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Sustainable Transplantation: Recycling
Untransplantable Donated Organs



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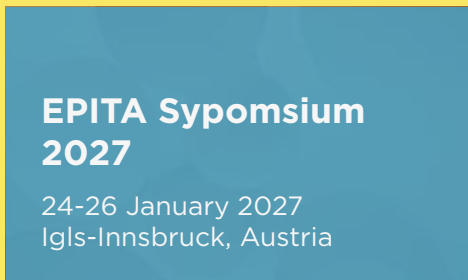


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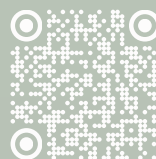
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Revealing the potential of non-transplanted donor organs: a comparative analysis in the Eurotransplant region

A. Kofler¹, F. J. Krendl¹, L. Prommegger¹, J. Hofmann¹, A. Weissenbacher¹, B. Cardini¹, A. T. Meszaros¹, T. Resch¹, G. Brandacher¹, T. Hautz¹, R. Oberhuber¹, E. de Buijzer², S. Eschertzhuber³ and S. Schneeberger^{1*}

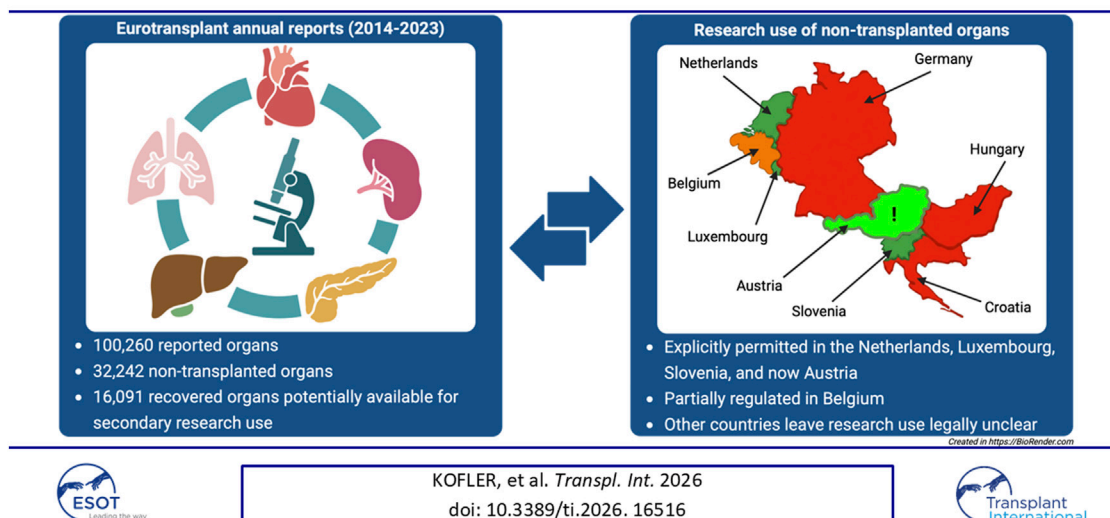
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Post-mortem organ donation is essential for modern transplantation medicine, yet a substantial proportion of recovered donor organs are not transplanted. These organs, although clinically declined, hold significant and untapped value for biomedical research and technological innovation. Eurotransplant reports and United States national data were reviewed to quantify transplanted and not used organs and to assess temporal trends. During the study period, 100,260 organs were reported in Eurotransplant, of which 32,242 (32.16%) were not transplanted. Of all reported organs, 16.05% were accepted for transplantation but not used, representing a stable and predictable number of organs suitable for secondary research use. A review of international, European, and national legislation demonstrated that, in many Eurotransplant countries, existing laws focus almost exclusively on transplantation and provide limited guidance on the research use of non-transplanted organs, with the Netherlands, Slovenia, Luxembourg, and partially Belgium as notable exceptions. Emerging technologies highlight the scientific and clinical relevance of these organs. Establishing legal and ethical pathways for their secondary use could reduce organ wastage, support innovation, and improve transplantation outcomes. Engagement with the Austrian Federal Ministry of Health, informed by the findings of this work, contributed to an amendment of the Austrian Organ Transplantation Act.

KEYWORDS

biomedical research, eurotransplant, legal framework, non-transplanted organs, organ donation

Revealing the Potential of Non-transplanted Donor Organs: A Comparative Analysis in the Eurotransplant Region



GRAPHICAL ABSTRACT
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Introduction

Initiated in 1967 by Professor Jon J. van Rood, the Eurotransplant International Foundation (Eurotransplant) is a non-profit organization coordinating the allocation of post-mortem donor organs in 8 European countries. Member countries of Eurotransplant are Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, Netherlands and Slovenia. Eurotransplant plays a central role in the just and efficient distribution of organs such as kidneys, livers, hearts, lungs, pancreases and intestines.¹ Allocation is based on medical and ethical criteria [1, 2]. The most important criteria for organ allocation are blood group, donor size and age, tissue characteristics (HLA groups especially for kidneys), clinical urgency, waiting time, and regional availability (depending on organ type).²

Three consent models exist for deceased organ donation. In Eurotransplant, Germany adopted the informed consent (opt-in) model, where the donor or their designated surrogate must explicitly confirm the donor's willingness to donate before organ recovery. All other Eurotransplant countries apply an opt-out model based on presumed consent. Individuals are considered organ donors upon death unless they have registered an objection.³ The third is the explicit authorization model, adopted in the United States, which

requires explicit authorization from the donor emphasizing individual autonomy.⁴ Each system reflects a different ethical and legal position on balancing personal choice with the need to maximize organ availability for transplantation.

The decision-making of organ suitability is guided by donor and recipient factors, transportation logistics, hospital and center policies, time of day, and, most importantly, the subjective assessment of the surgeons at the transplant centers. Notably, non-utilization rates increase during weekends and nighttime hours, highlighting the impact of human factors such as workload and decision fatigue [3, 4]. Hence, organ non-utilization is driven by subjective factors such as institutional risk aversion, labeling biases, and inconsistent interpretation of imperfect clinical data [5]. To reduce unnecessary organ non-utilization, it is crucial to establish more objective and standardized criteria.

Despite the efforts towards organ donation in the Eurotransplant region, the shortage of donor organs (1,424 waiting-list-deaths in 2024;⁵ 140 million population⁶) remains the key limiting factor in organ transplantation. Novel medical tools for organ preservation

1 Eurotransplant International Foundation. Cooperating saves lives. <https://www.eurotransplant.org/about-eurotransplant/cooperating-saves-lives/> [Accessed February 14, 2026].

2 Eurotransplant International Foundation. Eurotransplant Manual, Chapter 1: Introduction (2022). <https://www.eurotransplant.org/wp-content/uploads/2022/02/H1-Introduction-July-28-2016.pdf> [Accessed October 12, 2025].

3 Eurotransplant International Foundation. Legislation. <https://www.eurotransplant.org/region/legislation/> [Accessed October 14, 2025].

4 Organ Procurement & Transplantation Network. Ethics of deceased organ donor recovery (2016). <https://optn.transplant.hrsa.gov/professionals/by-topic/ethical-considerations/ethics-of-deceased-organ-donor-recovery/> [Accessed June 21, 2025].

5 Council of Europe. Newsletter Transplant 2024: International Figures on Organ, Tissue and Hematopoietic Stem Cell Donation and Transplantation Activities. Strasbourg: European Directorate for the Quality of Medicines & Healthcare (EDQM) (2024). <https://www.edqm.eu/en/-/newsletter-transplant-2024-organ-donation-increases-globally> [Accessed September 3, 2025].

6 Eurotransplant International Foundation. Annual Report (2023). <https://cdn.sanity.io/files/ngz8tmzz/production/24445ce7c521641ca1cd28e24ff7ff2442576fcb.pdf> [Accessed September 4, 2025].

combined with the development of new technologies for assessment and treatment of donor organs [6, 7] enable for data-based organ quality assessment and higher organ utilization rates.

Normothermic machine perfusion (NMP) enables safe transplantation of high-risk donor livers that would otherwise not be utilized [8]. Normothermic regional perfusion (NRP) is used in donation after circulatory death (DCD) and has demonstrated higher utilization rates and better outcomes [9]. Machine perfusion has enabled functional assessment and recovery of marginal liver [10–18], kidney [19], pancreas and lung [20, 21] grafts. In pancreas transplantation, *ex vivo* NMP has been applied in an experimental setting and select centers to assess function in declined grafts [22, 23]. *Ex situ* organ perfusion platforms also serve to test perfusion solutions and additives under controlled conditions [24–26]. Broader use of perfusion technologies may help meet transplant demand [8, 27]. However, the challenge lies in deciphering the significance of this information to determine its most effective and efficient use in organ transplantation.

The accelerating pace of technological advancement has dramatically expanded the capacity to gather, analyze, and interpret data. Combined with artificial intelligence, machine learning, and biomedical imaging, this fuels the prospect of a more robust, data-driven and fair allocation system.

To bridge the widening gap between data acquisition and biological insight, it is imperative to obtain a greater number and diversity of human organs for research. The study of organs across different ages, ethnicities, disease states, and environmental backgrounds, may reveal meaningful biological signals with predictive value towards the outcome after transplantation. Therefore, expanding access to human organs, that otherwise would not be used is essential for fully realizing the potential of contemporary and future biomedical technologies.

The aim of this manuscript is to assess the current state of research on human organs deemed unsuitable for transplantation and to examine the legal framework and practical application across Eurotransplant. It highlights the need for improved policies and handling of these organs to expand research opportunities and increase organ availability.

Materials and methods

Data sources

Annual Eurotransplant reports from 2014 to 2023 were used as primary data source.⁷

To provide a comparison with organ utilization in the United States, statistics from 2014 to 2023 were obtained from the Annual Data Reports of the US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients (OPTN/SRTR).⁸

The analysis includes only deceased-donor organs.

Organs are counted individually; lungs and kidneys separately, livers as whole organs (with splits counted separately) and hearts, pancreases, and intestines per organ.

Study variables

Annual data from 2014 to 2023 were obtained from Eurotransplant for kidney, liver, heart, lung, and pancreas transplantation. The total number of reported donor organs and their subsequent allocation outcomes were extracted. Reported organs were categorized according to their progression through the allocation process into mutually exclusive categories defined by Eurotransplant: (i) reported, (ii) not offered, (iii) offered but not accepted, (iv) accepted but not transplanted, and (v) transplanted.

For analytical purposes additional descriptive groupings were used. All organs that were not transplanted were collectively referred to as non-transplanted organs, regardless of the reason or stage which they exited the transplantation destination. The term “discarded” was avoided, in line with consensus in the field [28].

Within the non-transplanted group, organs categorized as accepted by a transplant center but eventually not transplanted were specifically referred to as “recovered organs” for the purpose of this analysis. Original Eurotransplant outcome categories were retained for reporting and figures. This category corresponds conceptually to “recovered organs” in the United States reporting system, representing organs recovered for transplantation but not ultimately transplanted.

Organ-specific utilization patterns were evaluated by comparing the proportion of transplanted organs across organ types.

For the United States comparator analysis, aggregated annual data from 2014 to 2023 were extracted from OPTN/SRTR annual reports. These data included counts of reported donor organs, transplanted organs, non-transplanted organs, reported categories of non-use, and organs used for scientific or technical purposes.

Utilization rate calculation

Organ-specific utilization rates were calculated by dividing the number of transplanted organs with the total number of reported organs for each organ type and expressing the result as a percentage.

Statistical analysis

Descriptive statistics were calculated for each annual variable. Normality was assessed using the Shapiro–Wilk test. To evaluate temporal trends over the ten-year observation period, linear regression analyses with year as a continuous predictor were performed for each outcome variable.

Cross-country comparison

To contextualize Eurotransplant findings, we compared reported organ numbers and utilization outcomes with United States OPTN/SRTR statistics over the same period (2014–2023). Per-million-population (pmp) values were

⁷ Eurotransplant International Foundation. Annual Reports. <https://www.eurotransplant.org/statistics/annual-report> [Accessed August 28, 2024].

⁸ Organ Procurement & Transplantation Network. Annual Data Reports. <https://srtr.transplant.hrsa.gov> [Accessed September 7, 2024].

TABLE 1 Number of reported and non-transplanted organs from 2014 to 2023 in the Eurotransplant region.

Year	Organs reported	Reported but not offered	Offered but not accepted	Accepted but not transplanted	Non-transplanted organs (total)
	n	n (%)	n (%)	n (%)	n (%)
2014	10,270	89 (0.87)	1,522 (14.82)	1,523 (14.83)	3,134 (30.52)
2015	10,271	68 (0.66)	1,458 (14.20)	1,615 (15.72)	3,141 (30.58)
2016	9,965	42 (0.42)	1,385 (13.90)	1,600 (16.06)	3,027 (30.38)
2017	9,695	52 (0.54)	1,422 (14.67)	1,624 (16.75)	3,098 (31.95)
2018	10,705	76 (0.71)	1,483 (13.85)	1,724 (16.10)	3,283 (30.67)
2019	10,259	80 (0.78)	1,522 (14.84)	1,693 (16.50)	3,295 (32.12)
2020	9,192	57 (0.62)	1,415 (15.39)	1,429 (15.55)	2,901 (31.56)
2021	9,382	82 (0.87)	1,532 (16.33)	1,417 (15.10)	3,031 (32.31)
2022	9,949	77 (0.77)	1,790 (17.99)	1,655 (16.63)	3,522 (35.40)
2023	10,572	117 (1.11)	1,882 (17.80)	1,811 (17.13)	3,810 (36.04)
Total	100,260	740 (0.74)	15,411 (15.37)	16,091 (16.05)	32,242 (32.16)

Non-transplanted organs are categorized as not offered, offered but not accepted, and accepted but not transplanted. The table also shows the percentage of each category relative to the total number of reported organs per year. Minor discrepancies may occur due to rounding of percentage values.

interpreted using Eurostat and United States Census estimates to enable direct comparison between regions and over time.

Legal and policy assessment

A structured document review was conducted of relevant international, European, and national legal instruments in all Eurotransplant member states. For each country, we identified the consent model and examined whether the respective transplantation laws explicitly addressed the research use of non-transplanted organs and especially recovered organs, whether additional consent beyond donation consent was required for research use, and whether national operational guidance or legislation referred to Eurotransplant policies governing the secondary use of declined organs. Findings were narratively synthesized by country.

Results

Organ utilization efficiency in eurotransplant

A total of 100,260 organs (kidney, liver, heart, lungs, pancreas) were reported for transplantation between 2014 and 2023 (as shown in Table 1).⁷ Of these, 32,242 (32.16%) were ultimately not suitable for transplantation. From the total number of non-transplanted organs, three subgroups can be identified: 740 (0.74%) organs were never offered for transplantation, 15,411 (15.37%) organs were offered but not accepted by any transplant center, 16,091 (16.05%) organs were initially accepted for transplantation, but the procedure was ultimately not carried out due to various reasons such as unexpected pathologies,

poor organ function, histological findings, and others.⁷ Also, organ utilization rates varied by organ. Kidneys had a utilization rate of 80.19%, while pancreas utilization was 21.45% (Table 2; Figure 1). The number of reported, transplanted, and not transplanted organs over the ten-year observation period is depicted in Figure 1.

The median annual number of transplanted organs was 6,850 (IQR = 703; n = 10 years; $\beta = -76.4$ organs/year; $R^2 = 0.37$; $p = 0.062$), indicating no statistically significant trend over time. The category “reported but not offered” had an annual median of 76.5 organs (IQR = 25; n = 10 years; $\beta = +3.2$ organs/year; $R^2 = 0.21$; $p = 0.177$), likewise showing no significant temporal change. For “offered but not accepted”, the median was 1,502.5 (IQR = 110; n = 10 years; $\beta = +38.3$ organs/year; $R^2 = 0.50$; $p = 0.023$), representing the only category with statistically significant upward trend over the study period. The “accepted but not transplanted” category showed a median annual count of 1,619.5 (IQR = 170; n = 10 years; $\beta = +8.1$ organs/year; $R^2 = 0.04$; $p = 0.585$), indicating a stable volume. The total number of reported organs had a median of 10,112 (IQR = 576; n = 10 years; $\beta = -26.7$ organs/year; $R^2 = 0.03$; $p = 0.649$). The total annual number of non-transplanted organs had a median of 3,137.5 (IQR = 264; n = 10 years; $\beta = +49.6$ organs/year; $R^2 = 0.31$; $p = 0.093$).

Donor utilization efficiency

The number of reported, utilized, and not utilized donors over the ten-year observation period is depicted in Figure 2. The total number of organ donors reported from 2014 to 2023 in the Eurotransplant region was 23,044 (as shown in Table 3). Of these, 3,024 (13.12%) donors were not considered suitable for donation.⁷ The annual number of reported donors ranged from 2,119 to 2,499 across the ten-year study period (mean 2,304; SD = 118.8; n = 10 years).

TABLE 2 Reported and non-transplanted organs by organ type in the Eurotransplant region from 2014 to 2023.

Organ	Organs reported n	Reported but not offered n (%)	Offered but not accepted n (%)	Accepted but not transplanted n (%)	Non-transplanted organs (total) n (%)
Kidney	39,837	283 (0.71)	3,021 (7.58)	4,587 (11.51)	7,891 (19.81)
Liver	20,399	41 (0.20)	1,018 (4.99)	3,933 (19.28)	4,992 (24.47)
Heart	8,790	43 (0.49)	1,629 (18.53)	936 (10.65)	2,608 (29.67)
Lungs	22,827	117 (0.51)	5,293 (23.19)	4,737 (20.75)	10,147 (44.45)
Pancreas	8,407	256 (3.05)	4,450 (52.93)	1,898 (22.58)	6,604 (78.55)

Nonutilized organs are classified as not offered, offered but not accepted, or accepted but not transplanted. The table additionally presents the percentage of each category in relation to the annual total number of reported organs.

The annual number of not utilized donors ranged from 248 to 420 (mean 302.4; SD = 52.87; $n = 10$ years). Linear regression analysis showed a significant upward trend in not utilized donors over time ($\beta = +11.8$ donors/year; $R^2 = 0.459$, $p = 0.031$).

Eurotransplant data specifies only limited information regarding why these donors were deemed unsuitable for transplantation. In total, 3,024 donors, corresponding to potentially 24,192 organs, were not utilized.

Comparison of organ utilization efficiency with the United States

The number of reported donor organs differed considerably between the Eurotransplant region and the United States (735 pmp vs. 2,157 pmp respectively; Figure 3). From 2014 to 2023 a total of 709,099 organs were reported in the United States, of which 319,410 (45.04%) organs were transplanted and 332,072 (46.83%) were not. This number of non-transplanted organs is composed of organs, for which consent for donation was not requested, consent was not obtained, and organs which were not recovered due to, e.g., presumed poor organ function, organ disease, donor medical history, time constraints, infection, trauma, anatomical or vascular damage, biopsy findings, etc. (Figure 4). From the 49,435 (6.97% of reported) organs used for science, a proportion (75.69%) was recovered with the immediate intention to use the organs for research while the remaining organs (24.31%) were recovered with the intent of transplantation but later repurposed for scientific use. Organs recovered for technical evaluations, heart valve procurement, islet cell isolation, hepatocyte extraction, etc., included 8,182 (1.15% of reported) organs.

The current reality is that the number of transplanted organs pmp differs substantially between Eurotransplant and the United States (499 pmp vs. 973 pmp). When Germany is excluded from the assessment, the ET transplantation rate is 657 pmp, indicating a regional effect in the ET data. The number of organs used for research are displayed in Table 4.

Reasons for non-procurement

There are several reasons, why donor organs may not be used, both during the initial assessment stage and after

provisional acceptance. Common factors include extended cold ischemia time, organ damage arising either from the retrieval process or from donor-related trauma, and anatomical abnormalities. Other reasons are poor organ function, the donor's medical history (e.g., comorbidities, infections, or malignancies) and donor age, logistical challenges such as transport, inability to locate a suitable recipient, or a positive crossmatch with the recipient. Center-specific and conservative acceptance criteria, recipient health status, and the need for a better immunological match may also contribute to an organ not being used for transplantation (Figure 4) [5, 29, 30].

The legal framework

Key international frameworks guiding ethical organ donation and transplantation include United Nations General Assembly Resolutions 71/322, 73/189, 75/195, and 77/236 [31], the Declaration of Istanbul of 2008 [32], the World Health Organization Guiding Principles on Human Cell, Tissue and Organ Transplantation of 2010 [33], and the World Health Assembly Resolution 62.22 of 2009 [34]. Together, they promote transparency, prohibit organ trafficking and transplant tourism, emphasize voluntary and informed consent, and call for equitable access and international cooperation in transplantation practices. The pathway of a donor organ from donation consent to transplantation crosses several institutional and, at times, national boundaries, and at each stage distinct legal instruments determine who may hold, assess, or ultimately use the organ, as summarized in Figure 5.

In Europe, key legal instruments include the European Treaty Series No. 005 [35], No. 050 [36], No. 164 [37], and No. 186 [38], as well as Council of Europe Treaty Series No. 197 [39], and No. 216 [40]. They are all issued under the framework of the Council of Europe, an intergovernmental organization founded in 1949 to promote human rights, democracy, and the rule of law across its member states.⁹ These

⁹ Council of Europe - Conseil de l'Europe. The Council of Europe at a glance (2023). <https://www.coe.int/en/web/portal/the-council-of-europe-at-a-glance> [Accessed March 5, 2025].

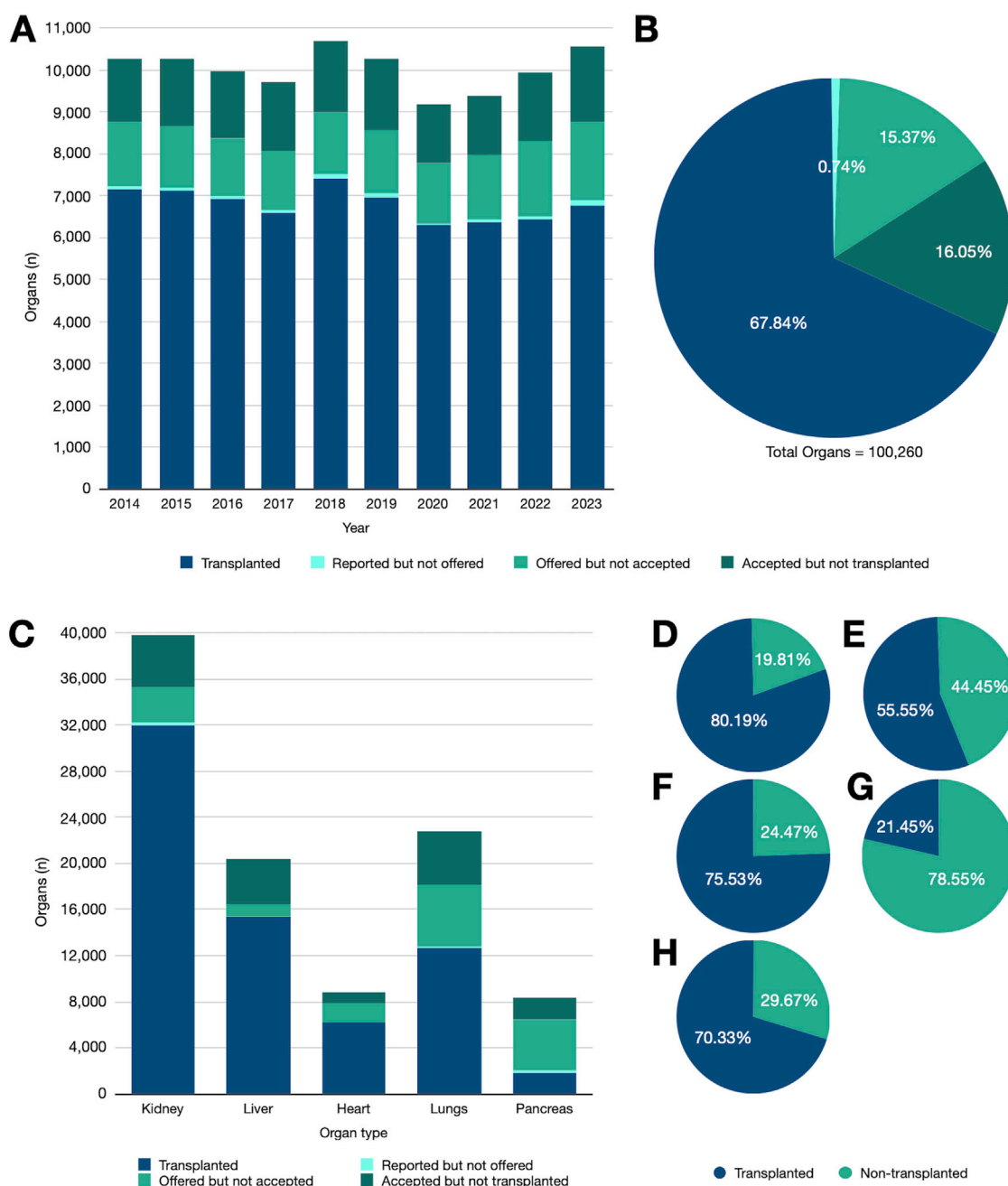


FIGURE 1

Fate of all reported donor organs in the Eurotransplant region from 2014 to 2023. (A) Yearly distribution of reported donor organs according to their destination (not offered, not accepted, not transplanted, and transplanted), illustrating temporal trends in organ utilization over the ten-year period. (B) Cumulative distribution of all reported donor organs during the study period, categorized by final destination, providing an overall overview of organ utilization and non-utilization. (C) Cumulative number of reported organs stratified by organ type. (D–H) Percentage distribution of transplanted versus non-transplanted organs by organ type: (D) kidney, (E) lungs, (F) liver, (G) pancreas, and (H) heart.

documents collectively establish ethical and legal standards for organ and tissue donation, ensure informed consent and donor protection, regulate the cross-border exchange of human substances, and explicitly prohibit trafficking in organs and humans for the purpose of organ removal.

At European Union level, the main legal instruments are Directive 2010/53/EU [41] (complementing Directive 2004/23/

EC) and Implementing Directive 2012/25/EU [42]. Directive 2010/53/EU sets minimum quality and safety standards for organs intended for transplantation, whereas Implementing Directive 2012/25/EU regulates cross-border exchange, traceability, and communication between member states.

Directive 2010/53/EU serves as the central legal basis for the regulations of the member states of the European Union and is

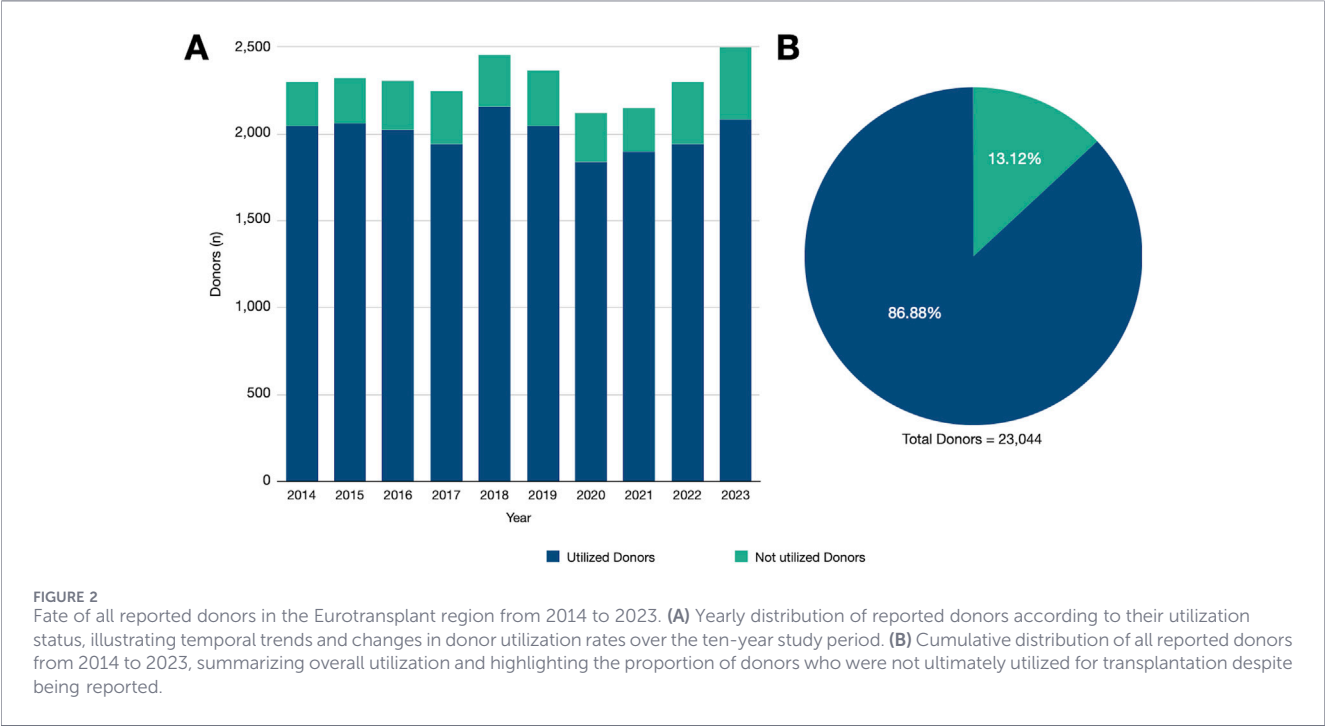


TABLE 3 Number of reported and utilized Donors from 2014 to 2023 in the Eurotransplant region.

Year	Reported donors	Utilized donors	Not utilized donors
	n	n (%)	n (%)
2014	2,299	2,041 (88.78)	258 (11.22)
2015	2,317	2,063 (89.04)	254 (10.96)
2016	2,306	2,021 (87.64)	285 (12.36)
2017	2,246	1,942 (86.46)	304 (13.54)
2018	2,455	2,159 (87.94)	296 (12.06)
2019	2,362	2,042 (86.45)	320 (13.55)
2020	2,119	1,837 (86.69)	282 (13.31)
2021	2,146	1,898 (88.44)	248 (11.56)
2022	2,295	1,938 (84.44)	357 (15.56)
2023	2,499	2,079 (83.19)	420 (16.81)
Total	23,044	20,020 (86.88)	3,024 (13.12)

The table also shows the percentage of each category relative to the total number of reported Donors per year.

intended to ensure high medical quality and the protection of organ donors and recipients. The harmonization of regulations at European level is intended to ensure that organs can be transplanted under comparable and safe conditions within the EU, regardless of their country of origin. The directive thus forms the basis for national legislation on organ donation and transplantation and contributes to improving the availability and quality of donor organs [43].

As a directive, it is intended to be transposed into national law by EU member states, where each member state determines the form

and the methods for the incorporation.¹⁰ In some, existing laws were amended to align with the directive, whereas in others, new legislation was enacted to ensure compliance.

Directive 2010/53/EU accentuates the removal of organs for transplantation and the research on those organs, but it remains

10 EUR-Lex Access to European Union Law. Summaries of EU legislation: Directive. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:directive> [Accessed March 3, 2025].

