmatch testing (flow cytometry and complement-dependent cytotoxicity [CDC]) was performed prior to desensitization in all patients. Crossmatch results were either positive or negative by

10.3389/ti.2026.16365

TABLE 1 Baseline characteristics, immunological profile, and outcomes according to desensitization strategy.

Variable	IVIg therapy (n = 20)	PP + IVIg + RTX (n = 45)	*P* value
Gender of recipients-male, n (%)	13 (65%)	25 (55.5%)	0.48
Age of recipients (years)	34.5 ± 9.5	33.5 ± 9.0	0.68
Age of donors (years)	37 ± 10	38 ± 12	0.75
Time on dialysis (years)	3.7 ± 2.9	3.4 ± 2.5	0.66
Serum creatinine at 12 months (mg/dL)	1.3 ± 0.5	1.6 ± 0.6	0.88
eGFR, mL/min/1.73 m^2	69 ± 27	75.5 ± 28	0.42
Flow cytometry crossmatch (FCXM)			0.74
Positive	10 (50%)	24 (53.3%)	
Negative	10 (50%)	20 (44.4%)	
CDC crossmatch (§)			--
Positive	0	2 (4.5%)	
Negative	0	0	
DSA flowby - luminex (MFI ≥1,000), median (IQR)			0.11
Class I	0.0 (0.0–5039)	2,736 (0.0–8,076)	0.18
Class II	2,112 (250–2,899)	7,551 (636–11105)	
Related living donor n (%)	17 (85%)	30 (66.7%)	0.13
Unrelated living donor n (%)	3 (15%)	15 (33.3%)	
Transplant number, n (%)			0.001*
First	17 (85%)	16 (35.6%)	
Second	3 (15%)	29 (64.4%)	
Histocompatibility n (%)			0.332
2 haplotype	2 (10%)	1 (2.2%)	
1 haplotype	10 (50%)	21 (46.7%)	
None haplotype	8 (40%)	23 (51.1%)	
AR incidence n (%)	3 (15%)	10 (22.2%)	0.502
Graft lost n (%)	1 (5%)	4 (8.9%)	0.59
Infectious events n (%)	7 (35%)	20 (44.4%)	0.34

*p = <0.05.
Data are presented as mean ± SD or median (IQR).
§CDC crossmatch positivity occurred only in the PP + IVIG + RTX group.

flow cytometry or CDC. Patients with detectable donor-specific antibodies (DSA), regardless of crossmatch result, were considered at increased immunological risk and therefore underwent desensitization according to institutional criteria.

All patients received standard maintenance immunosuppression (tacrolimus, mycophenolate mofetil [MMF], and prednisone), primarily antithymocyte globulin (ATG) induction, infection prophylaxis, and protocol and indication biopsies. Primary endpoints were acute rejection (AR) incidence and 12-month estimated glomerular filtration rate (eGFR; CKD-EPI); secondary endpoints included graft survival and infectious events.

AR occurred in 20% of patients (all AMR), with no differences between regimens; 12-month eGFR and graft survival were favorable and comparable. Infection-related mortality was low (6.2%). Infectious complications (predominantly urinary tract infections [UTIs]) were comparable between regimens; viral rates were low (cytomegalovirus [CMV] 1.5%, poliomavirus BK 6.2%). All variables with $p < 0.05$ in univariate analysis were entered into a multivariable logistic regression model using a forward stepwise approach. Graft survival was analyzed by Kaplan–Meier and log-rank tests; two-sided $p < 0.05$ was considered significant. Analyses used SPSS™ version 23.

High *de novo* or preformed DSAs, particularly class II, are typically associated with complement activation, microvascular inflammation, increased AMR, and worse outcomes [2, 3]. However, in our cohort, pre-transplant class II DSAs did not predict AR, graft loss, or reduced eGFR. Recipients of triple therapy had higher median class II DSA MFI (7,551), reflecting risk-based selection, yet outcomes were similar to those receiving IVIG alone, including patients with MFI >1,000. Notably, lower MFI values (<1,000) have also been linked to immunological risk [4], so patients treated with IVIG alone despite appearing lower risk remain