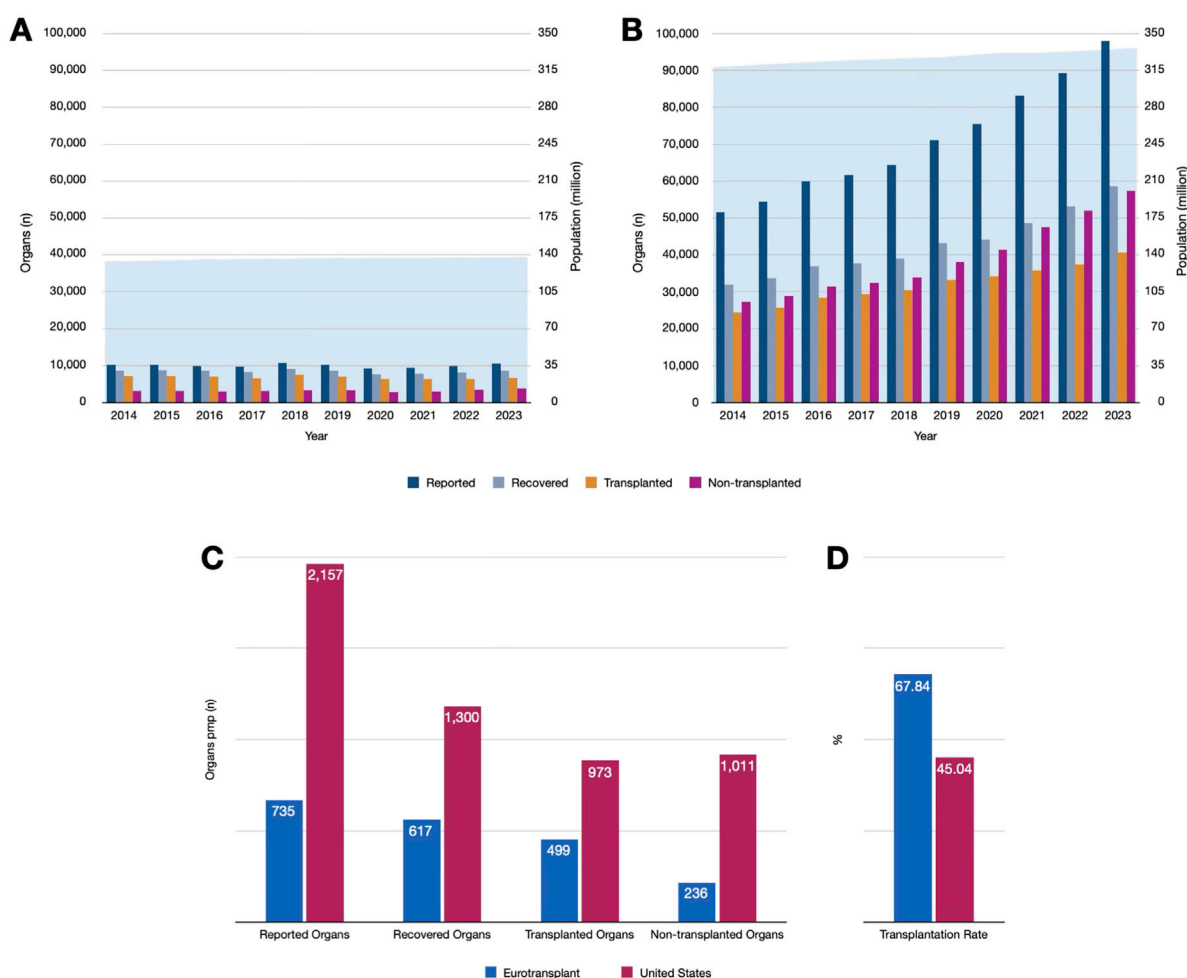


FIGURE 3

Comparison of organ transplantation efficiency in Eurotransplant and the United States from 2014 to 2023. (A) Organ activity in Eurotransplant (reported, recovered, transplanted, not transplanted); primary axis: absolute organ numbers; secondary axis: per million population (pmp), shown as blue shaded background. (B) Organ activity in the United States with the same categories and axis structure as in (A). (C) Head-to-head comparison of organ activity per million population (pmp) between Eurotransplant and the United States across all categories. (D) Direct comparison of organ transplantation efficiency (%) between Eurotransplant and the United States (transplanted relative to reported organs).

silent on the fate of organs that are unsuitable for transplantation from the outset or are deemed unfit during retrieval, transport, or prior to implantation. On the other hand, Implementing Directive 2012/25/EU regulating transparency and traceability in cross-border organ exchanges by mandating that Member States notify each other either of the recipient's identity (via a national code) or, if the organ was not transplanted, of its final use. Importantly, the directive does not define or limit what constitutes "final use" in cases where an organ is not transplanted. Conceptually, this lack of specification leaves the organs deemed unsuitable for transplantation, available to be repurposed for alternative uses, including scientific research, provided that this is in compliance with national laws and ethical guidelines.

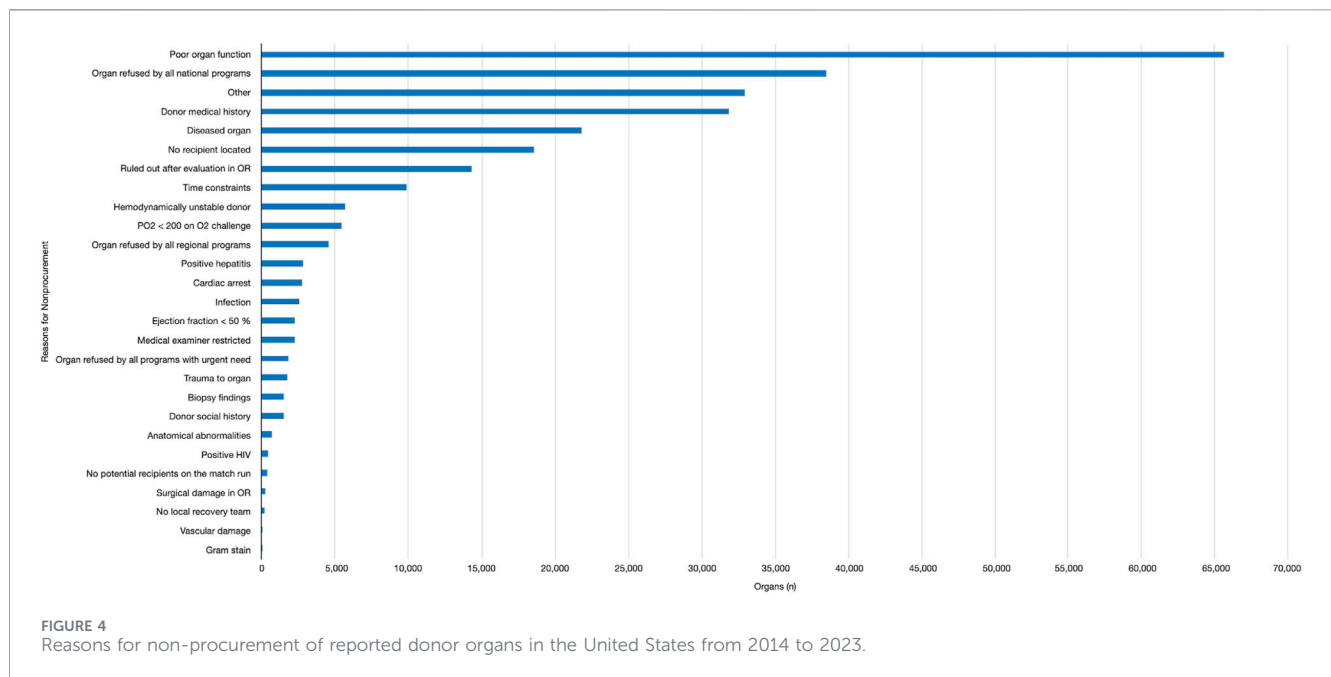
For the Eurotransplant member states, the organization's regulatory instruments serve as a supporting reference. These include the Ethical Charter and the Eurotransplant Manual, which provide binding guidance on operational and ethical standards. The prerequisite for any use of organs beyond transplantation is the decline for transplantation. This includes

the use of the organ for isolation of cells or tissues, or for research purposes. The allowance for any such use of organs is regulated by the national legislation. If no allowance exists, the organ must either be cremated, disposed of by another approved method, or returned to the donor country. Alternatively, the organ may remain with the donor.¹¹

Eurotransplant countries' transplant policies

The following sections summarize the relevant legal provisions for each Eurotransplant member state. A comparative overview is provided in Table 5.

¹¹ Eurotransplant International Foundation. Annual Report (2014). <https://cdn.sanity.io/files/ngz8tmzz/production/8b30d3687225237b1f9b73ca6f39828699d9c856.pdf> [Accessed January 18, 2024].



Austria

In Austria, the Organ Transplantation Act (*Organtransplantationsgesetz*) (OTPG) of 2012 governs the removal and transplantation of organs and implements Directive 2010/53/EU. The OTPG does not apply to the use of organs for scientific purposes. Therefore, the use of removed organs for research is not regulated by the OTPG [44].

Austria follows an opt-out system for organ donation: anyone who has not objected during their lifetime is considered a donor. However, this presumed consent applies only to transplantation [45].

Research on non-transplanted organs is not explicitly regulated within the donation process. If an organ is considered unsuitable for transplantation, a separate determination must be made as to whether it can be used for research. In practice, the deceased had given prior consent for their organs to be used for scientific purposes if not transplantable. Without such consent, unsuitable organs are typically disposed of through regulated medical waste procedures [46].

Austrian law explicitly refers to Eurotransplant in the context of vigilance and surveillance. Eurotransplant provisions therefore apply within this framework.¹²

Organ donation is centrally coordinated. The Austrian health authorities and the Austrian National Public Health Institute, maintain registers, and organ allocation is organized by Eurotransplant.¹³

There are also provisions for anatomical donation (body donation for scientific purposes), but these must be considered separately.¹⁴ A non-transplanted organ could, in principle, be treated as part of such a donation, provided appropriate consent exists. However, there is no specific regulation that comprehensively governs research use of non-transplanted or already recovered organs.

Subsequent to the completion of this analysis, engagement with the Austrian Federal Ministry of Health contributed to an amendment of the OTPG, passed unanimously by the National Council on 20 May 2026, which explicitly clarifies the legal permissibility of science use of procured organs that could not be transplanted, closing the regulatory gap described above.¹⁵

Belgium

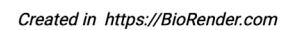
In Belgium, the opt-out system applies to post-mortem organ retrieval [47]. The use of recovered organs for research purposes is not directly regulated by the Law on the Retrieval and Transplantation of Organs (*Loi du 13 juin 1986 sur le prélèvement et la transplantation d'organes*), which was revised in 2012 to align with EU legislation [48]. This law states that recovered organs can be used for research purposes only if they are intended to be transplanted into the human body. Research involving organs that have been deemed unsuitable for transplantation is permitted but not necessarily covered by consent

¹² Eurotransplant International Foundation. Eurotransplant Manual, Chapter 3: Allocation General (2022). <https://www.eurotransplant.org/wp-content/uploads/2022/02/H3-Allocation-v-4.2-January-2022.pdf> [Accessed October 12, 2025].

¹³ oesterreich.gv.at. Organisationsstruktur der Organtransplantation (2025). <https://www.oesterreich.gv.at/de/themen/gesundheit/organtransplantation/1> [Accessed May 8, 2025].

¹⁴ Medizinische Universität Wien. Körperspenden an die Forschung. <https://www.meduniwien.ac.at/web/klinik-gesundheit/ambulanzen-services/koerperspenden-an-die-forschung/> [Accessed May 8, 2025].

¹⁵ Parlament Österreich, Parlamentskorrespondenz Nr. 439 vom 20.05.2026, Nationalrat stärkt Schutz vor kommerziellem Organhandel. https://www.parlament.gv.at/aktuelles/pk/jahr_2026/pk0439 [Accessed June 21, 2026].



<https://BioRender.com/5scwhix>.

TABLE 4 Organ donation and utilization in Eurotransplant and the United States from 2014 to 2023.

2014–2023	Eurotransplant n (% pmp)	United States n (% pmp)
Reported organs	100,260 (100, 735)	709,099 (100, 2,157)
Non-transplanted organs	32,242 (32.16, 236)	332,072 (46.83, 1,011)
Transplanted organs	68,018 (67.84, 499)	319,410 (45.04, 973)
Organs used for research	not available	49,435 (6.97, 150)
Organs used for others*	not available	8,182 (1.15, 25)
Recovered organs**	84,109 (83.89, 617)	427,029 (60.22, 1300)

*Other includes technical evaluations, heart valve procurement, islet cell isolation, hepatocyte extraction, etc.

**It is certain that organs within Eurotransplant were also used for research. However, Eurotransplant does not report separate categories for such secondary uses and only distinguishes between transplanted and not transplanted organs. Consequently, the Eurotransplant category “non-transplanted” may include both absolute non-utilization and scientific utilization, but this distinction cannot be quantified. The chosen approach represents the most methodologically consistent strategy given the available data, while acknowledging that differences in reporting granularity between the systems may introduce a degree of residual uncertainty.

Comparison of organ donation data between Eurotransplant and the United States, presented as absolute numbers, percentages, and per million population (pmp, figures are rounded), including reported, non-transplanted and transplanted organs, as well as organs assigned for research and other purposes.

TABLE 5 Overview of Eurotransplant member countries by donation system, legal framework for research, practical use of non-transplanted organs for research, and availability of body donation programs.

Country	Donation system	Explicit statutory approval for organ-based research	Body donation program
Austria	Opt-out	Yes*	Yes
Belgium	Opt-out	No	Yes
Croatia	Opt-out	No	Yes
Germany	Opt-in	No	Yes
Hungary	Opt-out	No	Yes
Luxembourg	Opt-out	Yes	No
Netherlands	Opt-out	Yes	Yes
Slovenia	Opt-out	Yes	Yes

This table summarizes key characteristics of Eurotransplant member countries, including whether they operate under opt-in or opt-out organ donation systems, their legal provisions for using non-transplanted organs in scientific research, the extent to which such research is actively conducted, and the presence of formal body donation systems for medical education or research.

*An amendment to the Austrian Organ Transplantation Act, passed unanimously by the National Council on 20 May 2026, now explicitly permits the scientific use of procured organs that could not be transplanted.

to organ donation. Instead, a different legal framework might apply: the Law on the Procurement and Use of Human Bodily Material for Human Medical Applications or Scientific Research (*Loi du 19 décembre 2008 relative à l'obtention et à l'utilisation de matériel corporel humain*) [49]. According to this legislation, explanted but non-transplanted organs could be classified as human bodily material and may be used for research purposes. In practice, explicit consent is required.

Transplant coordinators manage the transplantation process in collaboration with Eurotransplant, ensuring effective coordination between donor hospitals and transplant centers.¹⁶

In Belgium, as in many other European countries, it is also possible to donate the body after death for medical training or research. However, the Federal Public Service for Health distinguishes this from organ

donation, noting that organs are only removed for transplantation purposes not for research.¹⁷

Croatia

Croatia has adopted the opt-out system since 1988 [50, 51]. The Law on the removal and transplantation of human body parts for medical purposes (*Zakon o uzimanju i presađivanju dijelova ljudskog tijela u svrhu liječenja*) permits post-mortem organ retrieval provided that the individual did not object during their lifetime [52]. This legislation is exclusively focused on transplantation. It does not explicitly regulate the research use of organs that have been deemed unsuitable for

16 Health Food Chain Safety Environment. Transplant coordinators (2016). <https://www.health.belgium.be/en/transplant-coordinators> [Accessed April 8, 2025].

17 Santé publique. Don d'organes et don de corps à la science (2016). <https://www.health.belgium.be/fr/sante/prenez-soin-de-vous/debut-et-fin-de-vie/don-dorganes/citoyens/don-dorganes-et-don-de-corps-la> [Accessed April 8, 2025].

transplantation. Official oversight lies with the Ministry of Health and the National Transplantation Organization [50].

In exceptional cases, with approval from the Croatian Medical Chamber's ethical committee, the body of a deceased person who did not live with family and did not object in writing may be used for medical training, provided no next of kin object in writing.¹⁸

In Croatia, individuals can also choose to donate their bodies after death to support medical education and scientific research.¹⁹

Germany

The Transplantation Act (*Transplantationsgesetz*) (TPG) of 1997 exclusively governs the donation, removal, allocation, and transplantation of organs [53]. Research involving non-transplanted organs does not fall within the scope of the TPG.

The current legal framework regarding organ donation in Germany is known as the opt-in-related “informed consent” model. This means that organ donation is generally only possible if the potential donor gave consent during their lifetime, for example, by registering their decision in the national organ donor registry, or if the next of kin have given their approval [54]. The removal of organs is only permitted for the purpose of transplantation. This means that if an organ is removed but not transplanted, it may not automatically be used for research purposes. Without such specific consent, a non-transplanted organ must generally be properly disposed of [55].

There is no specific legal regulation that explicitly permits or prohibits the use of postmortem-removed organs for research purposes. The organ donor card in Germany provides the option to include additional notes, such as giving consent for research.²⁰

Oversight in Germany is regulated by the German Organ Procurement Organization and Eurotransplant.²¹

In Germany, individuals may also choose to donate their bodies posthumously for medical education and scientific research.²²

Hungary

Hungary regulates organ and tissue donation under the Healthcare Act of 1997 (1997 évi CLIV. törvény az egészségügyről), specifically the chapter on organ transplantation [56]. Additional provisions are contained in Ministerial Decree 18/1998 on Transplantation. According to this law, organ retrieval from deceased individuals is

permitted in the absence of a documented objection, hence establishing an opt-out system [57]. However, this legally presumed consent applies exclusively to transplantation for therapeutic purposes. The use of recovered organs for other purposes, such as scientific research, is not included under this presumed consent. More, organs removed from the deceased for transplantation but not used shall be subjected to histopathological examination.²³ Although the Hungarian Health Act does not mention the use of non-transplanted organs for research purposes, it does include provisions that allow for the transport of organs, including across national borders, for various purposes, one of which is scientific research.

Organ transplantation is centrally coordinated by the Organ Coordination Office of the Hungarian National Blood Transfusion Service.²⁴

Hungary also offers a body donation program, enabling individuals to contribute their bodies after death to support medical education and scientific research.²⁵

Luxembourg

Luxembourg enacted the Law on Organ Procurement (*Loi du 25 novembre 1982 relative au prélèvement d'organes*) as early as 1982 declaring all residents to be potential organ donors unless they have formally objected [58]. This law has since been amended to incorporate EU legislation. The opt-out system applies to organ retrieval for transplantation and scientific purposes, but the 1982 legislation does not explicitly address the possible use of non-transplanted organs for research. This core legislation has been amended notably by the Law of 25 June 2015 (*Loi du 25 juin 2015 modifiant la loi du 25 novembre 1982 réglant le prélèvement de substances d'origine humaine*), to update or adapt provisions in line with the EU directive [59]. Additionally, there are several Grand-Ducal-Regulations covering further aspects of organ transplantation.

Organ allocation is coordinated at the national level under the authority of the Ministry of Health, with operational responsibilities managed by Luxembourg-Transplant. The allocation process is integrated into the broader international framework of Eurotransplant.²⁶

It remains unclear whether a formal body donation program exists in Luxembourg, as no publicly available information or official framework has been identified.

18 Government of the Republic of Croatia. Organ donation. <https://gov.hr/en/organ-donation/782> [Accessed July 15, 2025].

19 Zavod za Anatomiju - Medicinskog Fakulteta u Rijeci. Program Donacije Tijela. <https://anatomedri.com/donacije-tijela-za-medicinsku-edukaciju/> [Accessed July 15, 2025].

20 Bundesinstitut für öffentliche Gesundheit. Gesetz zur Stärkung der Entscheidungsbereitschaft bei der Organspende (2022). <https://www.organspende-info.de/gesetzliche-grundlagen/gesetz-staerkung-entscheidungsbereitschaft/> [Accessed January 13, 2026].

21 German Organ Procurement Organization. <https://www.dso.de/homepage-english> [Accessed October 8, 2024].

22 Charité Universitätsmedizin Berlin. Anatomische Körperspende für die Charité Berlin. https://anatomie.charite.de/fuer_koerperspender [Accessed November 11, 2025].

23 European Federation for Organ Donation. National Laws on Organ Donation. <https://www.efod.eu/wp-content/uploads/2021/11/Legislazione-Ungheria-ENG.pdf> [Accessed July 23, 2025].

24 Organ Coordination Office. Welcome. <https://www.ovsz.hu/en/organ-coordination-office/welcome> [Accessed July 23, 2025].

25 Anatómiai - Szövet- és Fejlődéstani Intézet - Semmelweis Egyetem - Általános Orvostudományi Kar. HOLTTEST FELAJÁNLÁSA OKTATÁSRA. <https://semmelweis.hu/anatomia/tetemfelajanas-aktualis/> [Accessed July 24, 2025].

26 SanteSecu. Luxembourg-Transplant und Eurotransplant (2024). <https://santesecu.public.lu/en/espace-citoyen/departement-sante/prevention/don-organes/luxembourg-transplant-et-eurotransplant.html> [Accessed October 2, 2025].

Netherlands

The initial law governing organ donation in the Netherlands was the Law on Burial and Cremation (*Wet op de Lijkbezorging*), adopted in 1986 [60]. This law included provisions allowing for post-mortem organ and tissue donation, provided the deceased had not objected during their lifetime. It established a system based on presumed consent. The 1986 law was later replaced by the Organ Donation Act (*Wet op de Orgaandonatie*) in 1996, due to growing complexity of transplantation practices, and last amended in 2020 [61].

Netherlands is the Eurotransplant member state with the most clearly defined legal framework that explicitly permits the use of declined donor organs for scientific research, stating that “*consent, [...] (or lack of objection), is granted for the purpose of implantation, including scientific research aimed at implantation, if the organ after removal is found to be unsuitable for implantation*”. This means that if an individual does not object in the donor register, organs that are recovered but cannot be transplanted into a recipient may be used for scientific research aimed at advancing transplantation medicine. This use is legally permitted without requiring additional consent from the next of kin, unless the deceased explicitly stated during their lifetime that their organs must not be used for research purposes.²⁷

The Ministry of Health, Welfare and Sport, the Donor Registry, and the Dutch Transplantation Foundation maintain continuous coordination with Eurotransplant to optimize the cross-border allocation, matching, and transplantation of donor organs throughout the participating countries.²⁸

In the Netherlands, individuals can choose to donate their bodies after death to support medical research and education through an official body donation program.²⁹

Slovenia

In Slovenia, the main legal document is the Act on Regulation, the Procurement and Transplantation of Human Body Parts for the Purposes of Medical Treatment of 2000 (*Zakon o odvzemu in presaditvi delov človeškega telesa zaradi zdravljenja*) [62]. Organs that have been recovered but are subsequently deemed unsuitable for transplantation fall outside the specific legal framework of this law. This is where the 2015 Regulation on the Traceability and Disposal of Human Organs Intended for Transplantation and on the National Identification Number (*Pravilnik o sledljivosti in uničenju človeških organov namenjenih za presaditev ter o nacionalni identifikacijski številki*) comes into effect [63]. If an organ is found unsuitable for transplantation, it may be recalled and

offered to other EU countries. If no country accepts it, the law states that “*in the case of prior consent of the donor, [the organ can be] used for the purposes of medical education or scientific research*”.

Organ donation and allocation is centrally coordinated by the National Transplant Institute, which is responsible for reporting available organs to Eurotransplant and ensuring full compliance with applicable national and international regulation.³⁰

Slovenia also has a body donation program that allows individuals to donate their bodies to medical education and research after death.³¹

Laws for cross-border organ exchange

The applicable jurisdiction in the context of cross-border organ exchange within the EU primarily is likely to depend on the physical location of the organ at each stage of the process (Figure 5). The national law of the country where the organ is located governs the medical, ethical, and procedural aspects of organ procurement, testing, and storage. Once the organ crosses the border into another EU member state, it can be assumed that the legal framework of the recipient country becomes applicable, especially concerning transplantation procedures, patient safety standards, and documentation requirements. The national laws in this area are based on Directive 2010/53/EU, which sets minimum quality and safety standards for the donation, procurement, and transplantation of human organs across the EU. The Directive also emphasizes that health policy and transplantation systems remain under Member State competence. The principle is reinforced by Article 168 of the Treaty on the Functioning of the European Union, which requires EU health actions to respect Member State responsibility for healthcare systems. As a result, while the EU provides a harmonized framework for quality and safety, legal authority and jurisdiction in transplantation remain determined by national law. Jurisdiction therefore appears to be territorially anchored, with the national law of each state applying to activities carried out within its borders [41, 42, 64].

Discussion

Post-mortem organ donation remains a cornerstone of modern transplantation medicine, enabling life-saving treatments and improving quality of life. The public and academic discourse primarily focuses on successfully transplanted organs. Less attention is paid to organs recovered but ultimately deemed unsuitable for transplantation. It is important to emphasize from the outset that transplantation must remain the goal and overarching priority for every recovered organ. Any framework enabling research use of non-transplanted organs should only apply after all efforts towards transplantation have been exhausted. In case an organ is deemed non-transplantable, research addressing

27 Government of the Netherlands. Organ and tissue donation. <https://www.government.nl/topics/organ-tissue-donation/rules-organ-tissue-donation> [Accessed October 13, 2025].

28 Rijksoverheid. Contactgegevens andere (overheids)organisaties. <https://www.rijksoverheid.nl/contact/contactgids/donorregister#:~:text=Het%20Donorregister%20registreert%20of%20mensen,arts%20het%20Donorregister%20wil%20raadplegen> [Accessed October 15, 2025].

29 Erasmus MC. Body donation. <https://www.erasmusmc.nl/en/patient-care/body-donation> [Accessed October 15, 2025].

30 Slovenija-transplant. About us. <https://www.slovenija-transplant.si/en/about-us/> [Accessed November 2, 2025].

31 Inštitut za anatomijo - Univerza v Ljubljani. Izobraževanje na darovanih telesih. <https://www.mf.uni-lj.si/ian/izobrazevanje-na-darovanih-teselih?q=%2Fian%2Fizobrazevanje-na-darovanih-teselih> [Accessed November 3, 2025].

innovations that may foster to make currently non-transplantable organs transplantable in the future should be given priority over other research interests.

Non-transplanted organs hold considerable scientific value that remains largely untapped. Between 2014 and 2023, 332,072 and 32,242 organs were recovered but not utilized in the US and Eurotransplant, respectively. These numbers illustrate the huge potential in this field. Interestingly, organ utilization rates vary also by organ type. Abdominal organs (kidney, liver, and pancreas) tolerate longer cold ischemia times than thoracic organs and show heterogeneous acceptance rates. In contrast, thoracic organs (heart and lungs) have higher immediate functional requirements and limited ischemic tolerance, leading to more conservative donor selection and lower utilization [65–69]. The introduction of machine perfusion (NMP, HOPE, NRP) has mitigated some of these limitations by enabling functional assessment and extending preservation times³² [9, 27].

A deceased donor organ may be unsuitable for transplantation yet transformative for research and development. Utilizing non-transplantable organs can support the development and validation of novel diagnostic tools, surgical techniques, and therapeutic approaches under conditions closely reflecting human physiology. Moreover, biomedical research often struggles to account for the variability in human populations, which limits the effectiveness of pre-clinical models. Studying human organs declined for transplantation offers a powerful alternative for assessment prior to clinical trials. Such organs allow for early assessment of viability and function. However, establishing the viability of such organs for transplantation remains inherently challenging. Unless the organ is ultimately transplanted and its function can be assessed *in vivo*, any conclusions remain speculative [27, 70]. While cell cultures and animal models remain valuable, their role should follow validation in human tissue. Once validated, animal models could then provide deeper mechanistic insights (or *vice versa*) [71]. Repurposing procured but not transplantable human organs for research directly aligns with 3R principle of Directive 2010/63/EU [72] by replacing less predictive animal models, reducing unnecessary animal use, and refining preclinical testing.

This manuscript covers three distinct categories of not transplantable organs: those deemed unsuitable before retrieval and therefore not even offered for transplantation, those offered for transplantation but not accepted by any transplant center, and those accepted for transplantation but excluded during the procurement or evaluation process and ultimately not used. Among these, particular attention should be given to organs that were initially accepted and procured but ultimately not transplanted (herein referred to as recovered organs). These organs represent a valuable resource because they have passed selection and logistical assessments and are already recovered. Therefore, future efforts in policy, ethics, and clinical practice should focus on this group, exploring safe and ethically sound ways to repurpose them for research, without compromising donor dignity or public trust. Utilizing organs that have already been recovered may also

reduce dependence on animal testing. This is in line with broader ethical and scientific objectives.

Over the last 10 years, the number of non-transplanted organs within ET was stable. On average, 16.05% of all reported organs would qualify for potential secondary use under this framework. This consistency suggests a predictable source of organs for research. However, many Eurotransplant member countries lack a clear legal framework that governs the research use of organs not intended for transplantation. Current legislation is focused on transplantation, leaving little room for alternative, science-driven applications. This lack of regulation leads to uncertainty regarding research use. As a result, organs that could significantly advance medical knowledge are often disposed of.

What applies to non-transplanted organs also holds true for non-realized donors. The organs from these donors may hold considerable value. While the reasons for non-utilization of those donor organs are diverse and sometimes vague, the added value of using these organs for advancement and development in the field of transplantation and beyond needs to be considered. More, the conceptual link from unused organs to organ donors and further to whole-body donation for, e.g., anatomical education illustrates the close connection between these topics. At the same time, it reflects a broader societal attitude toward the idea of making one's own body available for scientific purposes. This connection emphasizes not only the individual willingness to contribute to research but also society's need to make use of such opportunities in order to advance medical knowledge and achieve improvements for the benefit of humanity.

The model of whole-body donation for research purposes is well established and widely accepted. Extending this framework to include individual organs that are not viable for transplantation appears ethically consistent. Such an extension would enhance scientific opportunities while respecting donor intent.

International comparisons highlight the feasibility of more inclusive policies. In the US research access to not transplantable donor organs is supported by both legal and institutional mechanisms, facilitating ethically sound and scientifically valuable work [73]. The number of reported donor organs differs considerably between the Eurotransplant region and the United States (735 pmp vs. 2,157 pmp respectively). Key factors influencing this discrepancy include the high donor rate resulting from the stronger incentivization system and the national guidance and coordination in the United States, the opioid crisis, as well as the low donor rate in Germany. Reasons why this system may capture a broader range of potential donors, including those whose organs are ultimately not used. While the incentive-based approach can be a strong driving force, it also exposes the system to scrutiny and demands strong objectivity in the decision-making process [74]. Hence, comparisons between reported donor numbers should be made with caution, as the underlying systems and reporting practices may differ. Anyway, these practices could serve as a point of reference for European countries seeking to modernize and refine their regulatory approaches.