vulnerable and require close monitoring and individualized management. Overall AR rates, 1-year graft function, and survival were favorable and comparable to other desensitization series, including contemporary meta-analytic evidence showing high 1-year graft survival after IVIg/plasmapheresis/rituximab desensitization [5] and single-center cohorts reporting AR incidences in the same range with acceptable longer-term graft survival [6]. These results also align with evidence that desensitization may offer survival comparable to, or better than, remaining on dialysis or awaiting a compatible deceased-donor transplant [7]. Complement-activating anti-HLA DSAs are associated with higher risk of allograft loss and AMR [3], but we could not determine whether preformed DSAs were complement fixing or were eliminated after desensitization. A notable proportion of patients underwent transplantation despite a positive crossmatch. Although desensitization is sometimes used for recipients with positive flow-cytometry or CDC crossmatches and/or very high pre-transplant DSA MFI, prior studies report higher AMR rates and poorer graft survival in such cases [1].

In our cohort, ~50% of IVIG-only and 53.3% of triple-therapy patients had a positive crossmatch, predominantly by flow cytometry; only 3.1% had a positive CDC crossmatch and underwent triple therapy, achieving CDC negativization prior to transplantation. One developed AMR at 12 months, which was successfully treated with preserved graft function (creatinine 1.0 mg/dL), while the other died from pneumonia and sepsis with a functioning graft. We observed no significant outcome differences by crossmatch status, whether comparing positive versus negative or flow-cytometry versus CDC positivity. Desensitization practices are heterogeneous across centers [8, 9]. We assessed immunological risk using flow cytometry and CDC crossmatches and Luminex SAB donor-specific antibody testing before desensitization. At our center, regimen selection was clinician-driven, influenced by immunological risk and the decision of the nephrology committee. We defined a sensitized patient (high risk) as one with a positive or negative flow cytometry crossmatch, with donor-specific antibodies (DSA) greater than 1000 MFI, and a history of exposure to sensitizing risk factors [10], with triple therapy used preferentially for higher DSA MFI (4,000–5,000), introducing indication bias that limits causal comparisons. Nevertheless, outcomes were encouraging, since sensitized recipients, including those with lower MFI, remain at substantial risk of AMR [4]. Protocol biopsies at 3–6 months are a strength: no subclinical AR was detected and all AR episodes were diagnosed on indication. Post-transplant DSA profiles were not available, so we could not determine whether AR episodes were driven by *de novo* or preformed DSAs. Beyond MFI, donor–recipient HLA compatibility was also relevant: in our regression analysis, fewer shared haplotypes was the only factor independently associated with increased AR risk, consistent with evidence that greater histocompatibility reduces rejection. Although follow-up was limited to 12 months, graft survival did not differ between groups and was comparable to other reports with similar AMR rates [5, 6]. Graft loss occurred in five recipients (6.2%), primarily due to immunological causes, namely hyperacute rejection (n = 1), acute antibody-mediated rejection (n = 2), and mixed rejection (n = 1), with one additional case attributable to BK virus–associated nephropathy.

Finally, although desensitization-related immunosuppression may increase infection risk, overall infectious complications—predominantly UTIs—were similar between regimens and comparable to non-sensitized KTRs at our center [11] with infrequent viral infections (CMV and BK). Overall mortality was 6.2%, entirely due to infectious causes, with deaths resulting from pneumonia and sepsis (n = 3) and COVID-19 (n = 1), consistent with contemporary desensitization cohorts [5], and was higher among patients with DSAs to both HLA classes ($p = 0.032$), with no differences between regimens. Extended follow-up is warranted to better define late infectious risk. Although desensitization remains controversial regarding rejection risk and graft survival, recent consensus supports individualized strategies based on each patient's immunological risk profile [9].

Limitations include the retrospective design and short follow-up. A lack of systematic post-transplant immunomonitoring limit analysis of DSA kinetics, distinction of *de novo* versus preformed DSAs, and assessment of long-term antibody-mediated injury and graft survival. Protocol biopsies at 3–6 months are a strength of the study—no subclinical AR was detected and all AR episodes were diagnosed on indication.

Overall, these findings support individualized desensitization as a feasible strategy to safely expand access to living-donor kidney transplantation in Latin America.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Specialties Hospital, National Western Medical Centre, Mexican Institute of Social Security. Institutional ethics and research committee (R-2025-1301-009). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HR, ER-C, JC-G, LE-C, and JA-S participated in the conceptualization and design of the study. HR, ER-C, JC-G, LE-C, AB-L, MC-L, AM-D, SS, EC, and JA-S participated in the analysis and interpretation. HR, ER-C, JC-G, LE-C, LA-F, LG-C, EA-M, PS-R, CS, MC-V, SM-C, CM, CR-A, KA-A, and JA-S participated in drafting the article and critical review for important intellectual content. Final approval of the version to be published: All the team.