An illustrative example from the United States is 34 Lives, a public benefit corporation dedicated to improving the utilization of viable donor kidneys at risk of not being utilized. 34 Lives employs advanced organ preservation strategies to sustain and, in some cases, restore kidney function. Preliminary data indicate that the initiative has led to higher transplantation rates, underscoring its potential to reduce organ wastage and improve outcomes for transplant recipients.³²

32 34 Lives. About. <https://34lives.com> [Accessed February 3, 2025].

Emerging technologies such as machine perfusion make it increasingly important to clarify access to non-transplanted human organs. In the liver, NMP has demonstrated feasibility for perfusion periods of up to 48 h, and even 7 days in some cases [75, 76], while maintaining key metabolic and structural functions. A human liver was perfused *ex vivo* for 3 days and subsequently transplanted, with the patient recovering normal liver function and quality of life without signs of rejection or bile duct injury after 1 year of follow-up [77]. Transcriptomic and metabolomic analyses during NMP have revealed activation of pro-survival and repair pathways in livers, along with effective autophagy and redox balance [78–80]. Composite viability criteria such as lactate clearance, pH, bile output, and vascular flow patterns have been successfully used to guide transplantation decisions [10, 12]. Long-term perfusion has also enabled metabolic interventions such as steatosis reduction [81, 82]. In addition, senolytic treatments applied during *ex vivo* liver perfusion have shown promise in preserving the regenerative capacity of the biliary system, by mitigating the detrimental effects of cellular senescence on cholangiocyte function and primary cilia integrity, which are crucial for biliary repair [83, 84]. In machine perfused human livers, adeno-associated virus (AAV) vectors were compared under neutralizing and non-neutralizing conditions, revealing distinct differences in transduction efficiency and antibody susceptibility [85]. Single-cell analyses further demonstrated that vector performance depends on liver condition and capsid choice [86]. Split-liver perfusion models enable direct intra-organ comparison of therapeutic interventions [87–89]. As a preclinical test, a liver from a patient with mitochondrial neurogastrointestinal encephalomyopathy was used to demonstrate AAV-mediated gene therapy in a human organ indicating feasibility of correcting the genetic defect [90].

In the kidney, 24- to 48-h normothermic perfusion with urine recirculation has shown stable flow and resistance, acid-base balance, and tissue morphology enabling functional assessment of organ condition [91–94]. Kidney NMP may eventually reduce non-transplantation rates and improve allocation [95, 96]. A study demonstrated that non-transplanted human kidneys can be preserved in a metabolically active and functionally stable state for up to 4 days using subnormothermic (25 °C) machine perfusion [97–99].

In the pancreas, NMP has been successfully applied in research settings to assess function in non-transplanted grafts. Stable perfusion, insulin secretion, and minimal histological injury was observed in preliminary studies [22, 23]. This approach remains investigational and is not currently part of routine clinical practice. Hypothermic perfusion also enables isolation of viable islets from DCD donor pancreases [100].

In lung transplantation, advances in machine perfusion have helped to preserve and treat organs. Techniques such as prone positioning may improve lower lobe function and reduce reperfusion injury [21]. Moreover, xenogeneic cross-circulation has demonstrated potential for the extracorporeal recovery of severely injured human lungs [20]. Some lungs initially deemed unsuitable were later found transplantable [21].

Beyond the immediate clinical use cases, *ex situ* organ perfusion facilitates decellularization of whole human livers and kidneys and generation of biological bioscaffolds [98, 99, 101]. In an attempt to generate bioengineered transplantable organs, these scaffolds have been reseeded with human cells. Delivery of multipotent adult progenitor cells during liver NMP resulted in transendothelial

migration and secretion of immunomodulatory factors, demonstrating compatibility of cell therapy with perfusion platforms [102].

In conclusion, organs that have already been recovered but not transplanted should not be automatically excluded from further use. When guided by robust ethical standards and clear legal frameworks, their use in biomedical research represents an opportunity to advance science, possibly reduce animal testing, and ultimately benefit future patients. Achieving this will require public dialogue, political initiative, and a shift in perspective. Such an effort would also render organ donation more meaningful and, in the long term, more effective.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Author contributions

AK: study design, data acquisition, data analysis, interpretation of the data, drafting of the manuscript. FK: interpretation of the data, revising the manuscript. LP: interpretation of the data, revising the manuscript. JH: interpretation of the data, revising the manuscript. AW: interpretation of the data, revising the manuscript. BC: interpretation of the data, revising the manuscript. AM: revising the manuscript. TR: revising the manuscript. GB: interpretation of the data, revising the manuscript. TH: revising the manuscript. RO: interpretation of the data, revising the manuscript. EB: interpretation of the data, revising the manuscript. SE: interpretation of the data, revising the manuscript. SS: study design, data analysis, revising the manuscript. All authors contributed to the article and approved the submitted version.

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Hypoimmune platforms: from rejection to immune evasion and regulatory implications

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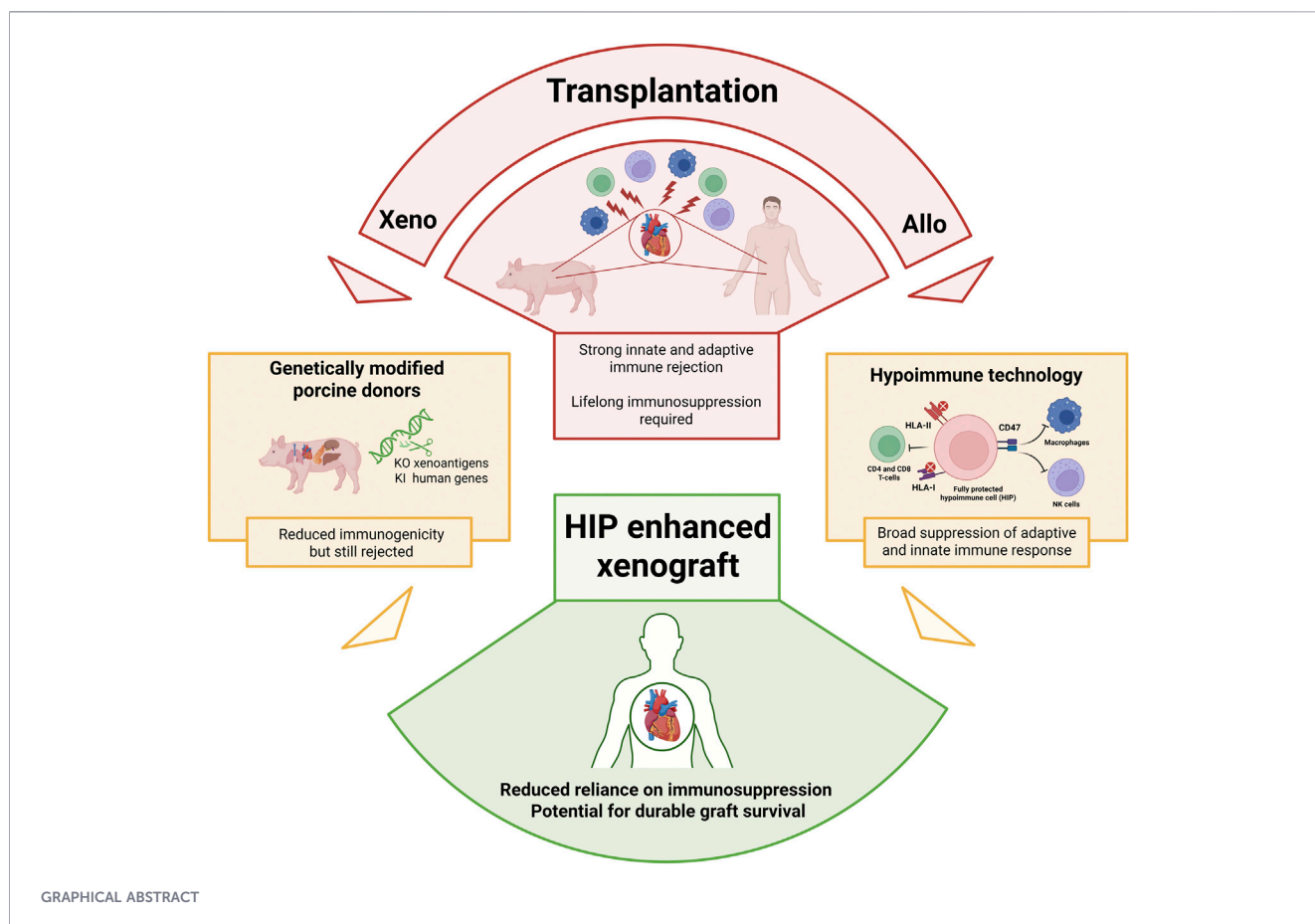
The growing gap between organ demand and clinical availability has renewed interest in immune-evasive graft strategies, yet rejection and lifelong immunosuppression remain major barriers to durable success. Advances in genome editing enable immune-evasive cell platforms designed to avoid immune recognition while replacing missing function in allogeneic settings. This review summarizes current strategies for engineering immune-evasive grafts that simultaneously suppress adaptive and innate immune responses. We discuss how coordinated modulation of antigen presentation and immune checkpoint pathways can protect transplanted allogeneic cells and tissues from T, NK, and macrophage-mediated rejection. We also present the emerging concept of integrating hypoimmune engineering with genetically modified porcine donors, where extensive genome editing has reduced, but not eliminated, xenogeneic immune barriers. Combining donor genome modification with immune-evasive graft design represents a promising conceptual advance toward xenograft survival, though whether full elimination of systemic immunosuppression is achievable remains to be established clinically. We further examine how the regulatory landscape for these products is evolving across major jurisdictions, and how differences in approval pathways, manufacturing standards, and long-term surveillance requirements shape the path to clinical translation. Finally, we outline the safety considerations and remaining limitations in immune evasion that must be addressed to enable clinical implementation.

KEYWORDS

genome editing, hypoimmune, islet transplantation, regulatory, xenotransplantation

Introduction

The success of cell, tissue, and organ transplantation has long been constrained by the host immune response, which recognizes donor tissues as non-self and triggers graft rejection (e.g., the pathways of allorecognition and T cell activation) [1]. Lifelong immunosuppressive therapy remains the cornerstone of clinical transplantation, but carries substantial risks, including infection, malignancy, metabolic complications, and chronic allograft dysfunction [2]. At the same time, the increasing demand for transplantable tissues, driven by organ shortages and the rising incidence of chronic diseases including end-stage organ failure [3, 4], has prompted the search for alternative, renewable sources of functional cells and tissues, including those derived from pluripotent stem cells (PSCs) and xenogeneic donors [5, 6]. Regardless of their



origin, overcoming immune incompatibility remains a central challenge to achieving durable graft survival without systemic immunosuppression [6].

Recent advances in genome editing have substantially expanded the immune-engineering toolkit, enabling a new class of immune-evasive cell products [7, 8]. By precisely modifying key genes involved in antigen presentation and immune recognition, it is now possible to engineer cells with markedly reduced immunogenicity; whether full immune evasion can be achieved while preserving physiological function remains under investigation [8]. Genome editing technologies such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)–Cas approaches enable precise genetic modifications, including the inactivation of classical human leukocyte antigen (HLA) molecules, modulation of co-stimulatory and inhibitory pathways, and incorporation of immune checkpoint ligands to dampen both innate and adaptive responses [5, 8]. Complementary strategies extend to xenotransplantation, where extensive genome engineering has produced porcine donors lacking xenoantigens and expressing human immunoregulatory molecules [9].

Together, these advances define a rapidly evolving field at the intersection of regenerative medicine [10], transplantation biology, and synthetic immunology. Genome-edited hypoimmune platforms represent an emerging strategy toward ‘off-the-shelf’ cell therapies and broadly compatible tissue grafts, with the potential to transform the clinical management of immune-mediated diseases [6]. Complementary strategies, including localized immune

modulation and biomaterial-based immune shielding, are also under active investigation and may contribute to future combinatorial approaches. However, significant challenges remain, including incomplete immune evasion, potential risks of malignant transformation, and the need for precise control of immunomodulatory gene networks [5].

To date, the clinical performance of allogeneic cell-based therapies has lagged behind that of autologous counterparts, largely due to immune rejection and limited persistence of donor cells *in vivo* [11]. This limitation is particularly evident in cancer immunotherapy, where the inability of allogeneic products to achieve long-term engraftment and sustained activity has constrained their therapeutic potential [11]. In contrast, in autoimmune diseases or acute inflammatory conditions, where transient activity rather than long-term persistence may be sufficient, early trials using allogeneic CAR-T cells have demonstrated encouraging results [12].

The next frontier for allogeneic therapies will depend on achieving durable immune evasion and functional stability comparable to autologous cells. Advances in genome editing and synthetic biology now enable the design of allogeneic, immune-evasive cell products with enhanced metabolic fitness, resistance to exhaustion, and improved trafficking within hostile or immunosuppressive environments [6]. However, such extensive engineering is logistically and economically feasible only for standardized, large-scale manufacturing of universal allogeneic products, rather than individualized autologous therapies [6].

In this context, pluripotent stem cell (PSC)-derived immune and parenchymal cells provide a highly scalable platform for iterative, multi-step genome editing and clonal selection [13]. If comprehensive immune cloaking can be reliably achieved, PSC-derived hypoimmune products may ultimately match, or even surpass, autologous therapies, combining broad compatibility with enhanced functional attributes, provided that key safety concerns, including genomic stability and long-term immune surveillance, are adequately addressed [14]. Accordingly, achieving robust and durable immune evasion represents a critical enabling step toward the next-generation of “off-the-shelf” immune and regenerative cell therapies.

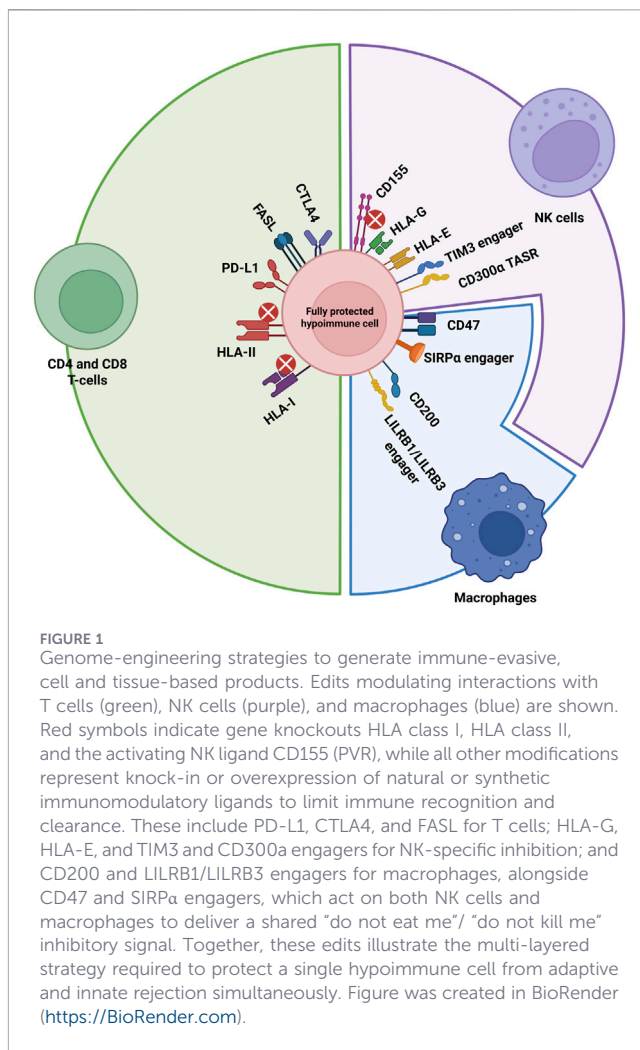
Here, we review current genome editing strategies for generating hypoimmune cells and organs, including xenografts. We discuss the molecular targets and design principles underlying immune cloaking, highlight key preclinical and translational advances, and explore the remaining biological and regulatory barriers to clinical implementation. Finally, we suggest future directions for integrating immune engineering with tissue biofabrication and vascularized organ design, toward the development of universally compatible, immune-protected grafts.

Engineering immune-evasive tissue-based products

The generation of immune-evasive tissue products, hereafter referred to as hypoimmune derivatives, is designed to elude immune recognition by reducing T-cell mediated detection and providing inhibitory signals to the innate immune system. Ideally, transplantation of hypoimmune tissues should avoid activating an immune response and prevent the induction of targeted immunological memory. The recipient's immune system should not recognize these allogeneic products as non-self; in preclinical models, this has been associated with tolerance of repeated administrations, although long-term clinical data remains limited.

To achieve this immunological bypass, the main challenge is to avoid activation of the adaptive T-cell response. A pivotal factor in this process is the presentation of alloantigens by HLA molecules. To prevent alloantigen presentation through HLA class I, many groups have targeted β 2-microglobulin (B2M) [15–17], which is essential for HLA class I molecule expression, or transporter associated with antigen processing 2 (TAP2), a transporter required for peptide loading and presentation via HLA class I. Regarding HLA class II, several cell types in the body constitutively express these molecules; endothelial cells and pancreatic islets can upregulate HLA class II expression during inflammatory conditions [18, 19]. Complete disruption of alloantigen presentation through HLA class I and II depletion prevents T-cell activation and effectively bypasses the adaptive immune response as extensively reviewed in other works [20–24].

However, adaptive immune cells are not the only mediators of graft rejection. Innate immune components, such as NK cells and macrophages, can independently sense HLA deletion, triggering the “missing self-response” and mediate a cytotoxic response [25]. NK cells express a broad repertoire of activating and inhibitory surface receptors whose balance governs cytotoxic output and immunological engagement (Figure 1). SIRP α has been identified



as a potent inhibitory immune checkpoint for NK cells and the overexpression of its ligand, CD47, results in potent inhibition of NK cells [26]. Accordingly, effective immune evasion in engineered cell therapies requires a multi-layered strategy. HLA-depleted cells rely on high CD47 expression, well above normal levels, to escape NK-cell attacks, exploiting the threshold-dependent “on/off” nature of NK cytotoxicity. This effect can be amplified through broadly expressed inhibitory receptors such as SIRP α , TIM3, and CD300a [27, 28], or by overexpressing HLA-E [16] and HLA-G [29] to target specific NK subsets. Removal of activating ligands, such as the poliovirus receptor (PVR/CD155), may further shift the balance toward inhibition, although this alone is insufficient, as shown in iPSC-derived T cells [16].

Partial retention of selected HLA molecules can reduce T-cell activation while preserving innate immune protection [30], yet this approach depends on patient matching, requires cell banks, and introduces logistical challenges. In HLA-depleted cells, combining checkpoint modulation, interference with antigen presentation, and secretion of immune-regulatory factors can further dampen rejection. Antibody-mediated responses can also be mitigated through engineered expression of modified CD64 or IgG-degrading enzymes, thereby broadening protection without compromising resistance to cellular immunity [31]. However,

clinical experience demonstrates that even HLA-matched grafts require immunosuppression, emphasizing the complexity of immune recognition and the need for caution when developing universal immune-evasion strategies.

HLA class I and II knockdown is not the only proposed strategy. Harding et al. worked on possible combinatorial overexpression of immunomodulatory factors such as PD-L1, CD200, CD47, FASL, SERPINB9, CCL21, MFGE8 and HLA-G without HLA class I and II knockout in hESCs to generate cloaked cells. Upon differentiation in retinal pigmented epithelial cells and coculture with allogeneic human PBMCs, cloaked cells were able to persist and to not elicit an allogeneic response. In addition, the same strategy was used to generate cloaked tissues in a subcutaneous site that serves as an immune-privileged site that protects allogeneic and xenogeneic uncloaked cells from rejection in immunocompetent hosts demonstrating the long-term survival of a solid tissue allograft without the need for systemic immunosuppression [32].

Regulatory considerations for clinical translation

Regulatory frameworks governing the clinical translation of genetically engineered hypoimmune pluripotent stem cell (HIP)-derived products and xenogeneic grafts are rapidly evolving across multiple jurisdictions to ensure safety, efficacy, product consistency, and long-term patient monitoring.

In the European Union (EU), genetically modified HIP products are classified as Advanced Therapy Medicinal Products (ATMPs) under Regulation (EC) No 1394/2007 and are regulated by the European Medicines Agency (EMA), which provides guidance on genomic stability, potency testing, biodistribution, tumorigenicity assessment, pharmacovigilance, and long-term follow-up requirements for advanced cellular therapies [33]. In addition, products involving genetically modified organisms (GMOs) must comply with both EU-wide and national biosafety regulations under the EU GMO framework, adding further complexity to clinical development.

In the United States, cell and gene therapies are regulated by the Food and Drug Administration (FDA), primarily through the Center for Biologics Evaluation and Research (CBER). Human cells, tissues, and cellular and tissue-based products are regulated under 21 CFR Parts 1270 and 1271, while more substantially manipulated or genetically modified products require Investigational New Drug (IND) applications and Biologics License Applications (BLAs) before clinical use. FDA guidance emphasizes donor eligibility, genomic integrity, off-target editing analysis, sterility, manufacturing reproducibility, potency assays, and prolonged post-transplant surveillance, particularly for genome-edited and stem cell-derived products [34]. Furthermore, the FDA has established a regenerative medicine framework to support the development of advanced cellular therapies while maintaining rigorous standards for safety and efficacy [35, 36].

Similarly, in the United Kingdom, Advanced Therapy Medicinal Products are regulated by the Medicines and Healthcare products Regulatory Agency (MHRA), which continues to maintain a framework closely aligned with EU ATMP principles while developing independent innovation pathways and specialized

guidance for GMP-compliant manufacturing, vector characterization, assay validation, and release testing [36, 37].

Outside Europe and the United States, regulatory frameworks across Canada, Australia, and Asia continue to evolve in response to advances in regenerative medicine, genome engineering, and xenotransplantation, reflecting a global effort to balance innovation with rigorous safety and quality standards. In Canada, cell and gene therapies are regulated by Health Canada under the Food and Drugs Act, following a risk-based framework broadly aligned with FDA and EMA principles that emphasizes GMP compliance, donor eligibility, potency and identity testing, genomic stability, traceability, and long-term safety monitoring; recent regulatory initiatives have further sought to facilitate the clinical development of innovative therapies without compromising these standards. Australia follows a comparable risk-based approach through the Therapeutic Goods Administration (TGA). TGA classifies genetically modified cellular products as biologicals or gene therapies depending on the degree of manipulation and intended clinical use, and requires GMP-compliant manufacturing, validated potency assays, donor screening, genomic integrity assessment, and comprehensive pharmacovigilance; growing alignment with international standards has facilitated Australia's participation in global clinical development programs. Among Asian countries, Japan offers a notably different model: through the Pharmaceuticals and Medical Devices Agency (PMDA) and the Act on the Safety of Regenerative Medicine, it has introduced conditional and time-limited approval pathways that allow earlier clinical access following demonstration of preliminary safety and probable efficacy [36]. This framework has already accelerated the translation of induced pluripotent stem cell (iPSC)-derived therapies and may offer a regulatory template for future hypoimmune cellular products [36]. Taken together, while Canada and Australia largely mirror the risk-based, evidence-heavy approach of the FDA and EMA, Japan's conditional-approval pathway illustrates an alternative route to earlier patient access, a distinction directly relevant to how hypoimmune platforms might reach the clinic outside Europe and the US.

Alongside national regulatory agencies, international scientific organizations are actively playing a major role in defining governance frameworks for xenotransplantation. The International Xenotransplantation Association (IXA) has published multiple consensus statements addressing ethical considerations, clinical trial design, microbiological safety, source animal standards, infectious disease surveillance, informed consent, traceability, and long-term recipient monitoring [38, 39]. In addition, the Changsha Communiqué [40] emphasized the urgent need for harmonized international oversight, coordinated bio-surveillance programs, standardized pathogen screening, transparent clinical reporting, and global data sharing to address zoonotic and biosafety risks associated with xenogeneic products [40]. These recommendations are particularly relevant for HIP-engineered xenografts and stem cell-derived tissues, where extensive genome editing may alter immune recognition while simultaneously complicating pathogen detection and long-term immunological surveillance.

Nevertheless, substantial regulatory challenges remain due to differences in regulatory terminology, approval pathways, GMO oversight, and long-term follow-up requirements. Limited

international harmonization creates significant burdens for developers pursuing global clinical translation of hypimmune cell products.

In parallel with regulatory approval pathways, successful clinical translation will critically depend on the establishment of robust manufacturing and quality control strategies. Clinical-grade production of hypimmune cellular products requires GMP-compliant workflows for genome editing, clonal selection, expansion, differentiation, and cryopreservation while maintaining genomic stability and phenotypic consistency throughout manufacturing. Rigorous release criteria will likely require verification of intended genetic modifications, assessment of off-target events, confirmation of stable expression of immunomodulatory transgenes, sterility testing, genomic integrity analysis, tumorigenicity assessment, and validated potency assays demonstrating durable immune evasion. Furthermore, scalable production platforms based on well-characterized pluripotent stem cell master and working cell banks must ensure reproducibility, traceability, and batch-to-batch consistency. Collectively, these considerations illustrate that successful clinical implementation of hypimmune cellular therapies will require not only advances in genome engineering, but also internationally harmonized regulatory policies, standardized manufacturing platforms, and coordinated long-term biosafety surveillance.

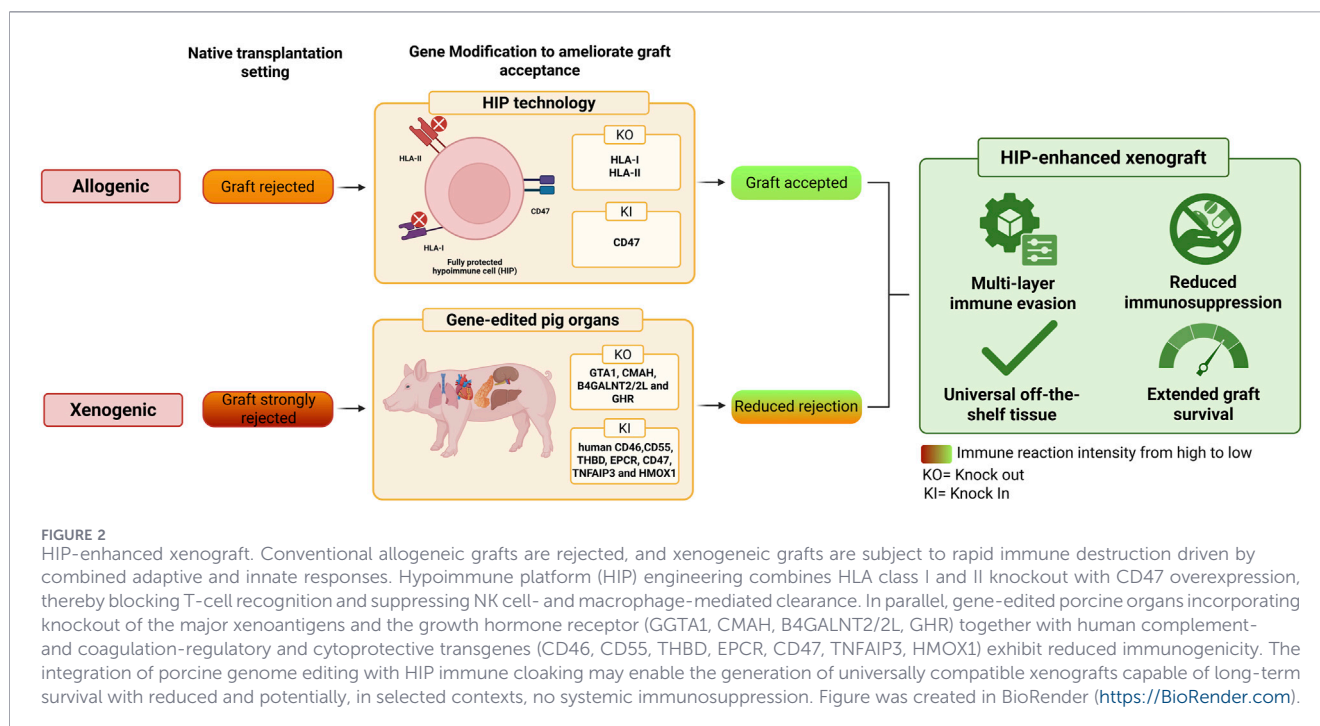
Hypimmune platform technology: design principles and preclinical evidence

The hypimmune platform (HIP) is one suggested approach to render engineered cells resistant to both innate and adaptive immune responses [7]. The platform combines knockout of genes encoding β 2-microglobulin (B2M) and class II transactivator (CIITA), to eliminate expression of HLA class I and II molecules, together with overexpression of CD47 which delivers a potent “do not eat me” signal that inhibits macrophage- and NK-cell-mediated cytotoxicity [26]. Although CD47’s role in preventing phagocytosis has been long established [41], its efficacy in suppressing NK-cell activity via the SIRP α pathway has only recently been clarified [26], with preclinical data suggesting broad inhibition across major NK subsets, though systematic evaluation across all human NK cell compartments is ongoing. In preclinical models, HIP engineering of primary human CAR T cells or iPSCs generates heterogeneous populations, yet only fully HIP-edited cells survive in environments where HLA-depleted or partially edited cells are eliminated, demonstrating their ability to withstand active immune rejection. Clinical experience with HIP CD19 CAR-T cells mirrors these findings: fully edited cells avoid T- and NK-cell mediated killing and do not induce antibody responses, whereas unedited or partially edited populations are rapidly rejected. Notably, current evidence suggests that HIP cells may not readily induce immunological memory. If confirmed, this feature could enable repeated dosing strategies, an important advantage over autologous therapies, which could

be limited to single administration due to the induction of immunological memory reducing overall survival of the transplanted cells [30]. By overcoming both innate and adaptive immune barriers, HIP technology offers a versatile platform for allogeneic cell therapies. Its durability has been demonstrated in preclinical models of beta cell replacement for T1D. HIP-engineered iPSC-derived and primary human islets survive, engraft, and restore glycemic control in fully allogeneic, immunocompetent humanized mice without triggering immune responses [8]. Importantly, HIP cells also resist autoimmune attack, as demonstrated in T1D-derived autologous humanized models [7]. Advances in gene-editing techniques now enable HIP modification of primary human islets, which retain superior endocrine function compared to iPSC-derived counterparts while maintaining immune evasion [7]. Nonhuman primate studies confirmed long-term engraftment and function of HIP-edited allogeneic islets for over 6 months without immunosuppressive therapy [42]. While HIP offers a powerful strategy to evade both innate and adaptive immune rejection, the long-term safety of HLA-depleted cells remains incompletely understood. Preclinical models in MHC class I-deficient mice show impaired viral clearance, though these animals also have severe CD8 T-cell deficiencies, limiting direct translation to immunocompetent humans [43, 44]. In real-world applications, the number of transplanted hypimmune cells is low, and recipients maintain fully functional immune systems, yet the possibility that HLA-deficient cells may impair intracellular antigen presentation and thus serve as undetected reservoirs for persistent viruses or intracellular pathogens cannot be excluded and warrants prospective clinical monitoring. The recently developed HIP mouse, globally deficient in MHC class I and II and overexpressing CD47, demonstrated normal viability, fertility, and no increased susceptibility to infections or tumors, suggesting limited intrinsic risk [45]. Nevertheless, potential concerns remain, including the unknown effects of long-term persistence, unexpected interactions with host immunity, and the theoretical risk of harboring pathogens undetected [45]. Careful pre-clinical evaluation and clinical monitoring will be essential to ensure safety as these platforms advance toward therapeutic use.

HIP islet cell transplantation: a clinical proof-of-concept

Allogeneic and xenogeneic beta cell replacement [46, 47] offers a promising approach to restore glycemic control in patients with diabetes, potentially overcoming the limitations of conventional insulin therapy [48] and autologous cell transplantation. Early clinical experiences with PSC-derived islets, including both autologous and allogeneic approaches, have demonstrated the capacity to improve C-peptide levels, improve glycemic control, and achieve insulin independence in some cases [47, 49, 50]. However, in these cases, recipients required systemic immunosuppression due to allogeneic nature of the graft or prior organ transplants, masking the true immune response and highlighting the substantial challenge of achieving durable engraftment in immunocompetent patients [49]. Partial immune-evasion strategies, including selective HLA class I



or I/II depletion, PD-L1 overexpression, or localized secretion of immunomodulatory factors such as IL-2 mutein, TGF- β or IL-10 have shown inconsistent results in preclinical models, often failing to fully protect transplanted cells from NK-mediated or autoimmune attack [18]. These limitations have motivated the development of more comprehensive immune-engineering approaches such as the HIP islet cells, which simultaneously target multiple immune recognition pathways as mentioned before [7, 8, 42]. The translational potential of HIP platforms has been explored in an initial human case report. HIP-engineered allogeneic islets were transplanted into a patient with type 1 diabetes without immunosuppression. Four weeks post-transplant, functional insulin secretion was evident through circulating C-peptide and mixed meal stimulated responses, and MRI confirmed graft survival. No immune activation or safety signals were detected over the reported follow-up period, providing preliminary evidence that comprehensive immune evasion may be achievable in selected clinical settings; however, these observations derive from a single recipient with only short-term (4-week) follow-up and limited immunological characterization, longer follow-up and larger cohorts are needed to assess durability and generalizability of the platform [51].

These findings suggest the potential of allogeneic endocrine cell therapy. HIP platforms may overcome key limitations of partial immune protection strategies, and preliminary data indicate a potential pathway toward immunosuppression-free treatment for diabetes; this remains to be validated in adequately powered clinical trials. By enabling repeated dosing, sustained glycemic control, and protection from both allorecjection and autoimmunity, allogeneic HIP-engineered cells represent a promising advance in regenerative medicine, with early data supporting their therapeutic potential in metabolic disease.

HIP technology in xenotransplantation

Advances in genome editing have substantially accelerated xenotransplantation research, enabling the development of multi-edited porcine donors with reduced immunogenicity [52]. With up to ten targeted genetic modifications, including knockouts of major carbohydrate antigens, the introduction of human complement regulatory transgenes, and other immune-evasive edits, porcine organs have become increasingly compatible with the human immune system. These typically include knockout of the major carbohydrate xenoantigens (GGTA1, CMAH, B4GALNT2/2L) and of the growth hormone receptor (GHR), together with knock-in of human complement- and coagulation-regulatory transgenes (CD46, CD55, THBD, EPCR), the anti-inflammatory and anti-thrombotic factor TNFAIP3, the cytoprotective enzyme HMOX1, and CD47 to limit macrophage-mediated clearance [9]. Preclinical studies and early clinical applications [53] involving hearts [54], kidneys [55], and livers [56] have demonstrated feasibility, yet even highly engineered organs remain vulnerable to residual immune-mediated injury, including antibody-mediated rejection, micro-vascular inflammation, NK cell-mediated cytotoxicity, and macrophage-driven clearance [9, 57]. These observations underscore that, despite substantial advances, additional strategies are needed to achieve long-term graft survival.

In this context, HIP engineering offers a powerful complementary approach. HIP platforms combine targeted depletion of MHC molecules with high CD47 expression, providing broad protection from both adaptive and innate immune attacks [6]. By inhibiting NK cell cytotoxicity, preventing macrophage phagocytosis, targeting polymorphonuclear cells [57] and reducing T and B cell activation, HIP modifications add an

additional layer of immune protection that could be particularly valuable in xenotransplantation, where multiple immune pathways act in parallel to reject grafts [52]. Preclinical studies suggest that HIP-modified cells and tissues can survive in highly immunogenic environments, resisting both early innate responses and subsequent adaptive immune recognition [7, 8, 42, 57]. HIP engineering may be integrated with existing porcine genetic modifications to further reduce antigenicity, mitigate complement and antibody-mediated injury, and enhance graft longevity [9] (Figure 2). In this direction, triple (GGTA1, CMAH, B2M) modified pigs expressing Swine Leucocyte Antigen class I at low level were generated. The KO of SLA class I showed to prevent human CD8 T cell activation in xenotransplantation setting demonstrating the feasibility of the approach [58]. However, complete SLA class I deficiency in porcine donors was associated with impaired immune development, including reduced CD4⁺ and CD8⁺ T-cell compartments, hypogammaglobulinemia, and decreased survival. Thus, specific housing and animal care conditions should be considered for these animals [58].

Despite these advances, several critical challenges remain.

The risk of viral transmission, particularly from porcine endogenous retroviruses (PERVs) and porcine cytomegalovirus (PCMV), represents a key safety concern. Inactivation of PERV sequence, normally integrated into the porcine genome, via CRISPR-Cas technology, has been demonstrated to be highly successful generating inactivated donor lines [59, 60]. In contrast PCMV still represents a concern since transmission to humans after transplantation of pig heart was observed and contributed to the death of the recipient [61, 62]. Thus, other mitigation strategies like stringent screening, and long-term recipient monitoring are needed as well as the use of donor animals raised in GMP facilities under strict, pathogen-free, and traceable conditions and thus suitable for human use. This strategy may complement donor genome-editing approaches or prophylactic anti-infective therapies [63]. HLA-deficient HIP grafts may complicate detection of infected cells due to impaired antigen presentation, adding additional safety challenges [64]. Adaptive changes in innate immunity or recognition of residual xenoantigens could emerge over time, necessitating long-term monitoring. Moreover, manufacturing, quality control, and regulatory challenges increase as HIP engineering is combined with multi-gene xenotransplantation platforms. Despite these hurdles, HIP approaches offer the potential to generate xenogeneic grafts with durable, multi-layered immune evasion, potentially reducing reliance on systemic immunosuppression, pending validation in well-controlled clinical trials.

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The potential of combining genome-edited porcine organs with HIP modifications is considerable, though it currently rests primarily on early preclinical evidence and remains largely unproven in clinical settings. Such an approach could extend graft survival, allow for repeated graft administration, and broaden the applicability of xenotransplantation to patients with metabolic, endocrine, or organ failure. By addressing both innate and adaptive immune barriers simultaneously, HIP-enhanced xenografts may bridge the remaining gap between experimental success and clinically viable organ replacement therapies, potentially offering a pathway toward safer, more durable therapies. In the long term, these advances may contribute to addressing the global shortage of transplantable organs, provided that remaining immunological, safety, and regulatory challenges are successfully resolved.

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FC and AC conceived the study. FC, MIB, HS, LP, and AC wrote the manuscript. All authors contributed to the article and approved the submitted version.

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"Innovative diagnostics and treatments of infections in transplantation," report from the 2025 spring highlights in transplantation sciences meeting

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Infectious complications remain a leading cause of morbidity and mortality after solid organ transplantation, driven by profound immunosuppression, emerging pathogens, and increasing antiviral resistance. The 2025 Spring Highlights in Transplantation Sciences (HITS) meeting, held in Paris under the auspices of the Société Francophone de Transplantation and endorsed by the European Society of Organ Transplantation, brought together international experts to discuss recent advances in the diagnosis, pathogenesis, prevention, and treatment of infections in transplant recipients. This report summarizes the key scientific presentations covering innovative approaches to viral hepatitis, cytomegalovirus (CMV), Epstein-Barr virus, human herpesvirus-8, BK polyomavirus, infectious encephalitis, and vaccination strategies. Particular emphasis was placed on the growing role of metagenomic next-generation sequencing for diagnosing unexplained infections, the integration of immune monitoring into clinical decision-making, and the development of adoptive

cellular therapies, including virus-specific $\alpha\beta$ T cells and $\gamma\delta$ T-cell-based immunotherapies for refractory CMV infection. The meeting also highlighted emerging concepts in donor-recipient immunogenetics, novel diagnostic technologies, and personalized preventive strategies. Collectively, these advances illustrate the transition toward precision medicine in transplant infectious diseases, combining cutting-edge diagnostics, immune profiling, and innovative immunotherapeutic approaches to improve the management and outcomes of solid organ transplant recipients.

KEYWORDS

BKvirus, cell-therapy, CMV, EBV, encephalitis

Introduction

The 2025 *Spring Highlights In Transplantation Sciences (HITS)* annual meeting was held in Paris on March 27–28, under the auspices of the *Société Francophone de Transplantation* and endorsed by the *European Society of Organ Transplantation*. This second edition of *Spring HITS* focused on innovative diagnostic and therapeutic approaches to infectious diseases, mainly viral-mediated diseases, in solid organ transplant recipients (SOT). We summarize in this report the presentations and discussions around the covered topics, highlighting recent knowledge gaps and technical achievements together with expert opinions. Each topic includes original/atypical clinical presentation, diagnostic and therapeutic innovations.

Transplant hepatitis: unusual suspects

Metagenomic evaluation of indeterminate hepatitis in immunocompromised patients

Hepatitis in immunocompromised individuals remains a significant diagnostic challenge due to its heterogeneous etiologies and wide range of clinical severity. Standard microbiological diagnostic methods, including targeted PCR assays and microbial culture, may fail to identify the causative infectious agents. Metagenomic next-generation sequencing (mNGS), a non-targeted approach that characterizes all nucleic acids present in a clinical sample, offers a promising alternative by enabling the detection of unexpected, rare, or novel pathogens.

Jacques Fourgeaud (Virology, Paris, France) reported that in his laboratory, from 2019 to 2022, 742 samples from 523 patients were analyzed using mNGS. This approach yielded an overall diagnostic rate of 19%, which was 2.5 times higher in immunocompromised patients compared with immunocompetent individuals [1].

Several case studies have highlighted the diagnostic performance of mNGS. Notably, mNGS enabled the identification of a novel virus, human circovirus 1 (HCirV-1), a recently described circular single-stranded DNA virus belonging to the family *Circoviridae*, in patients presenting with acute hepatitis, suggesting its potential role as a previously unrecognized pathogen in immunocompromised individuals [2–4]. In another illustrative example, Aichi virus, a non-enveloped positive-sense RNA virus of the genus *Kobuvirus* (*Picornaviridae*) typically associated with self-limited acute gastroenteritis, was detected in multiple children with chronic hepatitis and primary [5]. Following its initial detection by

mNGS, subsequent investigations supported the classification of both HCirV-1 and *Aichi virus* as opportunistic pathogens.

Collectively, these findings support the integration of mNGS into the diagnostic workflow, particularly as a second-line approach when conventional testing fails to yield a diagnosis. Despite inherent limitations, including higher cost, longer turnaround times, and challenges in data interpretation, mNGS offers a substantial advantage in detecting unexpected, rare, or emerging pathogens. When used as a second-line investigation, it can significantly improve the etiological diagnosis of unexplained hepatitis in immunocompromised individuals.

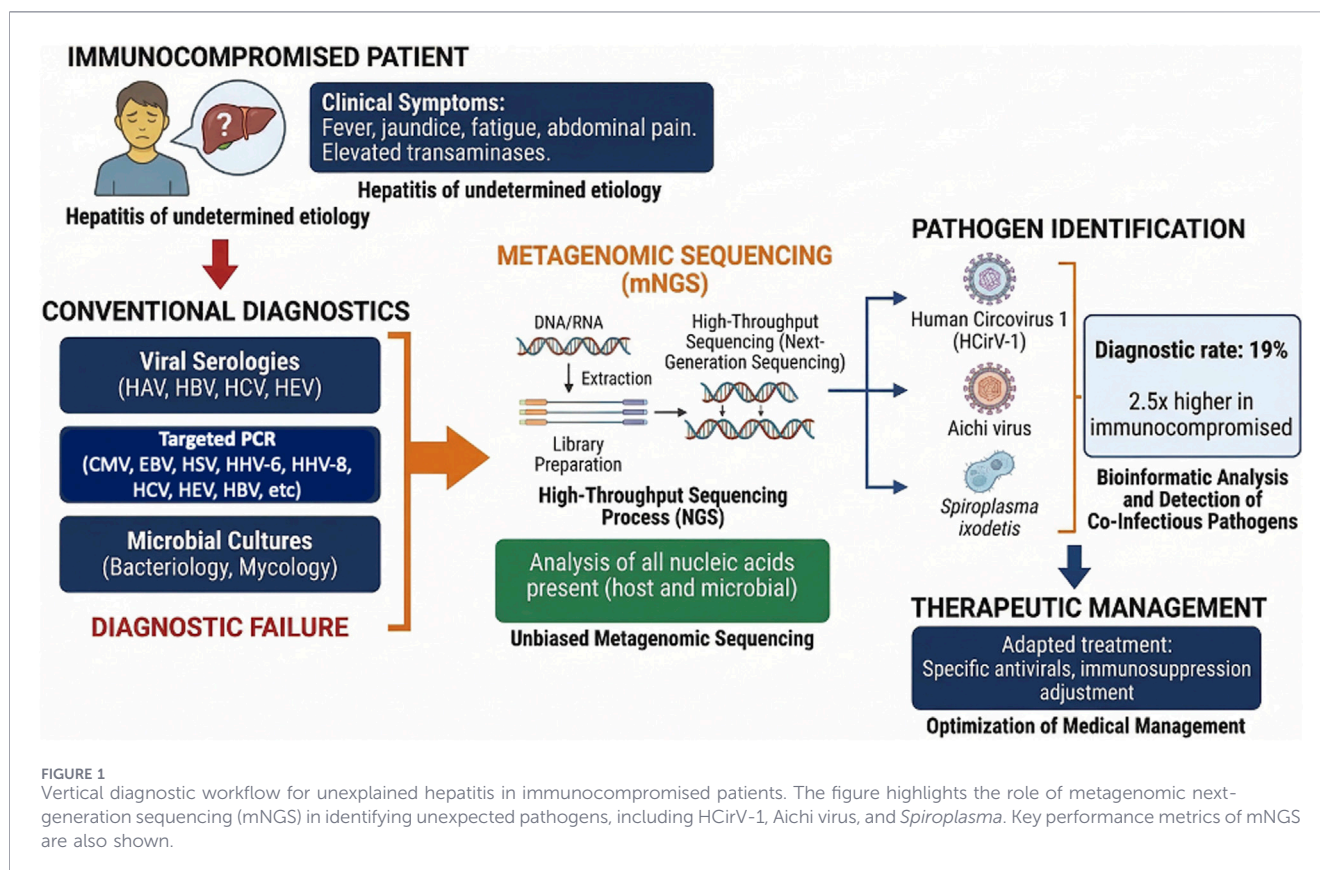
Clinical case: Spiroplasma hepatitis diagnosed by metagenomics

Imane Farhat (Kidney Transplantation, Dijon, France) presented a case highlighting the use of metagenomic sequencing to identify the cause of hepatitis of unknown origin in a kidney transplant recipient.

A 65-year-old kidney transplant recipient was admitted with isolated fever. Initial laboratory tests revealed pancytopenia and elevated CRP levels, but conventional investigations failed to detect any pathogen. A myelogram was performed due to symptoms suggestive of macrophage activation syndrome, but results were negative. Subsequently, the patient developed fulminant hepatitis. Liver biopsy showed severe acute cytolytic hepatitis with a neutrophil-rich infiltrate, suppurative hepatocytic necrosis, and hemophagocytosis. Treatment with etoposide, N-acetylcysteine and piperacillin-tazobactam was initiated. Unfortunately, the patient succumbed to hemorrhagic complications following the liver biopsy. Posthumous shotgun metagenomics (SMg) analysis of the liver tissue identified *Spiroplasma ixodetis*, a cell wall-deficient bacterium of the class *Mollicutes* previously recognized mainly as an arthropod-associated microorganism and an exceptionally rare human pathogen, as the causative agent, demonstrating the value of metagenomics in diagnosing rare or unexpected infections in immunocompromised patients [6], particularly when the identified pathogen is highly susceptible (here to doxycycline), allowing timely diagnosis and effective treatment.

Enteric viruses associated hepatitis

Chronic hepatopathy is a frequent complication in immunocompromised patients, particularly in those with antibody deficiencies. This condition, characterized by chronic



transaminitis and/or anicteric cholestasis, is often underrecognized and may progress to portal hypertension and its associated complications. Histologically, chronic hepatopathy is marked by lobular CD8⁺ T cell infiltration, with possible granulomas and nodular regenerative hyperplasia.

Benedicte Neven (Pediatric Immuno-hematology, Paris, France), reported the findings of an investigation involving 50 patients with primary or secondary antibody deficiency who developed chronic hepatopathy. A strong association with chronic enteric viral infections was identified, with viruses detected in 50% of affected patients, but not in a control group with similar immunodeficiencies and no liver abnormalities. Patients with hepatopathy exhibited an expansion of activated memory CD8⁺ T cells in peripheral blood mononuclear cells, along with enhanced type I and type II interferon responses, predominantly, though not exclusively, within the memory CD8⁺ T cell compartment. This entity was termed *enteric virus-associated hepatitis* (EVAH).

The main viruses implicated were norovirus and Aichi virus. Aichi virus infection was associated with a broader clinical phenotype, including tubulo-interstitial nephritis, kidney enlargement, and progressive renal impairment in addition to liver involvement. Notably, norovirus is typically detected in stool samples, whereas Aichi virus is more frequently identified in diseased tissues and organs. The underlying pathogenic mechanisms remain to be fully elucidated and may differ between norovirus and Aichi virus. Whether EVAH contributes to liver involvement, including nodular regenerative hyperplasia, observed in long-term transplant

recipients, particularly after B-cell depletion, remains to be investigated.

Figure 1 highlights the role of metagenomic next-generation sequencing (mNGS) in identifying unexpected pathogens, including HCirV-1, Aichi virus, and *Spiroplasma*.

Viral hepatitis transmitted by the donor (B, C, E)

Nassim Kamar (Solid Organ Transplantation, Toulouse, France) provided an overview of viral hepatitis transmission through organ donation.

Hepatitis E (HEV)

HEV is a common cause of viral hepatitis and is often underdiagnosed in SOT recipients. It is an RNA virus with four main genotypes: genotypes 1 and 2 are human-restricted and transmitted via the fecal-oral route, whereas genotypes 3 and 4 are zoonotic. Chronic HEV infection is defined by viral replication persisting for more than 3 months. Among SOT recipients, approximately two-thirds of HEV-infected patients develop chronic hepatitis. Tacrolimus use, compared with cyclosporin A, is a major predictor of chronicity. Reducing immunosuppressive therapy may serve as a first-line intervention. Ribavirin (RBV) has demonstrated efficacy in many immunosuppressed SOT recipients, with dosing and duration tailored to viral shedding patterns. RBV discontinuation is advised only when HEV RNA is undetectable in both serum and stool. In cases of treatment failure, pegylated interferon-α may be considered in liver transplant patients but is unsafe in recipients of

other organs due to the risk of rejection. Human-to-human transmission of HEV genotypes 3 and 4 is rare but possible via blood or organ transplantation. Screening is routine in the UK and France. In living donors, detection delays transplantation; for deceased donors, recipients are informed and monitored. Persistent infection beyond one to 3 months may be an indication to start RBV treatment.

Hepatitis C (HCV)

Current KDIGO guidelines recommend that all patients with kidney disease or undergoing transplantation who are HCV-positive receive direct-acting antiviral (DAA) therapy [7]. The timing of treatment depends on donor type, waiting list duration, liver function, and donor infection status. Since 2023 in France, organ recipients may receive transplants from anti-HCV-positive but RNA-negative donors, with PCR monitoring and DAA therapy ensuring complete viral clearance. Indeed, the risk of transmission from this group of donor is almost zero.

Conversely, HCV-positive PCR-positive donors are accepted in many other countries even for HCV-negative recipients, with good efficacy of prophylactic DAA [8].

Hepatitis B (HBV)

Since 2023 in France, kidneys from HBsAg-positive and/or HBV DNA-positive donors may be transplanted into recipients with chronic HBV infection, provided appropriate antiviral prophylaxis and post-transplant monitoring are maintained. Antiviral therapy is generally continued for at least 6–12 months and may be prolonged in patients with persistent HBsAg positivity or detectable HBV DNA.

In contrast, transplantation from HBV DNA-positive donors into HBV-seronegative recipients remains prohibited in France. However, this strategy has been explored in the United States in selected kidney and liver transplant recipients using intensive antiviral prophylaxis, with encouraging short-term outcomes (no chronic viremia, death or graft loss) and reduced waiting times [9].

CMV: when a big virus turns into a big problem

Resistant and refractory CMV

Oriol Manuel (Transplant Infectious Diseases, Lausanne, Switzerland) discussed the incidence, therapeutic options, and challenges associated with resistant and refractory cytomegalovirus (CMV) infection in SOT recipients.

Refractory CMV remains a significant clinical challenge in this population. It is defined by an increase in or persistence of viral load despite appropriately dosed antiviral therapy, with genotypic testing confirming resistance in approximately 50% of cases [10]. While many patients eventually clear CMV without treatment modifications, high viral loads and host factors, such as donor-recipient CMV serostatus mismatch (D+/R-) or lung transplantation, increase the risk of resistance.

CMV antiviral resistance is most commonly associated with mutations in the UL97, UL54, and UL56 genes. Available therapeutic options include (val)ganciclovir, foscarnet, maribavir, CMV-specific immunoglobulins, and adoptive T-cell therapies.

Maribavir, a pUL97 kinase inhibitor, offers an oral alternative to conventional therapies, with a favorable toxicity profile [11]. However, resistance to maribavir is an emerging concern, with studies showing that up to 48% of non-responders and up to 86% of patients with viral recurrence develop resistance [12]. To mitigate this risk, it is strongly recommended to initiate maribavir treatment when the viral load is below 50000UI/mL [10].

Management of refractory and resistant CMV requires a systematic approach, including adherence verification, genotypic testing, and adjustment of immunosuppressive therapy. For patients with high viral loads or end-organ disease, foscarnet remains the preferred antiviral treatment [10]. Switching to maribavir may be considered when toxicity is a concern, particularly once the viral load has been reduced [10]. The addition of CMV immunoglobulins is sometimes used in refractory cases, although robust clinical trial data are lacking. Letermovir is currently licensed for prophylaxis in D+/R- kidney transplant recipients [10]. Letermovir, used as secondary prophylaxis, may help reduce long-term maribavir exposure and prevent resistance. The combination of valganciclovir and letermovir as first-line therapy is currently being evaluated in kidney transplant recipients with CMV infection to accelerate viral clearance and reduce the risk of resistance emergence (LUCY trial; NCT06334497).

While antiviral resistance remains relatively rare, it is associated with significant morbidity, highlighting the need for ongoing research to optimize management strategies and improve outcomes for SOT recipients.

From a better understanding of the host-virus relationship in SOT to diagnostic and therapeutic perspectives

Martina Sester (Transplant and Infection Immunology, Homburg, Germany) presented the basic immunomodulatory strategies employed by herpesviruses, such as CMV, to evade the host immune system. These strategies include interference with innate immune mechanisms, disruption of antigen presentation, and mimicry of cytokines or other cellular proteins [13]. Recent studies have shown that mimicry between viral and host antigens not only occurs at the protein level but also at the peptide level. While short-peptide mimicry is a common feature of many viruses, herpesviruses and poxviruses more frequently exhibit mimicry of longer peptides with up to three mismatches, particularly among viruses that establish chronic infections. Viral mimicry appears to target host proteins non-randomly, notably sparing the human Y-chromosome. This suggests that viral mimicry may contribute to the development of autoimmunity while reflecting evolutionary pressure to evade the adaptive immune system and thereby establish latency [14]. These mechanisms may also help explain the unusually high levels of antigen-specific T cells required to control herpesvirus replication, including CMV [15].

Recent evidence supporting the use of CMV-specific T cells for individualized management of CMV complications in SOT recipients has been summarized in the Fourth International Consensus Guidelines on the Management of CMV in Solid Organ Transplantation of The Transplantation Society (TTS) [10]. Key recommendations include using CMV-specific T cells as an alternative to serology in patients with potential passive

immunity [16–18], employing CMV-specific cellular immunity measured at day 15 post-transplant in seropositive recipients as an indicator of low risk for subsequent reactivation [19, 20], and tailoring the duration of antiviral prophylaxis (typically 3–6 months) based on the presence of CMV-specific T cells [21–24]. Furthermore, emerging data suggest that CMV-specific T cells may guide the duration of antiviral treatment, the initiation of secondary prophylaxis [25], the identification of patients at risk of relapse, and the individualized management of patients intolerant to antiviral therapy [26]. However, controlled studies are still needed to validate these applications. Overall, substantial progress in CMV immunomonitoring has now been recognized in the latest consensus guidelines, which, for the first time, include recommendations for its use in transplant recipients [10].

Preclinical-stage therapy: gamma delta T cells for refractory CMV disease

Lionel Couzi (Kidney Transplantation, Bordeaux, France) emphasized that, despite recent advances with maribavir, the management of refractory CMV infections remains a significant challenge in SOT recipients. There is growing interest in developing adoptive cellular therapies targeting CMV. While current HLA-restricted $\alpha\beta$ T-cell-based therapies show promise, they have limitations, highlighting the need for complementary, HLA-independent immunotherapeutic approaches.

Human $\gamma\delta$ T cells play a key role in the immune response against CMV [27–33], and their expansion correlates with viral recovery in SOT recipients. Notably, $\gamma\delta$ T cells can recognize antigens via their T-cell receptor independently of MHC/HLA restriction [34] making them attractive candidates for allogeneic cell therapy. A robust, clinical-grade method has been developed for the selective, large-scale expansion of $\gamma\delta$ T cells, referred to as “Delta One T” (DOT) cells, characterized by a predominance (>70%) of V δ 1+ cells in the final product [35]. In a preclinical study conducted by the Immunoconcept group at Bordeaux University, DOT cells were successfully expanded from both CMV-seronegative and CMV-seropositive donors. Their anti-CMV activity was demonstrated both *in vitro* and *in vivo*, using a murine “DOT-like” cell model that recapitulated the characteristics of the human product. Importantly, DOT cells were also expanded from kidney transplant patients with refractory CMV infection and retained both viability and functionality in the presence of standard immunosuppressive treatments [36].

In summary, this preclinical study provides proof-of-concept for future clinical trials evaluating autologous or allogeneic DOT cells as a novel treatment for refractory CMV disease in SOT recipients, including high-risk CMV-naïve D + R- patients.

CMV-specific conventional T-cell therapy

Rajiv Khanna (Biological Sciences, Brisbane, Australia) highlighted advances in CMV-specific conventional T cell therapy, which has evolved from autologous approaches in solid organ transplantation [37–40] to scalable allogeneic “off-the-shelf” products for both transplant and oncology patients [41]. Immunocompromised individuals, particularly

after hematopoietic stem cell transplantation (HSCT) or solid organ transplantation (SOT), remain at high risk for severe viral diseases, including CMV, Epstein-Barr virus (EBV), BK-polyomavirus (BKPyV), and adenovirus, many of which lack effective drug treatments. Earlier work demonstrated that autologous virus-specific T cells can resolve drug-resistant viral infections and restore immunity, but manufacturing delays, limited scalability, and cost restrict their widespread use. To address this, allogeneic multi-virus-specific T cells are manufactured from carefully selected healthy donors using proprietary “pepmix” epitope pools that cover diverse HLA alleles. The Robin™ algorithm matches cryopreserved T-cell products to patients based on HLA compatibility, viral specificity, and product availability, enabling immediate treatment. Phase I clinical trials have shown that both therapeutic and prophylactic administration of these allogeneic products is safe, promotes immune reconstitution, and can lead to clearance or control of viral reactivation, even in drug-resistant cases [41]. Compassionate access programs across Australia and New Zealand have treated critically ill adults and children with various underlying diseases and following organ transplants, demonstrating encouraging clinical responses [42]. Single-cell RNA sequencing has revealed distinct functional gene signatures associated with superior survival outcomes. This platform also supports innovation in solid tumor therapy, integrating chimeric antigen receptors (CARs) targeting tumour antigens such as EphA3 [43].

Overall, this approach promises consistent, scalable, rapid-access T cell therapies with broad clinical potential for the treatment of viral infections and cancer.

Navigating pathogenesis: infectious diseases challenges in transplant recipients

From pathophysiology to diagnostic and therapeutic perspectives for EBV and HHV-8

David Boutboul (Immuno-hematology, Paris, France), focused on Epstein-Barr virus (EBV) and human herpesvirus 8 (HHV-8), two oncogenic herpesviruses implicated in various lymphoproliferative disorders (LPDs), particularly in immunocompromised hosts.

Primary EBV infection may present with severe manifestations such as hemophagocytic lymphohistiocytosis (HLH), which can be associated with underlying genetic defects (e.g., *IL-27RA* deficiency [44]; X-linked lymphoproliferative disease, *XLP*) or arise in the context of transplantation with an donor-positive/recipient-negative (D+/R-) EBV mismatch. Chronic EBV infection is associated predominantly with B-cell LPDs and, less frequently, with T/NK-cell LPDs, which are often diagnostically challenging and may exhibit resistance to rituximab.

HHV-8, a less prevalent virus, is associated with Kaposi sarcoma (KS), the potentially life-threatening HHV-8-associated multicentric Castleman disease (MCD), and primary effusion lymphoma (PEL).

These disorders are commonly observed in the setting of secondary immunodeficiency settings, such as HIV infection or post-transplantation, but may also occur in primary immunodeficiencies, particularly as EBV-positive B-cell LPDs.

Diagnosis of EBV- and HHV-8-associated diseases relies primarily on tissue biopsy, which remains the gold standard. For EBV, Epstein-Barr virus-encoded RNA (EBER) *in situ* hybridization (ISH) co-stained with B- or T/NK-cell markers is critical, while latency-associated nuclear antigen (LANA) staining is essential for HHV-8. Whole blood viral load monitoring is also commonly used. Recently, novel diagnostic approaches, such as flowFISH (combining flow cytometry and ISH for EBER or LANA), have emerged. This technique improves the detection of infected cells, including circulating “viroblasts” in HHV-8-MCD [45], thereby facilitating rapid diagnosis and improved characterization of cellular viral reservoirs [46].

Therapeutic strategies include rituximab for EBV-associated LPDs, etoposide combined with rituximab for HHV-8-associated MCD, and immune restoration whenever feasible. Overall, this presentation highlighted the critical importance of understanding disease pathogenesis to optimize diagnostic and therapeutic strategies in these vulnerable patient populations.