All authors contributed to the article and approved the submitted version.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

References

1. Noble J, Jouve T, Malvezzi P, Rostaing L. Desensitization in crossmatch-positive kidney transplant candidates. *Transplantation* (2023) 107(2):351–60. doi:10.1097/TP.0000000000004279

2. Lefaucheur C, Louis K, Morris AB, Taupin JL, Nickerson P, Tambur AR, et al. Clinical recommendations for posttransplant assessment of anti-HLA (human leukocyte antigen) donor-specific antibodies: a sensitization in transplantation: assessment of risk consensus document. *Am J Transpl* (2023) 23(1):115–32. doi:10.1016/j.ajt.2022.11.013

3. Al-Awadhi S, Raynaud M, Louis K, Bouquegneau A, Taupin JL, Aubert O, et al. Complement-activating donor-specific anti-HLA antibodies in solid organ transplantation: systematic review, meta-analysis, and critical appraisal. *Front Immunol* (2023) 14:1265796. doi:10.3389/fimmu.2023.1265796

4. Kitpermkiat R, Kantachuvesiri S, Thotsiri S, Thammanichanond D, Rostaing L, Wiwattanathum P. Impact of donor-specific antibody with low mean fluorescence intensity on allograft outcomes in kidney transplant. *Transpl Immunol* (2024) 84:102054. doi:10.1016/j.trim.2024.102054

5. Chandramohan D, Adisa O, Patel D, Ware E, Eleti N, Agarwal G. Outcomes of kidney transplantation in highly HLA-sensitized patients treated with intravenous immunoglobulin, plasmapheresis and rituximab: a meta-analysis. *Life (Basel)* (2024) 14(8):998. doi:10.3390/life14080998

6. Fernandez C, Calvo M, Leite N, Lopez A, Ferreiro T, Ribera R, et al. Kidney transplantation from HLA-incompatible live donors: efficiency and outcome of 32 patients after desensitisation. *Nefrologia* (2017) 37(6):638–45. doi:10.1016/j.nefro.2017.06.006

7. Montgomery RA, Lonze BE, King KE, Kraus ES, Kucirka LM, Locke JE, et al. Desensitization in HLA-incompatible kidney recipients and survival. *N Engl J Med* (2011) 365(4):318–26. doi:10.1056/NEJMoa1012376

8. Mancebo E, Diekmann F, Palou E, Vilches C, Crespo M, Mazuecos A, et al. Spanish guidelines for kidney transplantation in highly sensitized patients with donor-specific anti-HLA antibodies. *Transpl Rev (Orlando)* (2025) 39(3):100919. doi:10.1016/j.trre.2025.100919

9. Furian L, Bestard O, Budde K, Cozzi E, Diekmann F, Mamode N, et al. European consensus on the management of sensitized kidney transplant recipients: a Delphi study. *Transpl Int* (2024) 37:12475. doi:10.3389/ti.2024.12475

10. Bestard O, Couzi L, Crespo M, Kessaris N, Thaunat O. Stratifying the humoral risk of candidates to a solid organ transplantation: a proposal of the ENGAGE working group. *Transpl Int* (2021) 34(6):1005–18. doi:10.1111/tri.13874

11. Andrade-Sierra J, Andrade-Martinez JC, Fuentes-Lopez EA, Rojas-Campos E, Martinez-Mejia V, Gonzalez-Espinoza E, et al. A five-year retrospective study focused on urinary tract infections in kidney transplant recipients in the current era of immunosuppression. *Front Med (Lausanne)* (2025) 12:1606224. doi:10.3389/fmed.2025.1606224

Transplant International

Official journal of the European Society for Organ Transplantation

Editorial Office

Avenue du Tribunal Fédéral 34
CH – 1005 Lausanne
Switzerland

Tel +41 (0)21 510 17 40
Fax +41 (0)21 510 17 01

tieditorialoffice@frontierspartnerships.org
frontierspartnerships.org/journals/transplant-international

frontiers | Publishing Partnerships