Impact of donor HLA-DQ divergence on the control of post-transplant BKPyV infection

Sophie Caillat-Zucman (Immunology, Paris, France), presented a study examining the impact of donor and recipient HLA divergence on the risk of BK polyomavirus (BKPyV) viremia following kidney transplantation.

In the absence of specific antiviral therapies, BKPyV infection remains a major challenge after kidney transplantation, as management relies on a delicate balance between preventing allograft rejection and restoring antiviral immunity through reduction of immunosuppression [47].

The study assessed whether HLA genetic and functional diversity, by expanding the repertoire of viral peptides presented to T cells, could influence the control of post-transplant BKPyV replication in a large cohort of kidney transplant recipients. No effect of HLA diversity at any recipient locus was observed. In contrast, high genetic divergence (HED) at the donor HLA-DQ locus, reflecting heterozygosity for two highly divergent HLA-DQ heterodimer groups (i.e., DQα01 and non-DQα01), was correlated with the breadth of the BKPyV-derived immunopeptidome and independently predicted a BKPyV-free outcome.

Using a novel functional divergence metric based on the similarity of peptide-binding motifs between pairs of HLA-DQ molecules, the investigators further demonstrated that DQα01 and non-DQα01 groups are also functionally divergent. These findings provide a molecular explanation for the observed differences associated with specific HLA-DQ allele combination profiles.

Overall, the results indicate that donor HLA divergence, particularly heterozygosity for DQα01 and non-DQα01 HLA-DQ molecules, serves as a relevant proxy for the diversity of the BKPyV-derived peptides predicted to bind donor DQ molecules, and is associated with protection against BKPyV replication after kidney transplantation. These findings also underscore the critical role of DQ-restricted CD4+T cell-mediated immune responses in the control of BKPyV infection. These novel findings have recently been published [48].

Vaccination: physiopathology and strategies in immunocompromised patients

Jean-Daniel Lelièvre (Infectious Diseases, Créteil, France) provided an overview of vaccination strategies in immunocompromised patients.

SOT recipients are particularly susceptible to infections and often exhibit suboptimal responses to vaccination. The mechanisms underlying this impaired immunogenicity include the effects of immunosuppressive therapies, as well as immune dysfunction related to chronic organ failure, particularly chronic kidney disease. Consequently, vaccination should be initiated as early as possible, ideally prior to transplantation.

Vaccination schedules generally follow those recommended for immunocompetent individuals but often require earlier administration of certain vaccines, such as those targeting herpes zoster, pneumococcus and influenza, which are typically reserved for older adults in the general population. Strategies to enhance vaccine efficacy may include higher antigen doses, additional doses during the primary vaccination series, and more frequent booster vaccinations. Other approaches include the use of adjuvanted vaccines (e.g., influenza vaccines), heterologous vaccination schedules, and when feasible, modulation of the immunosuppressive regimen.

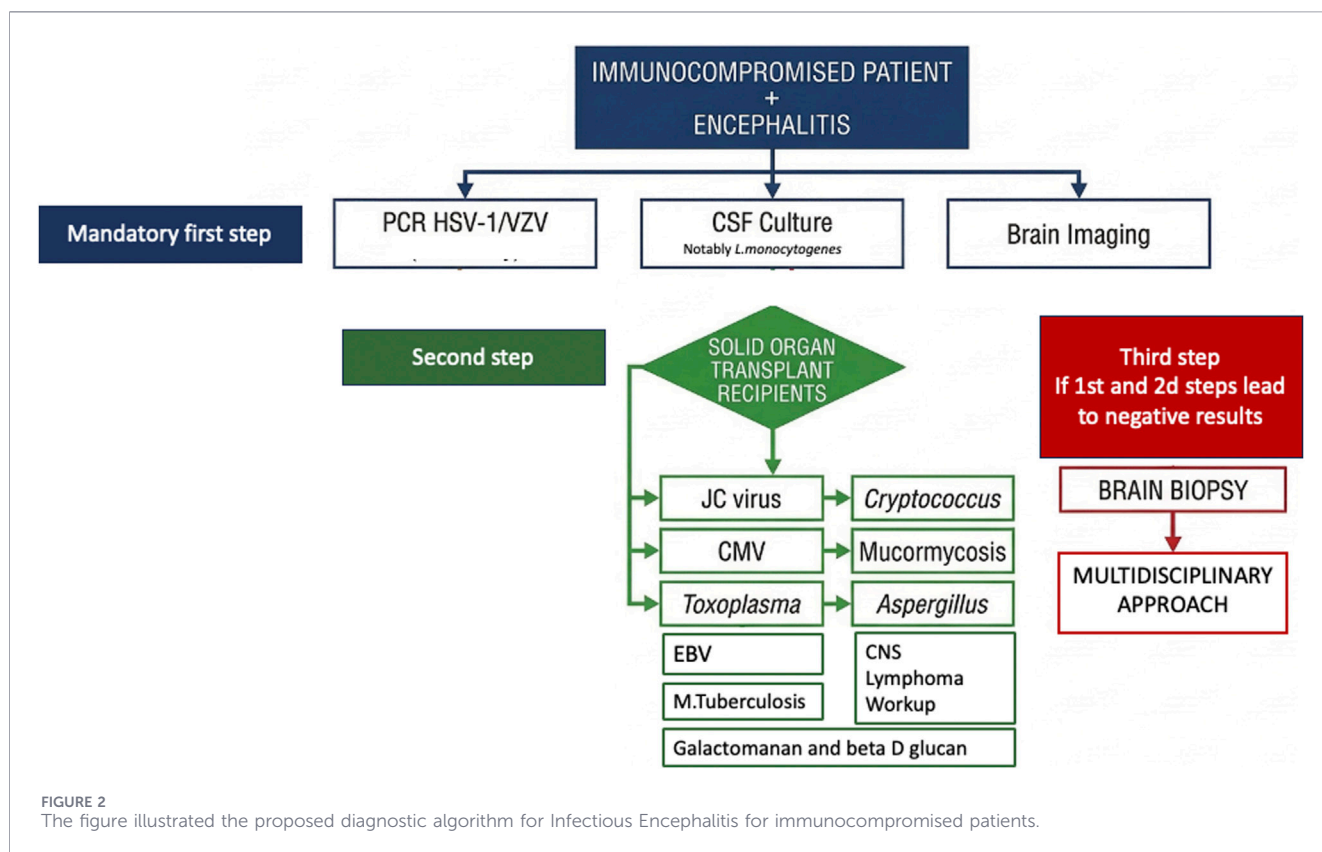
In addition, cocooning strategies (vaccination of close contacts) may help reduce household transmission of pathogens, including SARS-CoV-2 and *N. meningitidis*, to immunocompromised patients. Although the potential risk of graft rejection following vaccination remains a concern, a recent meta-analysis suggests that vaccination is generally safe in transplant recipients [49].

Ongoing research into novel vaccines, including those targeting norovirus and CMV, offers promising perspectives for preventing infections that are particularly relevant to immunocompromised populations. However, despite these advances, the number of clinical trials specifically involving immunocompromised patients remains limited, and evidence-based recommendations are still lacking for several vaccines.

Targeting infectious encephalitis in transplant recipients: diagnostic and therapeutic breakthroughs

Pegivirus, a case series

Marie Benedicte Le Stang (Kidney Transplantation, Paris, France) reported two kidney transplant recipients who developed Pegivirus-associated encephalitis. Both patients presented with acute visual loss secondary to retrobulbar optic neuritis, accompanied by additional neurological and cognitive manifestations. Next-generation sequencing (NGS) analysis of the cerebrospinal fluid (CSF) identified pegivirus, also known as human pegivirus (HPgV) as the causative agent of encephalomyelitis. Human pegivirus (HPgV) is an enveloped positive-sense RNA virus of the family *Flaviviridae* that commonly establishes persistent asymptomatic infection in humans and has only recently been implicated in neurological disease in severely immunocompromised patients.



This virus is carried by approximately one-sixth of the population, with a higher prevalence in South Africa and Asia. Seven distinct genotypes have been described. HPgV can infect splenic and bone marrow lymphocytes and is transmitted through percutaneous exposure, blood transfusion, and sexual contact. The infection may persist in a latent state. An estimated 26% of SOT patients are thought to be infected, especially within the first year post-transplantation.

HPgV infection has also been associated with an increased risk of non-Hodgkin lymphoma and encephalomyelitis, likely through infection of microglia and astrocytes. Diagnosis relies on brain biopsy, detection of viral RNA in serum and cerebrospinal fluids (CSF), and NGS analysis of CSF. The recent report of four cases over a two-year period from a single German institution suggests that this condition may be underdiagnosed and warrants greater clinical awareness [50]. Despite a poor prognosis in immunocompromised patients, there is currently no established therapeutic consensus or effective treatment strategy.

Diagnosis of indeterminate encephalitis in immunocompromised patients

Marion Le Maréchal (Infectious Diseases, Grenoble, France) provided an overview of the diagnostic approach to encephalitis in immunocompromised patients. Diagnosis in this population is particularly challenging because of the broad differential diagnosis, which includes hematological malignancies, treatment-related neurotoxicity, autoimmune encephalitis, and posterior reversible encephalopathy syndrome (PRES).

The most frequent infectious causes of encephalitis in immunocompromised patients overlap with those observed in immunocompetent individuals, notably herpes simplex virus type 1 (HSV-1), varicella-zoster virus (VZV), and *Listeria monocytogenes*. However, several pathogens are more specifically associated with immunosuppression, including EBV, CMV, JC virus, and *Cryptococcus neoformans*. The spectrum of likely pathogens varies according to the type and intensity of immunosuppression, such as that seen in SOT recipients, hematopoietic stem cell transplant recipients, or patients living with HIV. Diagnostic evaluation should follow a systematic and structured approach. First-line investigations should consistently include HSV-1 and VZV polymerase chain reaction (PCR) testing and cerebrospinal fluid (CSF) cultures. In HIV-positive patients, the diagnostic work-up should additionally screen for EBV, CMV, JC virus, *Mycobacterium tuberculosis*, *C. neoformans*, *Toxoplasma gondii*, syphilis, and central nervous system lymphoma as a key differential diagnosis.

In solid organ transplant recipients, investigations should include screening for JC virus, CMV, *C. neoformans*, Mucorales, *Toxoplasma gondii*, and *Aspergillus* spp. Adjunctive tests such as serum or CSF galactomannan and β -D-glucan assays may be useful in the diagnosis of invasive fungal infections. When blood and CSF investigations remain inconclusive, early consideration of brain biopsy is warranted in immunocompromised patients. Diagnosis and therapeutic decisions should be guided by a multidisciplinary team approach.

Figure 2 summarizes the diagnostic algorithm proposed for suspected Infectious encephalitis.

Encephalitis caused by JC virus in immunocompromised patients

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infectious disease affecting the central nervous system and is caused by the JC virus. Although it has been extensively studied in patients with HIV infection or those receiving immunotherapies, data on kidney transplant recipients (KTRs) remain limited. Hélène François (Kidney Transplantation, Paris, France) reported the results of a retrospective, multicenter, nationwide study. All kidney transplant centers in France were contacted to identify cases of PML, and the total number of KTRs was obtained from the registry of the French regulatory agency.

A total of 24 cases of PML were identified. The estimated minimum nationwide incidence of PML was 4.7 per 100,000 patient-years. The median time from kidney transplantation to PML diagnosis was 88 months (interquartile range: 9–355 months), and 8 of the 24 patients (33%) had been exposed to belatacept. Almost all patients underwent a reduction or withdrawal of immunosuppression, and 13 patients (54%) received PML-specific treatment such as anti-PD1/PDL1 (15.4%) or Interleukin 7 (11.5%). Fifteen patients (63%) died within 1 year of diagnosis; these patients had greater exposure to belatacept compared with those who survived.

In this nationwide study, the incidence of PML in KTRs was at least 4.7 per 100,000 patient-years, with a 1-year mortality rate of 63%. Further investigations are warranted to confirm a potential association between belatacept exposure and the occurrence of PML. This study has recently been published [51].

Conclusion

The Spring HITS meeting highlighted the growing complexity of infectious diseases in solid organ transplant recipients and underscored the need for integrated diagnostic and therapeutic strategies. Across a wide spectrum of viral infections, ranging from hepatitis viruses and enteric viruses to herpesviruses, polyomaviruses, and emerging neurotropic pathogens, the presentations emphasized how atypical clinical manifestations, prolonged viral persistence, and treatment resistance are tightly linked to the altered immune landscape of transplant recipients.

A major recurring theme was the transformative role of advanced diagnostics, particularly metagenomic NGS, which has proven invaluable for identifying unexpected or novel pathogens in unresolved hepatitis and encephalitis. These tools, combined with refined immunomonitoring approaches such as virus-specific T-cell assessment and HLA divergence analysis, offer new opportunities to better stratify risk, personalize treatment, and guide immunosuppressive management.

On the therapeutic front, while antiviral drugs remain central, their limitations, especially in resistant or refractory infections, have driven the development of innovative immunotherapeutic strategies, including adoptive T-cell therapies and notably $\gamma\delta$ T-cell-based approaches. These emerging modalities illustrate a paradigm shift from pharmacological suppression of viral replication toward restoration of antiviral immunity capable of achieving durable viral control.

Finally, the meeting emphasized the importance of prevention through optimized vaccination strategies and donor-recipient matching, as well as the necessity of multidisciplinary collaboration

in managing complex infectious complications. Despite significant advances, major knowledge gaps remain, particularly regarding rare pathogens, long-term outcomes, and evidence-based management of immunocompromised populations. Continued translational research and well-designed clinical trials are essential to improve the prognosis and quality of care for transplant recipients facing infectious diseases.

Author contributions

JF, BN, NK, IF, OM, MS, LC, DB, SZ, JL, M-BL, ML, HF, and HK wrote the manuscript. JZ and AD revised the manuscript. JZ, AD, and HK conceived the manuscript. All authors contributed to the article and approved the submitted version.

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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 used in the creation of this manuscript. Each speaker wrote an abstract of its talk, HK AD and JZ wrote the introduction and the conclusion and AI edited english and help for rephrasing when necessary.

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ABO-incompatibility and hepatocellular carcinoma recurrence after living donor liver transplantation: stratified by tumor burden

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ABO-incompatible (ABOi) living donor liver transplantation (LDLT) requires rituximab-based desensitization and intensified early immunosuppression, and whether this promotes hepatocellular carcinoma (HCC) recurrence remains controversial. We hypothesized that this effect depends on tumor burden, assessed morphologically (Milan criteria) and biologically (ADV score). In this single-center study, we analyzed 1,573 adults transplanted for HCC (ABOi, $n = 316$; ABO-compatible [ABOC], $n = 1,257$); the primary endpoint was recurrence-free survival (RFS). Crude recurrence was similar (21.8% vs. 20.7%; $P = 0.64$) despite a lower tumor burden in ABOi recipients. In a propensity score-matched cohort, RFS did not differ overall (hazard ratio 1.11, 95% CI 0.82–1.48), but beyond Milan recurrence was higher in ABOi recipients (53.7% vs. 38.5%; adjusted HR 1.45, 95% CI 1.00–2.09), whereas within Milan it was identical (13.3% vs. 13.4%). The same pattern held for tumor biology: recurrence was higher in ABOi only at ADV ≥ 5 log (64.0% vs. 44.6%; $P = 0.022$). Higher early tacrolimus exposure in ABOi recipients was associated with recurrence. Overall survival was similar ($P = 0.91$). ABO-incompatibility did not compromise survival. Recurrence was higher in ABOi recipients with a high tumor burden by either measure, although the formal interaction tests were not significant ($P = 0.23$ and $P = 0.088$). These exploratory subgroup findings are hypothesis-generating and support closer early surveillance.

KEYWORDS

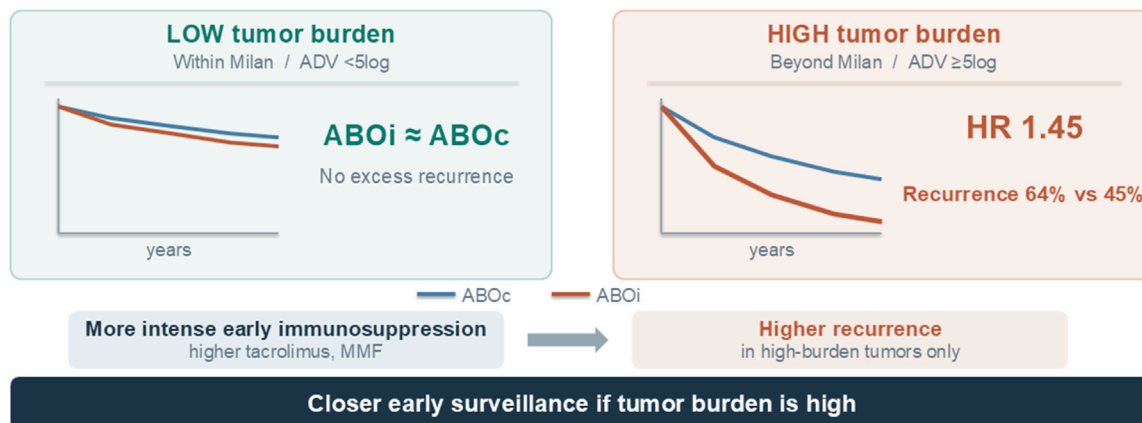
ABO incompatibility, hepatocellular carcinoma (HCC), living donor liver transplantation (LDLT), recurrence, surveillance

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer death and the most common oncologic indication for liver transplantation. Transplantation uniquely removes both the tumor and the underlying cirrhotic liver that drives further carcinogenesis [1]. Candidate selection has traditionally been based on the Milan criteria, which identify patients achieving post-transplant survival comparable to that for non-malignant disease [2]. Expanded morphologic criteria and biomarker-based models, such as the up-to-seven

ABO-Incompatibility and Hepatocellular Carcinoma Recurrence After Living Donor Liver Transplantation: Stratified by Tumor Burden

1,573 HCC recipients · ABOi 316 vs ABOc 1,257



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GRAPHICAL ABSTRACT

criteria and the alpha-fetoprotein (AFP) model, can extend this benefit to selected patients beyond the Milan criteria [3, 4]. In all frameworks, however, tumor burden and biological aggressiveness remain the principal determinants of recurrence, which still occurs in 15%–20% of recipients.

In many Asian countries, including Korea, the shortage of deceased donors means that living donor liver transplantation (LDLT) accounts for most transplant activity [5]. ABOi LDLT expands the living-donor pool for patients who lack an ABO-compatible donor and cannot wait for a deceased-donor graft. Early ABOi transplantation was complicated by frequent antibody-mediated rejection (AMR) and diffuse intrahepatic biliary complications, but rituximab-based desensitization improved outcomes, and contemporary series report survival comparable to ABO-compatible (ABOc) LDLT [6–9]. To overcome the immunologic barrier, ABOi recipients undergo B-cell depletion with rituximab and pretransplant plasma exchange to lower isoagglutinin titers, and they receive more intensive immunosuppression than ABOc recipients during the early postoperative period, when the risk of AMR is highest [6, 8].

This intensified immunosuppression, although necessary for graft survival, raises a biologically plausible oncologic concern.

Calcineurin inhibitors can promote tumor invasion and progression through cell-autonomous, transforming growth factor (TGF)-beta-dependent mechanisms independent of host immunity, and the depth of immunosuppression is a recognized, modifiable determinant of post-transplant malignancy and HCC recurrence [10–13]. Conversely, reduced early calcineurin-inhibitor exposure and mammalian target of rapamycin (mTOR) inhibition have been associated with lower recurrence in selected populations [12, 14]. The greater early immunosuppressive burden of ABOi transplantation could therefore impair tumor immunosurveillance when residual tumor cells are most likely to proliferate.

Nevertheless, comparative studies and a recent systematic review with meta-analysis have consistently reported no significant difference in recurrence-free or overall survival between ABOi and ABOc LDLT, supporting ABOi LDLT as an oncologically acceptable option [15, 16]. These analyses, however, treated the transplanted HCC population as a single group and were underpowered within high-risk subgroups, even though the impact of additional immunosuppression should differ between small and large or vascular-invasive tumors. Importantly, data from within ABOi cohorts suggest that the magnitude of the ABOi-specific immunologic burden is oncologically relevant: higher serum tacrolimus levels in the first weeks after transplantation and a greater number of pretransplant therapeutic plasma exchange sessions have each been independently associated with HCC recurrence [17, 18]. Taken together, these findings suggest that any adverse oncologic effect of ABO-incompatibility may be concentrated in patients with biologically aggressive tumors rather than distributed uniformly across the HCC population.

We therefore hypothesized that the effect of ABO-incompatibility depends on tumor burden, with an adverse effect on recurrence emerging in patients with advanced tumors. Because

Abbreviations: ABOc, ABO-compatible; ABOi, ABO-incompatible; ADV, alpha-fetoprotein-des-gamma-carboxyprothrombin-tumor volume score; AFP, alpha-fetoprotein; AMR, antibody-mediated rejection; CI, confidence interval; DCP, des-gamma-carboxyprothrombin; GRWR, graft-to-recipient weight ratio; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; LDLT, living donor liver transplantation; MELD, Model for End-Stage Liver Disease; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; MVI, microvascular invasion; OS, overall survival; PIVKA-II, protein induced by vitamin K absence-II; RFS, recurrence-free survival; SMD, standardized mean difference.

tumor burden comprises both anatomic extent and biological aggressiveness, and the Milan criteria capture only tumor size and number, we used two complementary measures: the morphologic Milan criteria and the biomarker-based ADV score, a composite of AFP, PIVKA-II, and tumor volume. Using a large single-center cohort and propensity score matching, we evaluated the overall effect of ABO-incompatibility on recurrence-free and overall survival, performed stratified analyses by tumor burden assessed both morphologically and biologically, and characterized the timing of recurrence to inform surveillance.

Materials and methods

Study population

We retrospectively reviewed consecutive adult recipients (aged ≥ 18 years) who underwent LDLT for HCC at a single high-volume center between December 2005 and December 2022. Eligibility required viable HCC confirmed on the final explant specimen. Patients with a complete pathologic response, pediatric recipients, recipients of deceased-donor whole-liver grafts, patients undergoing 2:1 (dual-donor) LDLT, and those with incomplete follow-up data were excluded. After applying these criteria, the final cohort comprised 1,573 recipients, of whom 316 (20.1%) underwent ABOi and 1,257 (79.9%) ABOc transplantation. Clinical, operative, and pathologic variables were obtained from a prospectively maintained database and medical records. The study was approved by the Institutional Review Board of [Institution blinded for review], which waived the requirement for informed consent because of the retrospective design and the use of de-identified data, and was conducted in accordance with the Declaration of Helsinki and the Declaration of Istanbul.

Desensitization and immunosuppression

ABOi LDLT was performed using an institutional rituximab-based desensitization protocol described previously [6]. In brief, a single dose of rituximab (375 mg/m^2) was given 2–3 weeks before transplantation, and pretransplant plasma exchange was performed as needed to reduce isoagglutinin titers to the institutional target. Local graft infusion and splenectomy, used in earlier eras, were not part of the current protocol. Maintenance immunosuppression in both groups was based on tacrolimus, mycophenolate mofetil (MMF), and a corticosteroid taper, with basiliximab induction used selectively. However, ABOi recipients received more intensive early immunosuppression than ABOc recipients: in addition to higher early tacrolimus trough targets used to reduce the risk of AMR, MMF was added more frequently as part of the institutional ABOi protocol. Serial quantitative measures of immunosuppression exposure were not uniformly available across the study period.

Definitions, endpoints, and follow-up

Tumor burden was classified by the Milan criteria on explant pathology, and microvascular invasion (MVI) was assessed on the explant by dedicated hepatobiliary pathologists. Serum AFP and protein induced by vitamin K absence-II (PIVKA-II) were recorded

at transplantation. Pre-transplant HCC treatment was defined as any bridging or downstaging locoregional therapy before transplantation. To capture tumor biology, tumor burden was additionally quantified using the ADV score, a pre-specified biomarker-based measure validated across hepatic resection and liver transplantation [19–23]. The ADV score is the product of serum AFP (ng/mL), des-gamma-carboxyprothrombin (PIVKA-II, mAU/mL), and tumor volume (mL), expressed on a base-10 logarithmic scale, capturing both biological activity and anatomic extent in a single continuous variable that complements the dichotomous Milan criteria. We applied the previously reported post-transplant cutoff of 5log (corresponding to an ADV product of 100,000), above which the risk of HCC recurrence is substantially increased [19, 20]. After transplantation, surveillance was protocol-driven and identical for ABOi and ABOc recipients. AFP and PIVKA-II were measured at every outpatient visit (monthly during the first year, then every 3 months). Chest and abdomen-pelvis computed tomography were obtained in all recipients at 3 months; thereafter, recipients within the Milan criteria were imaged every 6 months to 3 years, annually to 5 years, and every 2 years thereafter, and those beyond the Milan criteria every 3 months during the first year, every 4–6 months to 3 years, annually to 5 years, and every 2 years thereafter. Imaging frequency was therefore determined by tumor burden, not ABO compatibility. Recurrence was diagnosed primarily by cross-sectional imaging; histologic confirmation was obtained only when clinically indicated and was not routinely required. The primary endpoint, recurrence-free survival (RFS), was the interval from transplantation to first documented recurrence or last follow-up, with patients dying without recurrence censored at death. Overall survival (OS) was defined as the interval from transplantation to death from any cause.

Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQR) and were compared using the Mann-Whitney U test; categorical variables are presented as counts with percentages and were compared using the chi-square or Fisher exact test. Recurrence-free and overall survival were estimated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated using Cox models; the multivariable RFS model included ABO-incompatibility, recipient age and sex, MELD score, pre-transplant treatment, Milan status, tumor number and largest size, MVI, and log10-transformed AFP and PIVKA-II, with proportional hazards assessed by scaled Schoenfeld residuals. To address the baseline imbalance in tumor burden, 1:2 nearest-neighbor propensity score matching without replacement was performed with a caliper of 0.2 SD of the logit of the propensity score, estimated by logistic regression on tumor and clinical covariates; balance was assessed by standardized mean differences (SMD), with values below 0.10 acceptable. Pre-transplant treatment was included as a covariate rather than as a matching variable to preserve power in the small beyond-Milan subgroup. Stratified analyses by tumor burden were pre-specified. The Milan-based analysis was performed in both the whole and propensity-matched cohorts, whereas the continuous ADV score was analyzed in the whole cohort, where the larger number of high-burden events preserved statistical power. A multiplicative ABO-by-

TABLE 1 Baseline characteristics according to ABO compatibility (whole cohort).

Variable	ABO-compatible (n = 1,257)	ABO-incompatible (n = 316)	P value
Recipient age, yr, median (IQR)	55.0 (51.0–60.0)	55.0 (51.0–60.0)	0.735
Male sex, n (%)	1,069 (85.0)	262 (82.9)	0.394
MELD score, median (IQR)	10.0 (8.0–14.0)	9.0 (8.0–12.0)	<0.001
Pre-transplant HCC treatment, n (%)	972 (77.3)	264 (83.5)	0.020
Underlying liver disease, n (%)			
HBV	1,000 (79.6)	249 (78.8)	0.826
HCV	85 (6.8)	27 (8.5)	0.328
Alcoholic	107 (8.5)	24 (7.6)	0.679
Others	65 (5.2)	16 (5.1)	1.000
Graft type, n (%)			
Right lobe	1,161 (92.4)	288 (91.1)	0.545
Left lobe	13 (1.0)	3 (0.9)	1.000
Dual graft	83 (6.6)	25 (7.9)	0.485
GRWR, median (IQR)	1.0 (0.9–1.2)	1.0 (0.9–1.2)	0.423
AFP, ng/mL, median (IQR)	10.5 (4.1–48.0)	9.0 (4.0–34.1)	0.299
PIVKA-II, mAU/mL, median (IQR)	30.0 (19.0–79.0)	31.5 (21.0–66.0)	0.384
Tumor number, median (IQR)	2.0 (1.0–3.0)	1.0 (1.0–2.0)	0.010
Largest tumor size, cm, median (IQR)	2.3 (1.5–3.4)	2.1 (1.5–3.0)	0.028
Total tumor volume, cm ³ , median (IQR)	11.2 (3.1–34.5)	7.9 (1.8–26.8)	0.005
Beyond Milan criteria, n (%)	366 (29.1)	67 (21.2)	0.006
Microvascular invasion, n (%)	220 (17.5)	59 (18.7)	0.686

Data are median (interquartile range) or n (%). MELD, Model for End-Stage Liver Disease; GRWR, graft-to-recipient weight ratio; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II. Tumor number, size, volume, and Milan status were assessed on explant pathology. P values from the Mann-Whitney U test (continuous) or chi-square test (categorical).

tumor-burden interaction term was fitted in the whole cohort for each measure. Given their exploratory nature, no correction for multiple comparisons was applied. An exploratory mediation analysis used the 1-month tacrolimus concentration as the mediator, with bootstrap confidence intervals. As sensitivity analyses, recurrence was additionally analyzed in a competing-risk framework in which death without recurrence was treated as a competing event, with cumulative incidence functions estimated using the Aalen-Johansen method and subdistribution hazard ratios using Fine-Gray models; alternative ADV cut-offs (3 to 6log) and stratification by transplant era were also examined. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Analyses were performed using Python (version 3.11) with the lifelines and scikit-learn libraries.

Results

Patient characteristics

Of the 1,573 adults with viable HCC on explant pathology, 316 (20.1%) underwent ABOi and 1,257 (79.9%) ABOc transplantation,

and the median follow-up was 104 months. The groups were similar in recipient age, sex, underlying liver disease (predominantly hepatitis B virus), graft type, GRWR, AFP, PIVKA-II, and MVI (Table 1). However, ABOi recipients consistently had a lower baseline tumor burden, with a lower MELD score (median 9 vs. 10; $P < 0.001$), fewer tumors (median 1 vs. 2; $P = 0.010$), a smaller largest tumor (2.1 vs. 2.3 cm; $P = 0.028$), a smaller total tumor volume (7.9 vs. 11.2 cm³; $P = 0.005$), and a lower proportion of tumors beyond the Milan criteria (21.2% vs. 29.1%; $P = 0.006$); they were also more likely to have received pre-transplant locoregional therapy (83.5% vs. 77.3%; $P = 0.020$). This more favorable tumor profile in the ABOi group, probably reflecting more selective use of ABOi transplantation motivated the matched and stratified analyses.

Recurrence in the whole and propensity-matched cohorts

HCC recurred in 329 of the 1,573 patients (20.9%) during follow-up, comprising 260 ABOc and 69 ABOi recipients. Crude recurrence was similar between the groups (21.8% vs. 20.7%), with 1-, 3-, and 5-year RFS of 89.8%/81.3%/78.2% versus 89.1%/82.2%/80.0%, respectively (log-rank $P = 0.64$; Figure 1A). In univariable

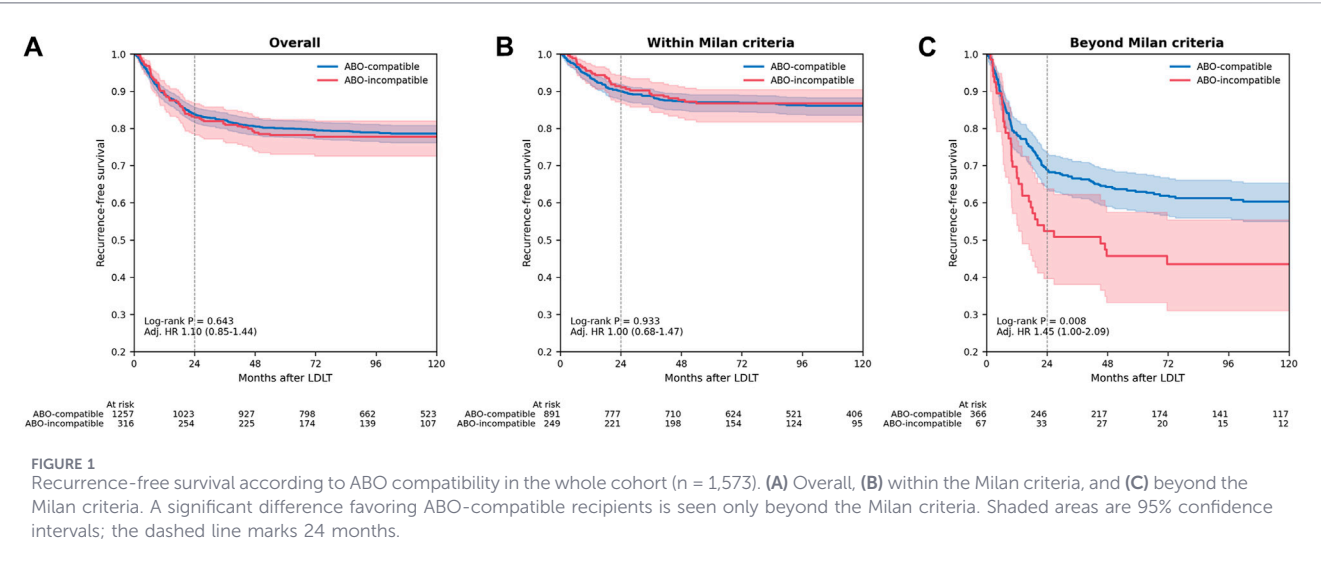


TABLE 2 Univariable and multivariable Cox regression for recurrence-free survival (whole cohort).

Variable	Univariable HR (95% CI), P	Multivariable HR (95% CI), P
ABO-incompatibility	1.06 (0.82–1.39), 0.648	1.19 (0.91–1.55), 0.210
Recipient age, per yr	0.98 (0.96–0.99), <0.001	1.00 (0.98–1.01), 0.818
Male sex	1.73 (1.21–2.49), 0.003	1.52 (1.05–2.19), 0.025
MELD, per point	0.99 (0.97–1.01), 0.304	0.98 (0.96–1.00), 0.099
Pre-transplant treatment	2.41 (1.71–3.39), <0.001	1.68 (1.18–2.40), 0.004
Beyond Milan criteria	3.69 (2.97–4.58), <0.001	1.70 (1.28–2.25), <0.001
Tumor number, per lesion	1.11 (1.09–1.13), <0.001	1.04 (1.01–1.07), 0.003
Largest tumor size, per cm	1.24 (1.21–1.28), <0.001	1.10 (1.05–1.16), <0.001
Microvascular invasion	5.53 (4.45–6.87), <0.001	3.11 (2.41–4.00), <0.001
log10 AFP	1.76 (1.57–1.97), <0.001	1.25 (1.10–1.40), <0.001
log10 PIVKA-II	1.91 (1.67–2.18), <0.001	1.17 (1.00–1.38), 0.053

HR, hazard ratio; CI, confidence interval. The multivariable model included all listed variables (n=1,565; 329 events). AFP and PIVKA-II were modeled as log10-transformed continuous variables.

analysis, ABO-incompatibility was not associated with recurrence (HR 1.06, 95% CI 0.82–1.39; Table 2). After adjustment for clinical and tumor factors, the point estimate increased toward higher risk (HR 1.19, 95% CI 0.91–1.55; P = 0.21), a shift that becomes apparent only after the more favorable baseline tumor burden of the ABOi group is taken into account. Beyond-Milan status, MVI, pre-transplant treatment, tumor number and size, AFP, and PIVKA-II were the dominant independent predictors of recurrence (Table 2).

To address the baseline imbalance in tumor burden, a 1:2 propensity-matched cohort was constructed (ABOi 315: ABOc 630), with excellent covariate balance (all SMD <0.05; Table 3). In the matched cohort, RFS again did not differ between groups (5-year RFS 78.1% vs. 80.5%; log-rank P = 0.50; HR 1.11, 95% CI 0.82–1.48), confirming the absence of an overall adverse effect of ABO-incompatibility (Figure 2A).

Overall survival

Overall survival was also similar between the groups. A total of 410 deaths occurred during follow-up (333 ABOc and 77 ABOi), and the 1-, 3-, and 5-year overall survival rates were 95.6%/85.7%/81.2% in the ABOc group and 95.3%/86.4%/81.4% in the ABOi group (log-rank P = 0.91). Thus, in the whole cohort, ABO-incompatibility compromised neither recurrence-free nor overall survival, consistent with contemporary ABOi LDLT being oncologically safe on average.

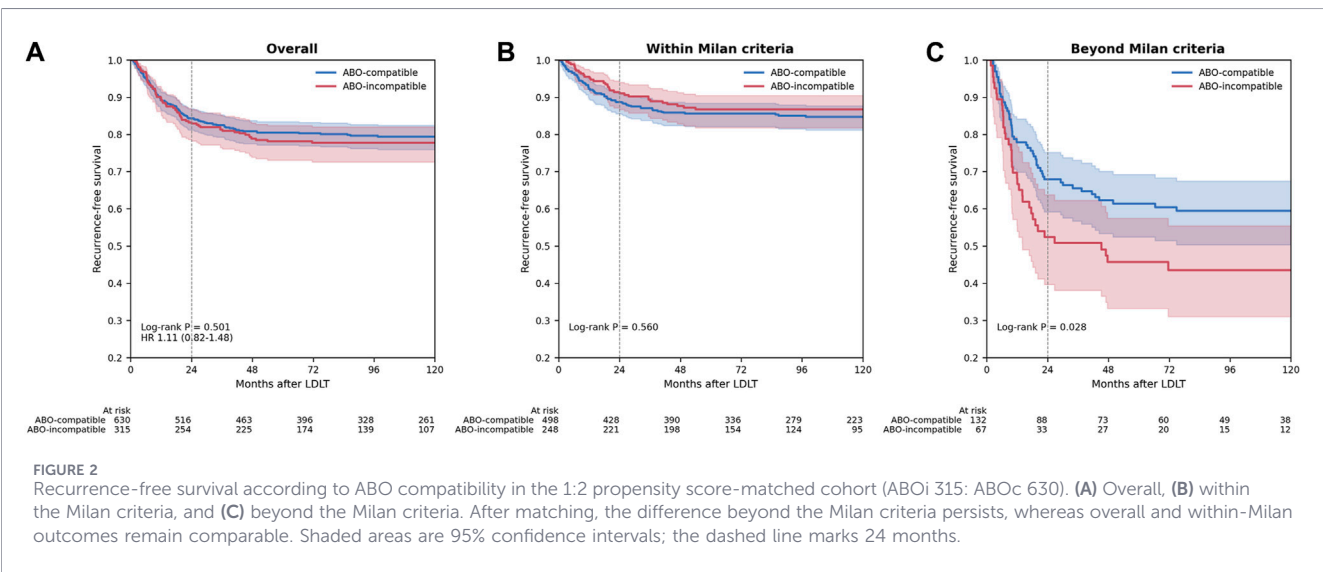
Tumor morphology (Milan criteria)

The effect of ABO-incompatibility differed according to tumor stage (Table 4). Among the 1,140 patients within the Milan criteria, 152 recurrences occurred (119 ABOc and 33 ABOi), and recurrence

TABLE 3 Propensity score-matched cohort and covariate balance before and after matching.

Covariate	ABO-compatible (n = 630)	ABO-incompatible (n = 315)	SMD before	SMD after
Beyond Milan criteria, %	21.0	21.3	−0.183	+0.008
Microvascular invasion, %	17.3	18.7	+0.030	+0.037
log10 AFP	1.00	1.00	−0.089	+0.014
log10 PIVKA-II	1.50	1.50	−0.021	+0.045
Recipient age, yr	55.0	55.0	−0.037	−0.013
Male sex, %	84.3	82.9	−0.058	−0.039
MELD score	9.0	9.0	−0.267	+0.032

Values are matched-group medians or percentages. SMD, standardized mean difference; a |SMD| <0.10 indicates acceptable balance. Covariates were matched 1:2 by nearest-neighbor matching on the logit of the propensity score (caliper 0.2 SD).



was nearly identical between groups (ABOi 13.3% vs. ABOc 13.4%; 5-year RFS 86.7% vs. 87.0%; log-rank $P = 0.93$; adjusted HR 1.00, 95% CI 0.68–1.47; Figure 1B), and this equivalence was maintained in the propensity-matched cohort (Figure 2B). Among the 433 patients beyond the Milan criteria, 177 recurrences occurred (141 ABOc and 36 AB Oi), and recurrence was significantly higher in AB Oi recipients (53.7% vs. 38.5%; 5-year RFS 45.7% vs. 63.0%; log-rank $P = 0.008$; adjusted HR 1.45, 95% CI 1.00–2.09; $P = 0.049$; Figure 1C). This difference persisted in the propensity-matched cohort (ABOi 53.7% vs. ABOc 40.2%; log-rank $P = 0.028$; Figure 2C). The multiplicative ABO-by-Milan interaction term was directionally consistent but not significant (HR 1.39; $P = 0.23$), reflecting the limited events in this subgroup (36 recurrences in 67 patients); the stratum-specific estimates are therefore best interpreted as a consistent gradient.

Tumor biology (ADV score)

Because the Milan criteria reflect only tumor size and number, we next performed a stratified analysis using a complementary, pre-specified measure of tumor biology, the AFP-DCP-volume (ADV) score, which combines serum tumor markers with tumor volume,

applying the established post-transplant cutoff of 5log [19, 20]. The results were directionally consistent with the Milan-based analysis (Table 5; Figure 3). Among patients with an ADV score below 5log, recurrence was nearly identical between groups (ABOc 14.0% vs. AB Oi 13.9%; log-rank $P = 0.94$). Among patients with an ADV score of 5log or higher, recurrence was higher in AB Oi recipients (64.0% vs. 44.6%; 5-year RFS 37.6% vs. 55.7%; log-rank $P = 0.022$), although this difference attenuated after adjustment for microvascular invasion and pre-transplant treatment (HR 1.31, 95% CI 0.88–1.93; $P = 0.18$). The continuous ADV-by-ABO interaction term approached significance ($P = 0.088$), and overall survival did not differ within either ADV stratum (ADV ≥ 5 log, log-rank $P = 0.29$). Thus, the tumor-burden-dependent effect of ABO-incompatibility was observed with an independent, biomarker-based measure of tumor burden as well as with the Milan criteria, although it remained statistically borderline. In a competing-risk analysis treating death without recurrence as a competing event, the findings were unchanged (beyond Milan: subdistribution HR 1.54, 95% CI 1.08–2.19; ADV ≥ 5 log: 1.58, 95% CI 1.07–2.32; Supplementary Table S1). The direction of effect was consistent across ADV cut-offs of 3 to 6log, reaching significance only at the pre-specified 5log threshold (Supplementary

TABLE 4 Recurrence and recurrence-free survival by ABO compatibility, stratified by the Milan criteria.

Stratum	ABOc: recurrence % (5-year RFS %)	ABOi: recurrence % (5-year RFS %)	Log-rank P	Adjusted HR for ABOi (95% CI), P
Overall (n = 1,573)	20.7 (80.0)	21.8 (78.2)	0.643	1.10 (0.85–1.44), 0.466
Within Milan (n = 1,140)	13.4 (87.0)	13.3 (86.7)	0.933	1.00 (0.68–1.47), 0.982
Beyond Milan (n = 433)	38.5 (63.0)	53.7 (45.7)	0.008	1.45 (1.00–2.09), 0.049

RFS, recurrence-free survival; HR, hazard ratio; ABOc, ABO-compatible; ABOi, ABO-incompatible. Adjusted HR for ABO-incompatibility within each stratum was derived from a Cox model including microvascular invasion, pre-transplant treatment, and log10-transformed AFP and PIVKA-II. The multiplicative ABOi-by-Milan interaction term was not statistically significant (P=0.23).

TABLE 5 Recurrence and recurrence-free survival by ABO compatibility, stratified by the ADV score (whole cohort).

Stratum	ABOc: recurrence % (5-year RFS %)	ABOi: recurrence % (5-year RFS %)	Log-rank P	Adjusted HR for ABOi (95% CI), P
ADV score <5log (n = 1,247)	14.0 (86.8)	13.9 (86.0)	0.944	1.02 (0.71–1.47), 0.921
ADV score ≥5log (n = 326)	44.6 (55.7)	64.0 (37.6)	0.022	1.31 (0.88–1.93), 0.180

RFS, recurrence-free survival; HR, hazard ratio; ADV, alpha-fetoprotein-des-gamma-carboxyprothrombin-tumor volume score. The 5log cutoff is the previously reported post-transplant threshold [19, 20]. Adjusted HR was derived from a Cox model including microvascular invasion and pre-transplant treatment; AFP, PIVKA-II, and tumor volume were not added as separate covariates because they constitute the ADV score. The continuous ADV-by-ABO interaction term was not statistically significant (P=0.088).

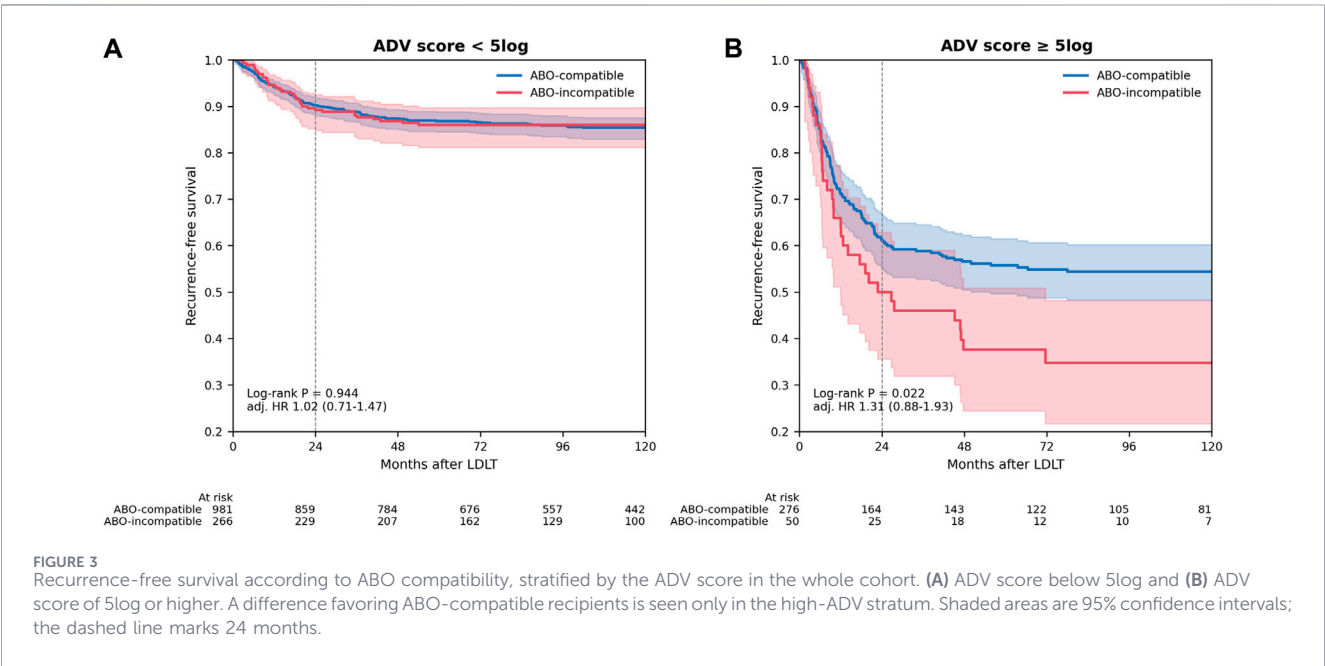


Table S2), and the results did not differ by transplant era (ABO-by-era interaction P = 0.52; Supplementary Table S3).

Timing of recurrence

Recurrences occurred early in both groups. Among patients who recurred, the median time to recurrence was similar (ABOi 12.6 vs. ABOc 11.7 months; P = 0.37), and approximately 77% of all recurrences occurred within 24 months in both groups (76.8% vs. 77.3%). ABO-incompatibility was therefore not associated with earlier recurrence. The absolute early-recurrence burden was

highest in beyond-Milan ABOi recipients (24-month recurrence 46.3% vs. 30.9%), identifying the main target for intensified surveillance.

Early tacrolimus exposure and recurrence

To explore the proposed mechanism, we examined tacrolimus trough concentrations at 1 and 3 months after transplantation, available in 1,532 and 1,526 patients, respectively. Consistent with the more intensive ABOi protocol, ABOi recipients had higher levels than ABOc recipients at both 1 month (9.5 vs.

9.1 ng/mL; $P < 0.001$) and 3 months (8.9 vs. 8.5; $P < 0.001$). A higher 1-month tacrolimus concentration was independently associated with recurrence in the whole cohort (adjusted HR 1.09 per ng/mL, 95% CI 1.01–1.19; $P = 0.03$). This association was largely confined to high tumor burden, being apparent beyond the Milan criteria (HR 1.12; $P = 0.06$) and at $ADV \geq 5\log$ (HR 1.11; $P = 0.09$) but not within Milan (HR 1.05; $P = 0.39$), although the tacrolimus-by-Milan interaction was not significant ($P = 0.54$). In an exploratory mediation analysis, the 1-month tacrolimus concentration accounted for only a small, statistically imprecise fraction of the ABO-incompatibility effect, modestly attenuating its estimate when added to the model. The association was weaker in the smaller propensity-matched cohort (HR 1.09; $P = 0.12$).

Discussion

In this large single-center cohort of HCC LDLT recipients, ABO-incompatibility had no detectable effect on recurrence in the overall population, a finding that was robust to multivariable adjustment and propensity score matching and that is consistent with previous comparative studies and a recent meta-analysis [15, 16]. The main observation of this study is that this overall null result may conceal clinically relevant heterogeneity, with the effect of ABO-incompatibility appearing to depend on tumor burden, whether assessed by tumor morphology (Milan criteria) or by tumor biology (the marker-based ADV score). Within the Milan criteria, recurrence was nearly identical between ABOi and ABOc recipients, whereas beyond the Milan criteria, ABO-incompatibility was associated with a significantly higher recurrence risk that persisted after propensity matching. To our knowledge, this is the first study to suggest that the oncologic risk of ABO-incompatibility may depend on tumor burden. Given the borderline beyond-Milan estimate and the non-significant interaction, however, this observation is hypothesis-generating.

This tumor-burden dependence is biologically plausible. ABOi recipients receive a greater early immunosuppressive load than ABOc recipients—B-cell depletion with rituximab, pretransplant plasma exchange, higher early calcineurin-inhibitor targets, and more frequent mycophenolate mofetil—all required to prevent antibody-mediated rejection [6, 8]. Because the cumulative depth of immunosuppression is a recognized, modifiable determinant of post-transplant HCC recurrence [10, 11, 13, 14], this additional burden would be expected to matter only when residual tumor is present: inconsequential in low-burden tumors, consistent with the identical within-Milan outcomes observed here, but of potential relevance beyond the Milan criteria, where micrometastatic disease is more likely and the balance between residual tumor and immune control is precarious.

Our own mechanistic evidence for this pathway is, however, limited. The between-group difference in early tacrolimus exposure was small (1-month trough 9.5 vs. 9.1 ng/mL), and although a higher 1-month level was independently associated with recurrence (adjusted HR 1.09 per ng/mL), particularly at high tumor burden, it accounted for only a small and imprecise fraction of the ABO-incompatibility effect in mediation analysis. Because the greater immunosuppression in ABOi recipients reflects not only tacrolimus but also more frequent mycophenolate mofetil use, this single-agent measure probably underestimates the total immunosuppressive load. The effect may

therefore relate to the net intensity of immunosuppression rather than the humoral alloimmune challenge itself—B-cell depletion with rituximab has not been shown to increase HCC recurrence [24], and the baseline isoagglutinin titer reflects the antibody barrier rather than a direct pro-tumoral stimulus—and is supported by independent ABOi cohorts in which recurrence tracked with early tacrolimus exposure and plasma-exchange burden [17, 18] and by an early series in which recurrence was concentrated beyond the Milan criteria [25]. These observations are consistent with, but do not establish, a causal pathway. Clinically, the principal modifiable factor in high-risk ABOi recipients may be the depth of maintenance immunosuppression rather than the desensitization itself, and this lever is most applicable beyond the early postoperative period. The proposed mechanism is hypothesis-generating and was not formally tested in this study.

The timing of recurrence has direct implications for surveillance. Recurrence occurred predominantly within the first two postoperative years in both groups, and ABO-incompatibility was not associated with earlier recurrence; the signal is one of absolute risk rather than accelerated timing, with beyond-Milan ABOi recipients carrying the highest early-recurrence burden and nearly half recurring within 24 months. These patients are strong candidates for intensified early surveillance. Under our current protocol, beyond-Milan recipients undergo imaging every 3 months during the first year and every 4–6 months thereafter; in high-burden ABOi recipients we suggest extending the 3-monthly interval through the second post-transplant year, with tumor markers at each visit, before returning to the standard schedule. This is a modest intensification of an existing protocol and should be regarded as a testable proposal. In ABOi recipients, higher early calcineurin-inhibitor exposure is largely unavoidable, constraining any early reduction in immunosuppression [12]. mTOR inhibitors may also attenuate the endothelial injury underlying antibody-mediated rejection, offering a potential dual benefit in ABOi recipients: mitigating alloimmune endothelial damage while permitting reduced calcineurin-inhibitor exposure. They have historically been avoided in the first postoperative months because of concerns about wound healing and hepatic artery thrombosis, but this concern is less clearly supported by contemporary data. Our practice has been to transition after the third month; the present findings suggest this timing warrants reconsideration in high-burden ABOi recipients, although the SILVER trial showed benefit mainly in lower-risk patients [14]. Post-transplant risk scores such as RETREAT may help refine surveillance [26, 27]. Although overall survival did not differ, earlier detection remains clinically meaningful, enabling curative-intent or timely systemic treatment.

A further consideration is that tumor burden was defined on explant pathology, which provides the most accurate assessment of tumor extent but limits direct translation to preoperative candidate selection. Notably, the ADV score is partly preoperative by construction: alpha-fetoprotein and PIVKA-II are measured before transplantation, and both retain long-term prognostic value after living donor liver transplantation [23], and tumor volume can be estimated from pre-transplant cross-sectional imaging, so a pre-transplant version is computable in principle. Systematic pre-transplant volumetry was unavailable in our

database; prospective validation of an imaging-based measure is therefore the logical next step, and until then our findings are best applied to post-transplant surveillance and immunosuppression rather than to candidate selection.

Our findings extend, rather than contradict, the existing literature. Previous series and a recent meta-analysis found no adverse oncologic effect of ABO-incompatibility, but did not formally test whether this effect varies with tumor burden or use a biologic measure of aggressiveness, and were underpowered for high-risk subgroups [15, 16]; our overall results are fully consistent with theirs. Independent series, including one combining rituximab with total plasma exchange, likewise identified AFP, tumor size, encapsulation, and microvascular invasion, not ABO status, as the relevant risk factors [24]. Using a large cohort with propensity matching and pre-specified stratified analyses, however, we found that the average safety of ABOi LDLT may conceal a clinically meaningful gradient. The consistency of this gradient across two conceptually distinct measures of tumor burden, the morphology-based Milan criteria and the marker-based ADV score, argues against a chance subgroup effect, although both analyses remained borderline [19, 20].

Strengths include the large size, explant-based pathologic staging, long follow-up, and a propensity-matched design. Limitations should also be acknowledged. First, the retrospective, single-center design carries risks of selection and residual confounding, although matching achieved excellent covariate balance. Second, the overall immunosuppressive load, including mycophenolate mofetil dosing and cumulative exposure, was not quantified, so the mechanistic and mediation analyses are exploratory. Third, the interaction term was not significant, reflecting limited events in the beyond-Milan ABOi subgroup, so the subgroup findings are hypothesis-generating and warrant external validation. Fourth, tumor burden was classified on explant pathology. Prospective studies with detailed immunosuppression-exposure data are needed to confirm the mechanism and define optimal strategies for this subgroup.

In conclusion, ABO-incompatibility did not adversely affect HCC recurrence overall but differed according to tumor burden, with a higher recurrence risk in patients with advanced tumors, defined by either the Milan criteria or the ADV score. Overall survival did not differ in any stratum. Because the formal interaction tests were not significant, these subgroup findings are hypothesis-generating and require external validation. Nevertheless, given that recurrences occur predominantly within the first two post-transplant years, ABOi recipients with advanced tumors may warrant intensified early surveillance, together with consideration of a calcineurin-inhibitor-sparing, mTOR inhibitor-based regimen beyond the early postoperative period.

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 Institutional Review Board of Asan Medical Center, University of Ulsan College

of Medicine, Seoul, Republic of Korea (IRB No. 2026-0819). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

W-HK contributed to study design, transplantation surgeries, data collection, statistical analysis, and drafting of the manuscript as the first author. SH contributed to study design, performed transplantation surgeries, critically revised the manuscript, and served as the corresponding author with final responsibility for the research. D-BM, C-SA, K-HK, D-HJ, T-YH, G-WS, G-CP, S-GL, Y-IY, B-GN, S-HK, and S-MK performed or assisted in transplantation surgeries, provided operative expertise, contributed to perioperative clinical decision-making, and participated in data acquisition. All authors contributed to the article and approved the submitted version.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontierspartnerships.org/articles/10.3389/ti.2026.17121/full#supplementary-material>

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Abdominal normothermic regional perfusion is associated with improved graft survival in liver transplantation from circulatory death donors

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Advanced preservation strategies are increasingly used in liver transplantation following donation after circulatory death (DCD). This nationwide observational study evaluated the association between abdominal normothermic regional perfusion (A-NRP) and 1-year graft survival in a Swiss cohort of 254 DCD liver transplants performed between 2017 and 2023. Recovery strategies compared included A-NRP and super-rapid recovery (SRR), both predominantly followed by end-ischemic hypothermic oxygenated perfusion (HOPE). Primary endpoint was 1-year graft loss; secondary endpoints included 1-year patient mortality, primary non-function, non-anastomotic strictures (NAS), biliary and vascular complications and need for re-transplantation. Overall, 53 grafts were retrieved using A-NRP (71% followed by HOPE) and 201 using SRR (90% followed by HOPE). Compared with SRR, A-NRP grafts demonstrated lower rates of graft loss (5.7% vs. 24.6%), 1-year mortality (1.9% vs. 13.3%), NAS (5.7% vs. 20.5%), other biliary complications (1.9% vs. 12.6%) and re-transplantation (3.8% vs. 12.8%). In multivariable Cox regression analysis, A-NRP was associated with lower risk of 1-year graft loss and patient mortality after

adjustment for UK DCD risk category and HOPE use. These findings suggest that A-NRP is associated with improved outcomes. Further studies are needed to define the role of *ex-situ* perfusion after A-NRP in optimizing results.

KEYWORDS

donation after circulatory death donor, end-ischemic hypothermic oxygenated perfusion, ischemic cholangiopathy, liver transplantation, normothermic regional perfusion

Introduction

Donation after circulatory death (DCD) has significantly expanded the donor pool, helping to address the persistent shortage of transplantable organs.

However, early experiences using super-rapid recovery (SRR) and static cold storage (SCS) yielded suboptimal outcomes, with higher rates of biliary complications and inferior graft survival compared with grafts from donation after brain death (DBD) [1, 2]. These inferior results were largely attributed to the additional functional warm ischemia time (fWIT) inherent to DCD, which exacerbates ischemia-reperfusion injury, particularly when combined with additional risk factors such as cold ischemia time (CIT) > 6 h, donor age > 50 years, macrovesicular steatosis > 30%, donor body mass index (BMI) > 30 kg/m² and complex recipient profiles (e.g., Model for End-Stage Liver Disease (MELD) score > 25 points, portal vein thrombosis or re-transplantation) [3].

The implementation of more restrictive selection criteria and predictive tools such as the UK DCD Risk Score [4], has enabled safer use of DCD grafts with results approaching those of DBD transplantation [5].

More recently, the introduction of advanced perfusion strategies including *in-situ* abdominal normothermic regional perfusion (A-NRP) and *ex-situ* preservation techniques such as normothermic machine perfusion (NMP) and hypothermic oxygenated machine perfusion (HOPE), has improved graft viability, thereby permitting broader utilization of marginal DCD donors [6–10].

In Switzerland, DCD donors currently represent nearly 35% of all liver transplants and this proportion is steadily increasing [11]. While HOPE has become the standard for *ex-situ* preservation, A-NRP is not uniformly implemented across procurement centers, with SRR still being the predominant retrieval technique for DCD livers.

This nationwide study compares outcomes of DCD liver transplantation using A-NRP versus conventional SRR, with both approaches most often combined with end-ischemic HOPE. By

auditing real-world practice, we aim to provide evidence to inform future standardization of retrieval and preservation and offer practical insights for centers considering a transition to NRP and perfusion-based preservation strategies.

Materials and methods

Study design and population

This observational cohort study included all adult DCD liver transplantations performed in Switzerland between 1 January 2017, and 31 December 2023, with outcomes evaluated through to 31 December 2024.

Switzerland comprises 10 procurement hospitals and three liver transplantation centers. Each donor hospital applied its own procurement strategy for abdominal organ recovery, either SRR or A-NRP. During the study period, A-NRP was performed exclusively at one of the three Swiss transplant centers. Livers recovered under A-NRP were subsequently allocated among the three centers and, in selected cases, transferred to collaborating transplant programs in northern Italy through the established Swiss–Italian organ sharing agreement. In both procurement settings, use of HOPE was protocolized and performed as part of routine practice. Its omission in some cases was solely due to logistical constraints rather than based on selective, case-by-case clinical judgment or graft-related factors.

At most centers, graft acceptance was guided by the UK DCD Risk Score [4] with predefined rejection thresholds set at > 10 points for externally retrieved donors and at > 11 for local donors. Donors older than 70 years were deemed ineligible. In contrast, one center primarily based graft acceptance on *ex-situ* viability assessment during HOPE [12] without age restrictions. Liver biopsy was performed in cases where there was concern regarding donor marginality based on donor comorbidities. A cut-off of 30% macrovesicular steatosis was adopted by the centers as a criterion for organ refusal.

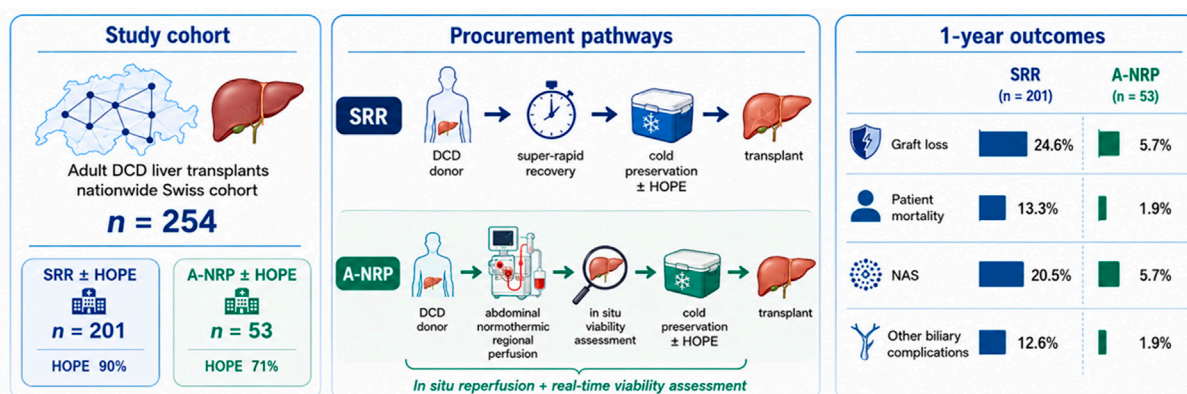
For grafts recovered using A-NRP, *in-situ* viability was assessed according to the biochemical criteria detailed in the “A-NRP Biochemical Assessment” section.

At the time of listing, each transplant center independently evaluated recipient eligibility for DCD liver transplantation according to local clinical protocols.

If the graft was declined by all Swiss centers according to local acceptance criteria, it was offered to Italian partner centers through the established Swiss–Italian organ sharing agreement, where final acceptance was determined according to the receiving center’s own clinical assessment and allocation framework. The study was conducted in accordance with the Declaration of Helsinki and the Declaration of Istanbul and was approved by the Institutional Ethics Committee of Geneva (BASEC 2022-00515). Recipient-level

Abbreviations: A-NRP, Abdominal Normothermic Regional Perfusion; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; BMI, Body Mass Index; CI, Confidence Interval; CIT, Cold Ischemia Time; DCD, Donation after Circulatory Death; DBD, Donation after Brain Death; ECG, Electrocardiogram; FMN, Flavin Mononucleotide; fWIT, Functional Warm Ischemia Time; HOPE, Hypothermic Oxygenated Machine Perfusion; ICU, Intensive Care Unit; IQR, Interquartile Range; LT, Liver Transplantation; MAP, Mean Arterial Pressure; MELD, Model for End-Stage Liver Disease; NAS, Non-Anastomotic Stricture; NMP, Normothermic Machine Perfusion; NRP, Normothermic Regional Perfusion; PNF, Primary Non-Function; RCT, Randomized Controlled Trial; RRT, Renal Replacement Therapy; SRR, Super-Rapid Recovery; SOAS, Swiss Organ Allocation System; STCS, Swiss Transplant Cohort Study; TTE, Transthoracic Echocardiography; UK DCD Risk Score, United Kingdom DCD Risk Score.

Abdominal normothermic regional perfusion is associated with improved graft survival in liver transplantation from circulatory death donors



A-NRP was associated with improved graft and patient outcomes despite the widespread use of HOPE. The added value of end-ischemic HOPE after A-NRP remains unresolved.



GRAPHICAL ABSTRACT

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outcome data from grafts transplanted in Italy were provided by the collaborating Italian transplant program in accordance with its local ethics-approved retrospective liver transplant registry and recipient consent framework. Italian recipients had provided informed consent for data collection and research use, including DCD liver transplantation and machine perfusion. Data shared for the present analysis were coded and contained no directly identifying information (Registry number: 202-30032022).

Data sources and variables

Recipient data were extracted from the Swiss Transplant Cohort Study (STCS-FUP 173) database, while donor-related data were obtained from the Swiss Organ Allocation System (SOAS). Missing data were retrieved directly from transplant centers.

The following donor variables were recorded: age, sex, BMI. Graft-specific parameters included functional warm ischemia time (fWIT), defined according to Swiss national DCD standards, as the interval between sustained donor MAP <50 mmHg and cold perfusion in SRR or initiation of A-NRP in perfused donors; peripheral oxygen saturation was not included in the definition of fWIT under national guidelines during the study period. Cold ischemia time (CIT) was defined as the period between the *in-situ* cold flush of the donor liver and portal vein unclamping in the recipient. Time spent on machine perfusion was not included in the CIT calculation. Recipient variables included: age, sex, BMI, laboratory MELD score at the time of transplantation and the UK DCD Risk Score [4]. Post-transplant outcomes were assessed at 1 year and included primary non-function (PNF), non-anastomotic biliary strictures

(NAS), anastomotic strictures (AS), other biliary complications, arterial complications, re-transplantation, and patient death.

PNF was defined as irreversible graft failure leading to re-transplantation or death within the first 7 days post-transplantation. NAS was defined by the presence of a patent hepatic artery associated with clinical and biochemical signs of cholestasis, and imaging evidence of intra- and/or extrahepatic biliary strictures [13].

Study end points

The primary endpoint of this study was 1-year graft loss, defined as graft failure resulting in re-transplantation or patient death within 1 year after transplantation. This outcome was compared between recipients of liver grafts recovered via A-NRP with or without HOPE and those retrieved using SRR with or without HOPE.

Secondary endpoints included all-cause mortality within 1 year post-transplantation, PNF, biliary complications (including both non-anastomotic and anastomotic biliary strictures, bile duct stones or casts and biliary leaks), hepatic artery thrombosis (HAT) and hepatic artery stenosis (HAS) and re-transplantation, within 1 year of the index procedure.

DCD recovery methods

DCD donor preparation

The process of DCD donor identification is described in the [Supplementary Material S1](#). On the day of the procedure, the donor was transferred to a dedicated room for therapeutic withdrawal. Fifteen minutes before extubation, intravenous heparin (300 IU/kg) was administered. A sustained drop in mean arterial pressure below

50 mmHg for more than 2 min marked the onset of the fWIT. Cardiac arrest was confirmed by electrocardiographic asystole and the absence of cardiac motion on transthoracic echocardiography (TTE). A mandatory 5-min “no-touch” period was observed. Once death was legally declared, organ recovery was initiated using one of two techniques: SRR or A-NRP.

Super-rapid recovery (SRR)

A midline laparotomy was performed. The thoracic cavity was not routinely opened before initiation of abdominal cold perfusion for liver recovery. The distal abdominal aorta was cannulated, the supra-celiac aorta was clamped, and cold perfusion was initiated using a 4 °C preservation solution, vented through the inferior vena cava. This step marked the end of the warm ischemia period and the start of cold ischemia. The abdominal cavity was then packed with sterile ice, and the liver was recovered as quickly as possible according to standard surgical protocols.

Abdominal normothermic regional perfusion (A-NRP)

The procedure was explained to the family on the day preceding retrieval, and consent was obtained. Since 2021, femoral vessel catheters have been placed prior to death confirmation under ultrasound guidance. Once cardiac arrest occurred, family members present were accompanied out of the unit by a staff member, and the donor was transferred to a nearby room pre-equipped for A-NRP. After legal confirmation of death, the ICU team performed cannulation for A-NRP, initially under ultrasound guidance, visualizing the inferior vena cava and abdominal aorta for guidewire placement, cannula insertion and occlusion balloon placement, and, since 2022, under fluoroscopic guidance.

Once vascular access was established and the occlusion balloon was correctly positioned and inflated, no surgical clamping of the aorta was performed, and no venting procedure was used. Correct balloon positioning and complete exclusion of cerebral reperfusion were verified by continuous invasive monitoring of the radial arterial pressure, which was required to remain <20 mmHg throughout A-NRP.

A-NRP was then initiated. Target parameters included a blood flow of 3–4 L/min, MAP 50–70 mmHg, temperature of 36 °C–37 °C, abdominal PaO₂ > 20 kPa, and PaCO₂ 4–5 kPa. Hemoglobin level was maintained > 60 g/L, with red blood cell transfusions as required. Blood pressure and A-NRP flow were maintained with norepinephrine and 0.9% NaCl fluid infusions. Arterial blood gases were analyzed every 30 min from A-NRP initiation and hepatic transaminases, and Factor V were measured hourly.

After typically 90–120 min of A-NRP, the donor was transferred to the operating room for organ recovery. Hepatectomy was performed according to standard surgical protocols. Once the liver was ready for retrieval, A-NRP was discontinued, and the same circuit was used for cold perfusion (4 °C) with IGL® solution.

A-NRP biochemical assessment

Arterial blood gas analysis was obtained at the onset of A-NRP and repeated every 30 min until the start of cold perfusion with IGL® solution. Liver transaminases (AST and ALT) were measured

after the first hour of A-NRP and subsequently every hour until the termination of the perfusion.

Criteria for early termination of the A-NRP procedure were predefined in the institutional protocol. Hepatic perfusion was considered inadequate in the presence of a sustained increase in transaminase levels and/or the absence of a clear downward trend in arterial lactate concentration during perfusion. Because no validated thresholds for transaminases and lactate dynamics during A-NRP exist in the published literature, decisions were based on the overall biochemical evolution rather than on fixed numerical cut-offs.

Organ transport and post-recovery protocol

Regardless of the procurement technique, all liver grafts were placed in sterile, temperature-controlled transport containers and transferred to the recipient center under cold preservation conditions. In most cases, the graft subsequently underwent HOPE for approximately 120 min before implantation.

Ex-vivo HOPE

Following back-table preparation, HOPE was performed using the Liver Assist® device (Organ Assist B.V., Groningen, Netherlands) in two centers and the VitaSmart™ (Bridge to Life™ Ltd., CE-marked) in one center. The use of HOPE was protocolized across all three participating centers and was performed as part of routine practice. Its omission in some cases was solely due to logistical constraints; otherwise, it was systematically applied rather than based on selective, case-by-case clinical judgment or graft-related factors. *Ex-situ* liver perfusion was performed via the portal vein only, under active oxygenation and controlled low-pressure and low-flow (3 mmHg, 150–250 mL/min). All HOPE procedures in this study utilized the University of Wisconsin Machine Perfusion solution (Belzer MPS, Bridge to Life™) as perfusate. In one center, liver graft quality was additionally assessed after 30 min of perfusion by fluorescence spectroscopic analysis of the perfusate, as previously described [2].

Statistical analysis

Patients were categorized according to the organ procurement technique: SRR or A-NRP. Categorical variables were reported as absolute counts (n) and percentages (%), while continuous variables were expressed as medians with interquartile ranges (IQR). Comparisons between groups were performed using the Chi-squared or Fisher exact tests for categorical variables as appropriate, and the Mann-Whitney U test was used for continuous variables. One-year patient survival and graft loss were estimated using the Kaplan-Meier method and compared using a log-rank test. To evaluate the association between the use of A-NRP (compared with SRR) and the risk of graft loss and mortality within 1-year, a Cox proportional hazards regression model was fitted. Because organ preservation method (HOPE vs. SCS) differed between procurement strategies and may independently influence graft outcomes, we treated preservation method as a separate binary covariate in all multivariable models, together with the UK DCD Risk Score, which was specified *a priori*. Given the limited number of outcome events, multivariable

TABLE 1 Patient characteristics.

N = 254	SRR (n = 201)	A-NRP (n = 53)	p
Donor characteristics			
Age, median (IQR)	60 (49.0–71.0)	61 (52.0–69.0)	0.892
BMI, median (IQR)	25.7 (23.6–27.8)	26 (23.0–29.4)	0.954
Hepatectomy time, (median IQR)	41.5 (29.7–55.0)	45.5 (36.0–54.5)	0.178
Recipient characteristics			
Age, median (IQR)	60 (53.0–64.0)	60 (55.6–64.0)	0.430
Sex, Male n (%)	159 (79.0%)	44 (83.0%)	0.66
MELD, median (IQR)	12 (8–19)	11 (8–18)	0.528
Surgery details			
Transplant center, n (%)			
-Bern	32 (15.9%)	15 (28.3%)	<0.01
-GE	47 (23.4%)	12 (22.6%)	
-ZH	122 (60.7%)	20 (37.7%)	
-Italy	0 (0%)	6 (11.3%)	
HOPE, n (%)	181 (90.0%)	38 (71.7%)	<0.001
Functional warm ischemia, median (IQR)	24 (18–29)	26 (22–29)	0.155
Total cold ischemia time (minutes), median (IQR)	370 (270–474)	377 (317–480)	0.211
UK DCD risk score, median (IQR)	8 (6–10)	8 (6–10)	0.429
UK DCD risk group, n (%)			
-Futile	49 (24.4%)	14 (26.42%)	0.552
-High risk	108 (53.7%)	31 (58.5%)	
-Low risk	44 (21.9%)	8 (15.1%)	

Chi-2, or Fisher-exact for categorical variables, Wilcoxon Ranksum test for continuous variables.

adjustment was intentionally restricted to clinically prespecified covariates rather than based on univariable screening, to reduce the risk of overfitting. A two-sided p -value ≤ 0.05 was considered statistically significant. As a sensitivity analysis, we performed a propensity score–based inverse probability of treatment weighting (IPTW) analysis. The propensity score estimated the probability of receiving A-NRP using HOPE use, UK DCD risk category and transplant era as a proxy for temporal learning-curve effects. Stabilized weights were applied in Cox proportional hazards models with robust standard errors. Covariate balance before and after weighting was assessed using standardized mean differences and displayed in a love plot. All statistical analyses were performed with Stata version 16.0 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

This nationwide cohort included 262 adult liver transplants from DCD donors performed between 2017 and 2023. Of these, 8 patients were excluded from the analysis due to missing data and/or absence of informed consent. Of the remaining 254, 201 grafts (79.1%) were procured using SRR and 53 (20.9%) using A-NRP.

Additional HOPE was applied in 181 grafts of the SRR group (90%), and 38 cases (71.7%) of the A-NRP group ($p < 0.001$) (Table 1).

All A-NRP procedures considered for liver recovery were successfully completed, with no conversion to SRR. No A-NRP graft was excluded or reclassified because of technical failure, inadequate regional perfusion, or unfavorable biochemical evolution during perfusion.

Donor characteristics were comparable between groups. Median donor age was 60 years (IQR 49–71) in the SRR group and 61 years (IQR 52–69) in the A-NRP group. Median BMI was 25.7 kg/m² (IQR 23.6–27.8) and 26 kg/m² (IQR 23.0–29.4), respectively.

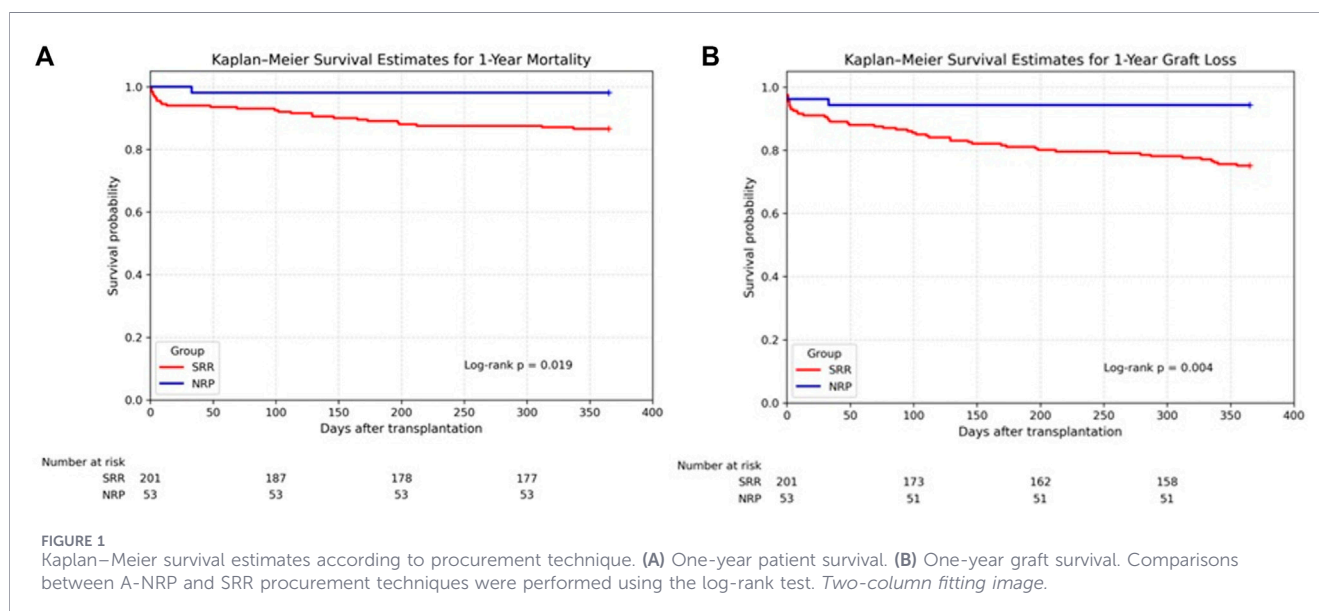
Median fWIT did not differ significantly between groups, 24 min (IQR 18–29) for SRR and 26 min (IQR 22–29) for A-NRP ($p = 0.155$). Similarly, total CIT was comparable: 370 min (IQR 270–467) for SRR and 377 (325–480) for A-NRP ($p = 0.211$).

Recipient demographics were also well balanced. The majority were male (79% in the SRR group and 83% in the A-NRP group, $p = 0.66$), with a median age of 60 years in both groups ($p = 0.403$). Median MELD score at transplantation was 12 (IQR 8–19) for SRR and 11 (IQR 8–18) for A-NRP ($p = 0.528$). The median UK DCD Risk Score was 8 (IQR 6–10) in both groups ($p = 0.429$). In both groups, approximately 25% of grafts were classified as futile, despite two of the centers having set a cutoff of 10 for organ acceptance.

TABLE 2 Patient outcomes.

N = 254	SRR (n = 201)	A-NRP (n = 53)	p
Primary non-function, n (%)	13 (6.40%)	2 (3.77%)	0.468
Graft loss at 1-year, n (%)	50 (24.63%)	3 (5.66%)	0.002
Biliary non-anastomotic stenosis, n (%) - 3 missing (3 SRR)	41 (20.50%)	3 (5.66%)	0.011
Other biliary complications, n (%) - 4 missing (4 SRR)	25 (12.56%)	1 (1.89%)	0.023
Hepatic artery thrombosis, n (%) - 1 missing (1 A-NRP)	6 (2.96%)	2 (3.85%)	0.742
Hepatic artery stenosis, n (%)	11 (5.42%)	1 (1.89%)	0.279
Re-transplantation, n (%)	26 (12.81%)	2 (3.77%)	0.061
Death at 1-year, n (%)	27 (13.30%)	1 (1.89%)	0.018

Fisher exact test for categorical variables.



Most transplants were performed at the largest participating center (55.9%), followed by two medium-sized centers (23.2% and 18.5%). A small proportion of recovered organs (2.3%) included in the present study were ultimately transplanted abroad.

Patient outcomes

At 1-year post-transplantation, 20.8% (53/254) of patients experienced graft loss, 17.3% (44/254) developed NAS, 10.2% (26/254) presented with other biliary complications, 5.9% (15/254) developed PNF, 11% (28/254) required re-transplantation, and 11% (28/254) ultimately died.

Across all major outcomes, adverse events were more frequent among recipients of grafts procured via SRR compared to those recovered using A-NRP (Table 2).

One-year graft loss occurred in 24.6% of SRR +/- HOPE cases (of which 17% were attributable to PNF or NAS), versus 5.7% in the A-NRP +/- HOPE group (all due to PNF or NAS; $p = 0.002$).

NAS were observed in 20.5% of SRR recipients versus 5.7% in the A-NRP group ($p = 0.011$) (Supplementary Figure S1), while

other biliary complications affected 12.6% of SRR grafts compared to 1.89% of A-NRP grafts ($p = 0.023$).

The need for re-transplantation was higher in the SRR group (12.8%) compared with the A-NRP group (3.8%), though this difference did not reach statistical significance ($p = 0.061$). One-year mortality was significantly higher among SRR recipients (13.3%) than among A-NRP recipients (1.9%, $p = 0.018$).

Kaplan-Meier survival analysis demonstrated significantly improved graft and patient survival in the A-NRP group compared to SRR (Figure 1). In multivariable Cox regression analysis adjusted for UK DCD Risk Score and for the use of HOPE (Table 3), A-NRP was associated with a lower risk of 1-year graft loss (HR 0.20, 95% CI 0.06–0.67, $p = 0.008$) and 1-year mortality (HR 0.11, 95% CI 0.02–0.85, $p = 0.034$). In the propensity score-based IPTW sensitivity analysis including HOPE use, UK DCD risk category, and transplant era, A-NRP remained associated with a lower risk of 1-year graft loss (HR 0.28, 95% CI 0.08–0.95, $p = 0.040$). The mortality estimate remained directionally consistent with the primary analysis but was no longer statistically significant (HR 0.21, 95% CI 0.03–1.56, $p =$

TABLE 3 Survival analysis.

N = 254		HR for 1-year death (95% CI)	p
Univariable			
A-NRP		0.13 (0.02-0.98)	0.047
Multivariable			
A-NRP		0.11 (0.02-0.85)	0.034
HOPE (yes)		0.60 (0.20-1.77)	0.356
UK DCD classification			
Low-risk		Reference	
High risk		1.41 (0.46-4.33)	0.551
Futile		2.81 (0.88-8.95)	0.080
N = 254		HR for 1-year graft loss (95% CI)	p
Univariable			
A-NRP		0.21 (0.07-0.67)	<0.01
Multivariable			
A-NRP		0.20 (0.06-0.67)	<0.01
HOPE (yes)		0.96 (0.41-2.29)	0.941
UK DCD classification			
Low-risk		Reference	
High risk		1.18 (0.57-2.43)	0.645
Futile		1.27 (0.56-2.86)	0.571

Cox regression analysis.

0.129), reflecting the limited number of mortality events in the A-NRP group (Supplementary Table S1). Covariate balance improved after IPTW, although residual imbalance persisted for transplant era (Supplementary Figure S2).

Organ utilization rate

The exploratory organ utilization analysis is presented in the Supplementary Material S2. Importantly, no organ was discarded because of the use of A-NRP itself or because of an A-NRP-related technical or perfusion complication.

Trend of biochemical biomarkers during A-NRP

Supplementary Figures S3, S4 show the trends of biochemical biomarkers during A-NRP stratified by transplant outcomes and UK DCD Risk Score. Notably we observed a modest influence of ‘donor quality’ stratified according to UK DCD Risk Score on biomarkers during perfusion, as well as weak stratification according to outcomes.

Discussion

In this nationwide Swiss multicenter cohort study, we compared outcomes of DCD liver transplantation following A-NRP versus conventional SRR, both predominantly combined with HOPE. To our knowledge, this is one of the largest contemporary analyses on

this topic and uniquely includes detailed documentation of HOPE utilization. Consistent with previous studies and recent meta-analyses, A-NRP was associated with a reduced risk of 1-year graft loss compared with SRR, mainly driven by lower rates of PNF and NAS [9, 14, 15]. This association remained significant after adjustment for HOPE use and UK DCD Risk Score and was further supported by an IPTW sensitivity analysis accounting for HOPE use, UK DCD risk category, and transplant era.

When benchmarked against internationally accepted outcome thresholds for DCD liver transplantation [16], A-NRP-retrieved grafts met expectations, with 1-year graft loss and NAS rates of 5.7%, and a 1-year patient mortality of 1.9%. In contrast, SRR +/- HOPE exceeded benchmark thresholds across all parameters. These poorer outcomes may partly reflect the early phase of our DCD program, when extended-criteria grafts were used during the early learning curve. These results are less favorable than the Schlegel benchmarks, which are based on low-risk DCD populations and experience from high-volume centers [16].

A-NRP was associated with lower 1-year graft loss and patient mortality in the primary multivariable analysis adjusted for HOPE and the UK DCD Risk Score. This association was further explored in the IPTW sensitivity analysis including HOPE use, UK DCD risk category, and transplant era, in which the association with lower graft loss remained statistically significant, whereas the association with mortality remained directionally consistent but lost statistical significance, likely due to the low number of deaths in the A-NRP group. These findings should therefore be interpreted as supportive rather than definitive evidence of an independent effect of A-NRP. Together, they support further structured implementation and prospective evaluation of A-NRP within standardized DCD programs.

Whether end-ischemic HOPE following A-NRP provides additional benefit remains uncertain. Recent multicenter observational data suggest a potential synergistic effect [17]. In addition, national data from Italy, where the combination of A-NRP and HOPE is routinely used, reported lower rates of post-transplant acute kidney injury [18].

Several European countries, including France, Italy, and Norway, have integrated A-NRP into national DCD procurement pathway [19] while Spain increasingly favors A-NRP over SRR [8]. In contrast, North American experience remains limited, with only a few pioneering centers having developed A-NRP programs [14, 20]. Unlike much of the existing literature, often derived from high-volume expert centers with highly selective donor practices, our study reflects real-world conditions in which both SRR and A-NRP are actively practiced, enhancing the external validity of our findings.

A major advantage of A-NRP over SRR is the ability to enable real-time functional graft assessment during perfusion. By restoring oxygenated blood flow after circulatory arrest, A-NRP creates a physiological window for *in-situ* viability assessment. Although recent ELITA consensus guidelines acknowledge this advantage, substantial variability persists in the viability parameters used, and no universally accepted thresholds exist [21]. According to ELITA consensus recommendations, key assessment parameters during A-NRP should include macroscopic appearance, transaminase kinetics, and lactate clearance [21]. Emerging biomarkers during *ex-situ* perfusion such as flavin mononucleotide (FMN), a marker of mitochondrial injury, may further refine viability assessment [22, 23].

Several limitations must be acknowledged. Causal inference is limited by the observational design and non-random allocation of procurement strategies, with potential residual confounding despite adjustment. Randomized evaluation is challenging in this setting, where procurement and allocation strategies are increasingly individualized and risk-adapted [24]. A-NRP was routinely performed in only one national DCD procurement center; therefore, center-, team-, era-, donor-selection, preservation-strategy, and HOPE-related effects cannot be fully disentangled from the effect of A-NRP, despite national allocation of A-NRP-retrieved grafts. Although transplant era was included in the IPTW analysis to partly account for learning-curve effects, residual temporal and practice-related confounding cannot be excluded. Survival analyses were limited by the low number of events in the A-NRP cohort, particularly for mortality, resulting in wide confidence intervals. This was reflected in the IPTW sensitivity analysis, in which the mortality estimate remained directionally consistent but was no longer statistically significant. Follow-up was limited to 1 year, precluding assessment of longer-term outcomes. Finally, although the present study focused on liver outcomes, A-NRP should not be regarded as a liver-directed intervention only. By restoring abdominal circulation, A-NRP may also affect the assessment, utilization, and outcomes of kidneys and pancreas, as well as the coordination of thoracic recovery workflows when lungs or heart are considered. Non-liver recipient outcomes were not evaluated, but no organ was discarded because of an A-NRP-related technical or perfusion complication. Future national studies should evaluate the broader impact of A-NRP on overall organ utilization, non-liver graft outcomes, logistics, and costs.

Despite these limitations, this nationwide study provides important insights for the development of DCD liver transplantation programs. The favorable outcomes associated with A-NRP support further structured implementation and prospective evaluation within standardized DCD pathways. The study also highlights the need for harmonized procurement and preservation protocols and structured viability assessment criteria to facilitate the dissemination of best practices. Whether grafts recovered using A-NRP derive additional benefit from end-ischemic HOPE remains unresolved and warrants prospective investigation. Collectively, these measures may improve organ utilization, reduce discards, and optimize long-term outcomes in DCD liver transplantation.

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 study was conducted in accordance with the Declaration of Helsinki and the Declaration of Istanbul and was approved by the Institutional Ethics Committee of Geneva (BASEC 2022-00515). Recipient-level outcome data from grafts transplanted in Italy were provided by the collaborating Italian transplant program in accordance with its local ethics-approved retrospective liver transplant registry and recipient consent framework. Italian recipients had provided informed

consent for data collection and research use, including DCD liver transplantation and machine perfusion. Data shared for the present analysis were coded and contained no directly identifying information (Registry number: 202-30032022).

Author contributions

Concept and study design: GM, HW, and RG. Data collection: GM, HW, AS, BM, VB, JV, AD, MK, PT, and RG. Data management and verification: GM, HW, PT, AP, MK, NS, and RG. Statistical analysis: GM, HW, BM, and RG. Interpretation of data: GM, HW, BM, CT, BA, KB, PC, and RG. Clinical coordination and national data integration: GM, BM, MK, NS, FI, NS, and RD. Critical revision of the manuscript for important intellectual content: All authors. Manuscript drafting: GM, HW, BM, and NG with major input from PC and RG. Supervision and senior authorship: RG. GM and HW contributed equally and share co – first authorship. RG is the senior author of this work. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontierspartnerships.org/articles/10.3389/ti.2026.16004/full#supplementary-material>



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Improving outcomes in donation after circulatory death vs. donation after brain death liver transplantation for acute-on-chronic liver failure

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Acute-on-chronic liver failure (ACLF) carries high short-term mortality, and liver transplantation (LT) remains the curative treatment. Donation after circulatory death (DCD) grafts expand the donor pool but carry higher risks of dysfunction compared to donation after brain death (DBD) grafts, and data directly comparing their outcomes in ACLF are limited. Using the Scientific Registry of Transplant Recipients (SRTR), we conducted a retrospective cohort study of 67,201 adult LT recipients from 2004 to 2023, stratified into three eras (Era 1: 2004–2012, Era 2: 2013–2018, Era 3: 2019–2023). Patients with prior LT, fulminant liver failure (status 1A), active hepatocellular carcinoma, or multivisceral transplants (excluding liver-kidney) were excluded. Estimated ACLF (EST-ACLF) severity was defined using EASL-CLIF criteria. One-year graft failure and survival were assessed using multivariable Cox regression and Kaplan-Meier analyses. Of 67,201 recipients, 62,510 received DBD and 4,691 DCD grafts. DCD grafts did not show clinically meaningful differences in 1-year hazards of graft failure compared to DBD grafts. One-year graft survival in EST-ACLF-2/3 improved over time from 87.2% in Era 1–96.0% in Era 3, approaching the 97.5% observed with DBD grafts. DCD grafts may represent a viable and increasingly safe strategy for expanding LT access in ACLF.

KEYWORDS

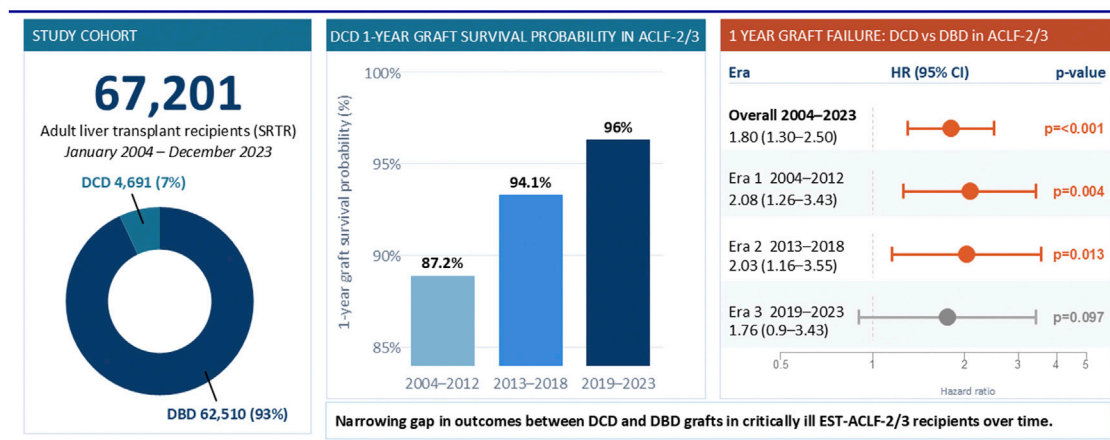
graft failure, graft survival, liver grafts, liver transplant, survival analysis

Introduction

Acute-on-chronic liver failure (ACLF) is a systemic syndrome with high 28-day mortality characterized by acute hepatic deterioration and extrahepatic organ failure (OF) in patients with cirrhosis or chronic liver disease [1–3]. ACLF severity is commonly graded by the European Association for the Study of the Liver–Chronic Liver Failure (EASL-CLIF) consortium criteria, which is based on the number of OFs [4]. ACLF grade 3 (ACLF-3), defined as three or more OFs, has a poor prognosis with 28-day mortality of up to 80% for those who do not receive a liver transplant (LT) [5–7]. Improving access to LT is the only option for long-term survival [8–10].

In the context of donor liver shortages, donation after circulatory death (DCD) grafts have played a role in increasing the availability of LT organs and improving waitlist outcomes [11]. However, the utility of DCD grafts is controversial [12, 13]. DCD liver grafts are associated with higher rates of early allograft dysfunction and ischemic cholangiopathy

Improving outcomes in donation after circulatory death (DCD) vs donation after brain death (DBD) liver transplantation for acute-on-chronic liver failure (ACLF)



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GRAPHICAL ABSTRACT

compared to donation after brain death (DBD) grafts, but patient-centered outcomes such as days alive and out of hospital, graft failure, re-transplantation, and 1-year mortality are similar between the two groups [14–16]. DCD grafts are more likely to be discarded, and DCD recipients have a higher risk of graft loss compared to DBD recipients [17, 18]. Five-year mortality is modestly higher for DCD recipients, but survival remains acceptable [11]. DCD livers remain underutilized in the United States (US), with significant center-level variation, although high-utilization centers achieve similar 1-year patient and graft survival as low-utilization centers, suggesting that careful selection and center experience mitigate risk [19].

The use of DCD grafts may be the most feasible option to ensure timely LT, especially in ACLF-3 patients with high waitlist mortality [20]. The current system of allocation based on the model of end-stage liver disease (MELD) or MELD-Na may disadvantage ACLF patients by failing to capture extrahepatic OFs [21]. In a recent analysis of the Organ Procurement and Transplantation Network and United Network for Organ Sharing (OPTN/UNOS), Kitajima et al. found that DCD grafts in patients with ACLF were a risk factor for patient death within 1 year [22]. However, these studies did not directly compare outcomes between DCD and DBD grafts in patients with ACLF.

To our knowledge, there are no studies that directly compare DCD to DBD grafts in ACLF. Examining the utility of DCD grafts

for ACLF is important for expanding the donor pool and improving waitlist mortality [20]. This is relevant with the advent of perfusion technologies which may significantly increase the utility of DCD grafts [23]. This study aimed to investigate 1-year post-LT outcomes in ACLF, specifically in graft failure and survival probability, after the use of DCD compared to DBD grafts.

Materials and methods

Ethics

The study was deemed as exempt from review by the institutional review board. The study followed the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.

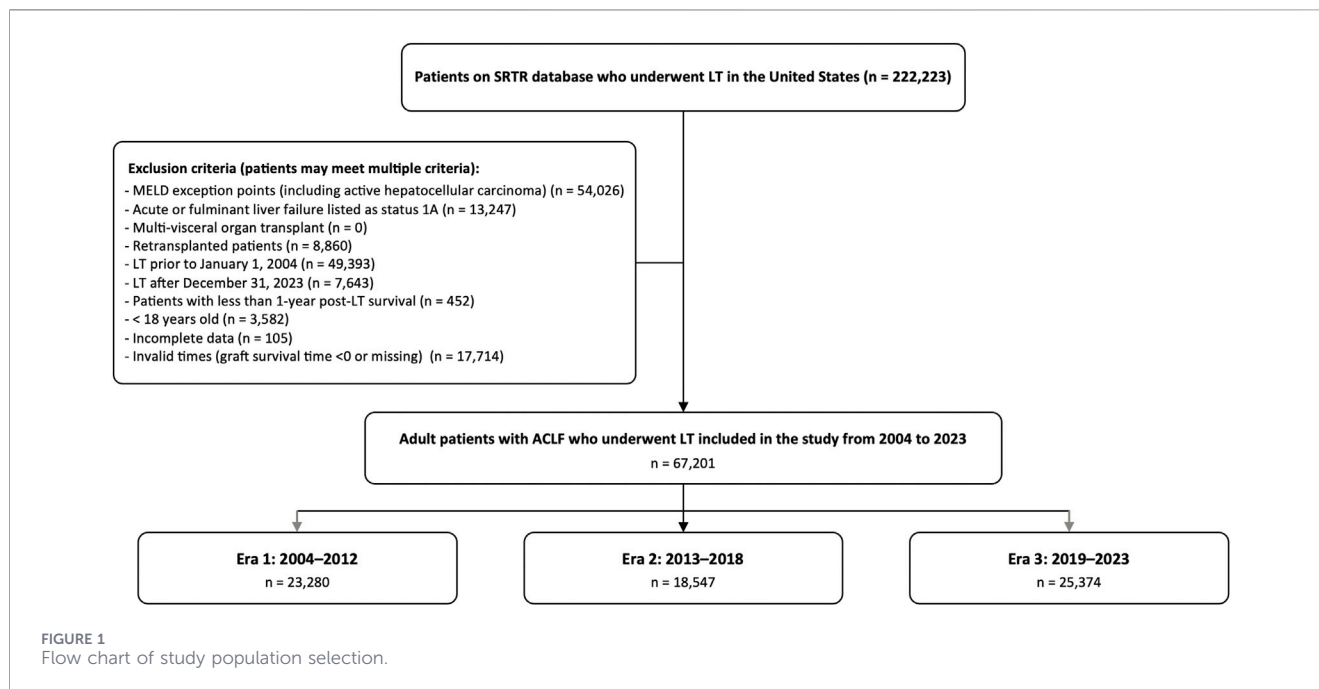
Patient population

We used data from the Scientific Registry of Transplant Recipients (SRTR) collected mostly by the OPTN, which captures all patients who received an LT in the US [24].

Inclusion/exclusion criteria

Adult patients (≥ 18 years old) listed for LT from 1st January 2004 to 31st December 2023 were evaluated. Patients with acute or fulminant liver failure (status 1A), prior LT, or active hepatocellular carcinoma at time of waitlist registration were excluded. Patients who underwent multivisceral organ transplant, except for simultaneous liver-kidney transplant were also excluded. We collected data on patient and donor characteristics at time of transplant and at regular follow-up intervals including age, gender, and race/ethnicity. Donor characteristics also included

Abbreviations: ACLF, Acute-on-chronic liver failure; CI, Confidence interval; DCD, Donation after circulatory death; DBD, Donation after brain death; DRI, Donor risk index; HR, Hazard ratio; LT, Liver transplantation; MASH, Metabolic associated steatohepatitis; MCID, Minimum clinically important difference; MELD, Model of end-stage liver disease; NMP, Normothermic machine perfusion; OF, Organ failure; OPTN, Organ procurement and transplantation network; SHR, Subdistribution hazard ratios; SRTR, Scientific registry of transplant recipients; UNOS, United network of organ sharing.



cause of death, history of diabetes, history of hypertension, and high-risk donor status. Recipient characteristics also included last bilirubin, INR, creatinine, encephalopathy, and ventilator use for life support. Only patients with at least 1 year of post-LT survival were included. The flow chart of study population selection is shown in [Figure 1](#).

Creation of cohorts

ACLF severity was graded using the EASL-CLIF criteria based on the number of OFs at time of LT across five domains: hepatic failure (bilirubin ≥ 12 mg/dL), coagulopathy (INR ≥ 2.5), renal failure (creatinine ≥ 2 mg/dL or dialysis within the preceding week), cerebral failure (hepatic encephalopathy), and respiratory failure (mechanical ventilation) [25]. Given inherent issues with the SRTR coding of vasopressor use, circulatory failure was not included. Since the SRTR dataset lacks sufficient detail to definitively diagnose ACLF, we used the term estimated ACLF (EST-ACLF). Patients were categorized into three grades: EST-ACLF-1 (1 OF), EST-ACLF-2 (2 OFs) and EST-ACLF-3 (≥ 3 OFs). Lower ACLF severity patients were grouped to avoid artificially excluding patients whose OF count at transplant may have been transiently lower. Non-critically ill patients were grouped as having a maximum of one OF (No ACLF or EST-ACLF-1), and critically ill patients were grouped as having two or more OFs (EST-ACLF-2, EST-ACLF-3).

We then stratified patients as either DBD or DCD graft recipients. This resulted in four cohorts: 1) Non-critically ill DBD recipients, 2) Non-critically ill DCD recipients, 3) Critically ill DBD recipients, and 4) Critically ill DCD recipients. Non-critically ill patients served as a comparator group for contextualising DCD outcomes across illness severity.

Era analysis

Trends were evaluated over time based on three eras: Era 1 (2004–2012), Era 2 (2013–2018), and Era 3 (2019–2023). To address whether recipient factors were independently associated with 1-year graft failure in Era 3, we performed a sensitivity Cox proportional hazards model. This included donor type, MELD, and recipient age. Pretransplant diabetes and drug-treated hypertension were excluded because extensive missing or blank coding produced an unstable complete-case model with very few events.

Data preparation and variable selection

Full details of data preparation, missingness and imputation, variable selection, model selection and model validation are provided in the [Supplementary Material](#). From 128 clinically preselected predictors, 10-fold cross-validated Cox-LASSO retained 13 variables with non-zero coefficients at the one-standard-error penalty ($\lambda_{1se} = 0.0037$; [Supplementary Figure SA1](#)). Clinical review subsequently excluded nine variables with non-intuitive, implausible or unstable directions of effect. Specifically, variables regarding recipient or graft status at follow-up, recipient hepatic artery thrombosis or rejection, were excluded as post-transplant adverse events that biased results whereas our focus was on the identification of pre-transplant risk factors. Covariates with counter-intuitive effects, including recipient immunosuppression, recipient race and recipient ventilator status, were excluded to ensure model stability and interpretability. This left four covariates for multivariable modeling: donor type/ACLF stratum (reference: DBD with EST-ACLF-2/3, representing higher-risk DBD cases), donor diabetes, donor hypertension, and standardized donor age (interpreted per 10-year increase).

Statistical analysis

The primary endpoint was 1-year post-transplant graft failure, defined as retransplantation or graft loss excluding death. This was expressed as HRs with 95% confidence intervals (CIs). Graft survival was estimated using Kaplan–Meier methods, with between-group differences assessed by log-rank test. Collinearity was evaluated using variance inflation factors. Model fit and proportional-hazards assumptions were determined using Schoenfeld residuals. Continuous variables were summarized as medians with interquartile ranges, and categorical variables as frequencies and percentages. Missing values were imputed using the median for continuous variables and the mode for categorical variables. Group comparisons were conducted using chi-squared tests for categorical variables and analysis of variance or Kruskal–Wallis tests for continuous variables. Significance was defined as $p < 0.05$.

We applied an exploratory minimum clinically important difference (MCID) framework using a distribution-based approach to assess whether statistically significant differences were clinically meaningful. Since death with a functioning graft precludes subsequent graft failure, we performed a competing-risk sensitivity analysis in which death with a functioning graft was treated as a competing event rather than as censoring alone. Subdistribution hazard ratios (SHR) were estimated using Fine–Gray regression models, allowing the association between donor-recipient strata and graft failure to be re-evaluated while explicitly accounting for the competing risk of death. Statistical analyses were performed using RStudio Version 2025.05.1 + 513 (Boston, MA, USA).

Results

Study population characteristics

67,201 adult liver-only transplant recipients with ACLF were included between January 1, 2004 and December 31, 2023 (Supplementary Figure SA1). Of these, 62,510 (93%) received DBD grafts and 4,691 (7%) received DCD grafts.

Donor characteristics

Donor characteristics are summarized in Table 1. Compared with DBD donors, DCD donors were younger (median 38 years [IQR 27–49] vs. 41 years [IQR 28–54]; $p < 0.001$), more frequently male (67% vs. 60%; $p < 0.001$), and more often White (87% vs. 78%, $p < 0.001$). Anoxia was a more frequent cause of death among DCD donors (50% vs. 33%), whereas cerebrovascular/stroke (17% vs. 33%) and head trauma (28% vs. 31%) were less common compared with DBD donors ($p < 0.001$). Compared to DBD donors, more DCD donors did not have diabetes (91% vs. 87%, $p < 0.001$) and fewer had hypertension (27% vs. 35%; $p < 0.001$). More DCD donors met CDC high-risk donor status (20%) than DBD donors (19%) ($p < 0.001$). Donor risk index was higher among DCD than DBD donors (2.35 [IQR 2.09–2.73] vs. 1.65 [IQR 1.45–1.95]; $p < 0.001$).

Recipient characteristics

Recipient characteristics are summarized in Table 1. Compared with DBD recipients, DCD recipients were older at treatment (median 56 years [IQR 49–62] vs. 54 years [IQR 47–61]; $p < 0.001$) and listing (median 56 years [IQR 49–62] vs. 54 years [IQR 46–60]; $p < 0.001$). Gender distribution was similar. DCD recipients were more frequently White (91% vs. 87%, $p < 0.001$). DCD recipients had a significantly lower MELD score than DBD recipients (median 17 vs. 24, $p < 0.001$).

DCD recipients were less ill at transplant with lower median bilirubin (3.90 mg/dL [IQR 2.20–7.40] vs. 7.80 mg/dL [IQR 3.40–18.90]; $p < 0.001$), lower INR (1.70 [IQR 1.40–2.10] vs. 2.00 [IQR 1.60–2.60]; $p < 0.001$), and lower creatinine (1.00 mg/dL [IQR 0.77–1.30] vs. 1.18 mg/dL [IQR 0.83–1.90]; $p < 0.001$) compared with DBD recipients. More DCD recipients had grade 1–2 encephalopathy (58% vs. 54%) and less had grades 3–4 (13% vs. 18%) ($p < 0.001$). Ventilator use was less frequent among DCD recipients (1.8% vs. 5.5%; $p < 0.001$).

Sensitivity Cox proportional hazards model was performed on LT recipients in Era 3 to see whether recipient factors were associated with 1-year graft failure. The recipient-factor model included 25,374 recipients and 698 1-year graft-failure events. After adjustment for MELD and recipient age, DCD donor type remained independently associated with higher 1-year graft failure (HR 2.00, 95% CI 1.65–2.42; $p < 0.001$). MELD was not significantly associated with 1-year graft failure (HR 0.99, 95% CI 0.98–1.00; $p = 0.06$). Recipient age showed a small association (HR 0.99, 95% CI 0.99–1.00; $p = 0.03$).

DCD-specific graft complications

Biliary tract complications (20% vs. 11%; $p < 0.001$) and infection (28% vs. 21%; $p = 0.03$) were more frequently reported causes of graft failure in DCD than DBD recipients. Conversely, primary graft failure (8.9% vs. 15%; $p = 0.04$) and recurrent hepatitis (15% vs. 31%; $p < 0.001$) were less frequent, and vascular thrombosis was numerically lower (4.1% vs. 7.7%; $p = 0.11$) in DCD versus DBD grafts. *De novo* hepatitis, recurrent non-hepatitis disease, acute and chronic rejection did not differ significantly between DCD and DBD graft complications. Cause indicators were non-mutually exclusive fields. Thus, individual patients could have more than one cause attributed.

Hazard ratios of one-year graft failure over eras

DCD grafts

Compared with the critically ill DBD EST-ACLF-2/3 reference group, critically ill DCD recipients had significantly higher hazards of graft failure overall (HR 1.80, 95% CI 1.30–2.50, $p < 0.001$), with consistent associations in Era 1 (HR 2.08, 95% CI 1.26–3.43, $p = 0.004$) and Era 2 (HR 2.03, 95% CI 1.16–3.55, $p = 0.013$) (Table 2). This effect was attenuated and nonsignificant in Era 3 (HR 1.76, 95% CI 0.9–3.43, $p = 0.097$).

TABLE 1 Donor and recipient characteristics by donor type for patients with ACLF that received a LT between 1 January 2004 and 31 December 2023, n = 67,201.

Variable	Outcome	Overall	DBD	DCD	P-value
Total n, (%)		67,201	62,510 (93%)	4,691 (7%)	
1-year graft failure n, (%)		7131	6,366 (89%)	765 (11%)	
Donor characteristics					
Age at organ recovery/referral years median [IQR]		41.00 (28.00, 54.00)	41.00 (28.00, 54.00)	38.00 (27.00, 49.00)	<0.001
Gender n, (%)	Female	26,248 (39%)	24,721 (40%)	1,527 (33%)	<0.001
	Male	40,953 (61%)	37,789 (60%)	3,164 (67%)	
Race n, (%)	Asian	1,542 (2.3%)	1,458 (2.3%)	84 (1.8%)	<0.001
	Black	12,237 (18%)	11,762 (19%)	475 (10%)	
	Multi	205 (0.3%)	192 (0.3%)	13 (0.3%)	
	Native	357 (0.5%)	325 (0.5%)	32 (0.7%)	
	Pacific	166 (0.2%)	157 (0.3%)	9 (0.2%)	
	White	52,685 (78%)	48,610 (78%)	4,075 (87%)	
Cause of death n, (%)	Anoxia	22,913 (34%)	20,552 (33%)	2,361 (50%)	<0.001
	Cerebrovascular/ stroke	21,658 (32%)	20,850 (33%)	808 (17%)	
	Head trauma	20,959 (31%)	19,635 (31%)	1,324 (28%)	
	CNS tumor	270 (0.4%)	266 (0.4%)	4 (<0.1%)	
	Other	1,400 (2.1%)	1,206 (1.9%)	194 (4.1%)	
Diabetes n, (%)	Duration unknown	866 (1.3%)	824 (1.3%)	42 (0.9%)	<0.001
	0–5 years	2,526 (3.8%)	2,372 (3.8%)	154 (3.3%)	
	6–10 years	1,408 (2.1%)	1,343 (2.1%)	65 (1.4%)	
	>10 years	2,878 (4.3%)	2,737 (4.4%)	141 (3.0%)	
	None	58,883 (88%)	54,629 (87%)	4,254 (91%)	
	N/A	639 (1.0%)	604 (1.0%)	35 (0.7%)	
Hypertension n, (%)	Yes	23,209 (35%)	21,967 (35%)	1,242 (27%)	<0.001
Meets CDC guidelines for high risk donor n, (%)	Yes	12,636 (19%)	11,693 (19%)	943 (20%)	<0.001
	No	53,451 (80%)	49,704 (80%)	3,747 (80%)	
	Unknown	86 (0.1%)	85 (0.1%)	1 (<0.1%)	
	N/A	1,028 (1.5%)	1,028 (1.6%)	0 (0%)	
Donor risk index (DRI)		1.65 (1.45, 1.95)	2.35 (2.09, 2.73)	<0.001	1.65 (1.45, 1.95)
Recipient characteristics					
Age at treatment (years) median [IQR]		54.00 (47.00, 61.00)	54.00 (47.00, 61.00)	56.00 (49.00, 62.00)	<0.001
Age at listing (years) median [IQR]		54.00 (46.00, 60.00)	54.00 (46.00, 60.00)	56.00 (49.00, 62.00)	<0.001
Gender n, (%)	Female	24,557 (37%)	22,889 (37%)	1,668 (36%)	0.15
	Male	42,644 (63%)	39,621 (63%)	3,023 (64%)	

(Continued)

TABLE 1 Continued

Variable	Outcome	Overall	DBD	DCD	P-value
Race n, (%)	Asian	2,023 (3.0%)	1,458 (2.3%)	84 (1.8%)	<0.001
	Black	5,579 (8.3%)	11,762 (19%)	478 (10%)	
	Multi	339 (0.5%)	192 (0.3%)	13 (0.3%)	
	Native	595 (0.9%)	331 (0.5%)	32 (0.7%)	
	Pacific	101 (0.2%)	157 (0.3%)	9 (0.2%)	
	White	58,537 (87%)	48,610 (78%)	4,075 (87%)	
MELD median [IQR]		23 (16.60, 31.59)	24 (16.97, 32.10)	17 (13.54, 22.46)	<0.001
Last bilirubin (used for MELD) median [IQR]		7.30 (3.30, 18.00)	7.80 (3.40, 18.90)	3.90 (2.20, 7.40)	<0.001
Last INR (used for MELD) median [IQR]		2.00 (1.54, 2.60)	2.00 (1.60, 2.60)	1.70 (1.40, 2.10)	<0.001
Last serum creatinine mg/dL (used for MELD) median [IQR]		1.15 (0.82, 1.80)	1.18 (0.83, 1.90)	1.00 (0.77, 1.30)	<0.001
Last encephalopathy (used for MELD) n, (%)	None	18,640 (28%)	17,311 (28%)	1,329 (28%)	<0.001
	1–2	36,447 (54%)	33,713 (54%)	2,734 (58%)	
	3–4	12,110 (18%)	11,482 (18%)	628 (13%)	
	N/A	4 (<0.1%)	4 (<0.1%)	0 (0%)	
Ventilator n, (%)		3,519 (5.2%)	3,434 (5.5%)	85 (1.8%)	<0.001

Abbreviations: DBD, donation after brain death; DCD, donation after circulatory death.

TABLE 2 Multivariable stratified Cox proportional hazards regression model for 1-year graft failure in each ACLF cohort severity overall and according to eras.

Variable	Overall: 2004–2023			Era 1: 2004–2012			Era 2: 2013–2018			Era 3: 2019–2023		
	HR (95% CI)	p	VIF	HR (95% CI)	p	VIF	HR (95% CI)	p	VIF	HR (95% CI)	p	VIF
DBD												
EST-ACLF-2 and 3	Referent		1.01	Referent		1	Referent		1.01	Referent		1.01
No ACLF and EST-ACLF-1	0.93 (0.86–1.01)	0.08		0.82 (0.74–0.91)	<0.001		0.84 (0.71–0.99)	0.043		0.92 (0.77–1.09)	0.321	
DCD												
EST-ACLF-2 and 3	1.80 (1.30–2.50)	<0.001		2.08 (1.26–3.43)	0.004		2.03 (1.16–3.55)	0.013		1.76 (0.9–3.43)	0.097	
No ACLF and EST-ACLF-1	1.42 (1.23–1.64)	<0.001		1.38 (1–1.91)	0.05		1.88 (1.4–2.51)	<0.001		2.11 (1.71–2.6)	<0.001	
Donor characteristics												
Diabetes	1.30 (1.18–1.44)	<0.001	1.07	1.33 (1.15–1.54)	<0.001	1.07	1.45 (1.17–1.81)	<0.001	1.08	1.46 (1.2–1.77)	<0.001	1.08
Hypertension	1.21 (1.11–1.33)	<0.001	1.2	1.08 (0.96–1.22)	0.194	1.2	1.22 (1–1.48)	0.046	1.21	1.49 (1.24–1.78)	<0.001	1.19
Age	1.01 (1.01–1.01)	<0.001	1.18	1.01 (1.01–1.02)	<0.001	1.18	1.01 (1–1.01)	0.009	1.2	1 (1–1.01)	0.321	1.19

The reference category was DBD with EST-ACLF-2 or 3. Bold type indicates statistically significant difference. Abbreviations: DBD, donation after brain death; DCD, donation after circulatory death; ACLF, acute-on-chronic liver failure; HR, hazard ratio; CI, confidence interval; VIF, variable inflation factors.

(Table 2). Similarly, non-critically ill DCD recipients had an increased risk of graft failure overall (HR 1.42, 95% CI 1.23–1.64, $p < 0.001$) and across all eras, ranging from HR 1.38 (95% CI 1–1.91, $p = 0.05$) in Era 1 to HR 2.11 (95% CI 1.71–2.6, $p < 0.001$) in Era 3 (Table 2).

DBD grafts

DBD grafts in non-critically ill recipients were not associated with graft failure compared to the critically ill DBD reference group overall (HR 0.93, 95% CI 0.86–1.01, $p = 0.08$) (Table 2). DBD grafts

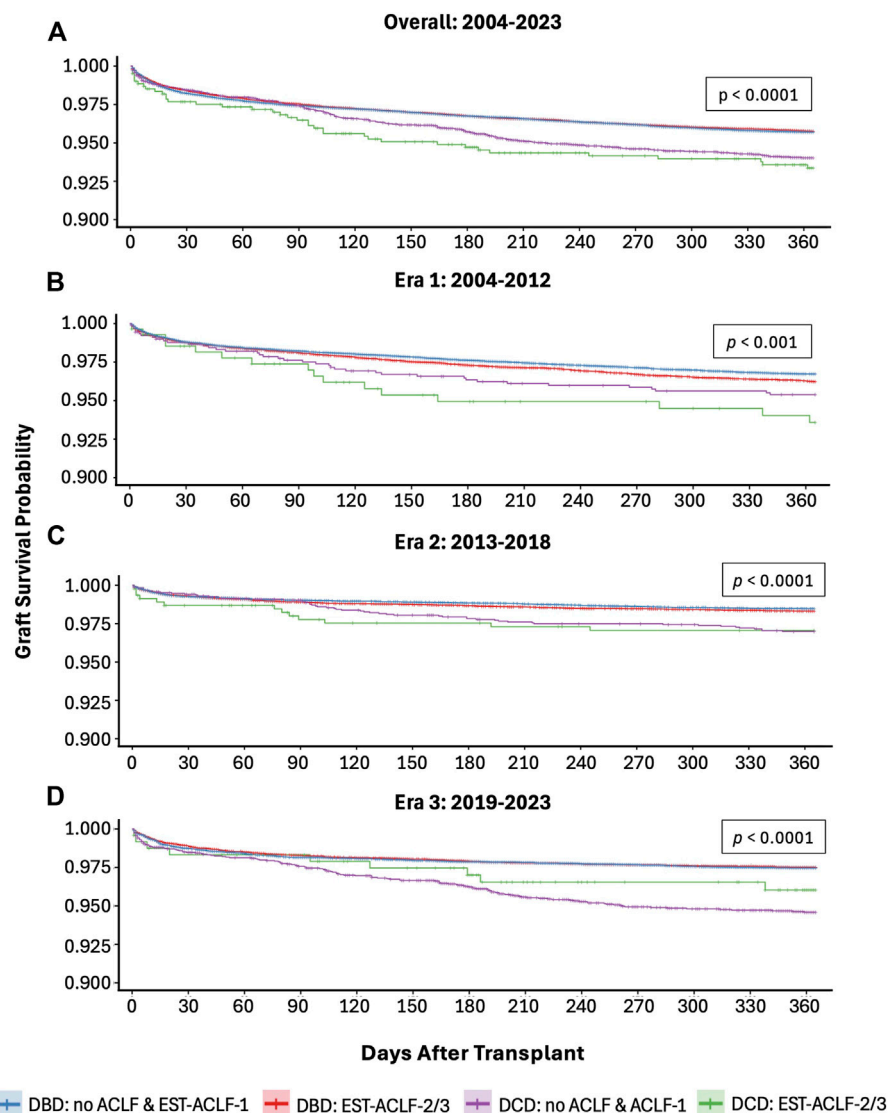


FIGURE 2
Kaplan-Meier 1-year graft survival curves stratified by eras and estimated ACLF (EST-ACLF) severity. (A) Overall: 2004–2023, (B) Era 1 (2004–2012), (C) Era 2 (2013–2018), (D) Era 3 (2019–2023). P values were calculated by log-rank test. Hazard ratios and corresponding confidence intervals are further detailed in Table 2.

in non-critically ill patients had a lower risk of 1-year graft failure compared to DBD grafts in more critically ill patients in Era 1 (HR 0.82, 95% CI 0.74–0.91, $p < 0.001$) and Era 2 (HR 0.84, 95% CI 0.71–0.99, $p = 0.043$), but this was not significant in Era 3.

Donor comorbidities

Donor diabetes was associated with increased graft failure risk overall (HR 1.30, 95% CI 1.18–1.44, $p < 0.001$), particularly in Era 2 (HR 1.45, 95% CI 1.17–1.81, $p < 0.001$) and Era 3 (HR 1.46, 95% CI 1.2–1.77, $p < 0.001$) (Table 2). Donor hypertension was also associated with higher hazards overall (HR 1.21, 95% CI 1.11–1.33, $p < 0.001$) and in most eras (Table 2). Increasing donor age was associated with a modest increase in graft failure risk overall (HR 1.01 per year, 95% CI 1.01–1.01, $p < 0.001$), particularly in Era 1 and Era 2 (Table 2).

Survival analysis over eras

Cox regression findings were consistent with Kaplan-Meier analysis (Figure 2) which showed significant differences in 1-year graft survival between groups. Across all eras, 1-year graft survival was significantly lower among DCD recipients compared to DBD counterparts although absolute differences were small (Figure 2). DCD recipients with EST-ACLF-2/3 had the lowest graft survival at 93.4% compared to other groups (Figure 2A). One-year graft survival probabilities for DBD and no ACLF/EST-ACLF-1 increased over time from 93.4% (Era 1), 97% (Era 2), and 97.5% (Era 3). A similar increase was seen for DBD EST-ACLF-2/3 with 92.5% (Era 1), 96.6% (Era 2), 97.5% (Era 3), respectively ($p < 0.0001$). There were no significant differences between the survival probabilities of critically ill and non-critically ill DCD recipients. For patients with DCD EST-ACLF-2/3 recipients, 1-

year graft survival increased from 87.2% in Era 1, 94.1% in Era 2, and 96% in Era 3 respectively. For DCD recipients with no ACLF/EST-ACLF-1, 1-year graft survival also increased from 90.8% in Era 1, 94% in Era 2, and 94.6% in Era 3.

Effect-size, competing-risk, and fine-grain analyses

Overall, 1-year Kaplan-Meier graft survival was 95.72% for DBD and 93.94% for DCD grafts. Across the eras, 1-year graft survival was 93.13% versus 89.97% in 2004–2012, 96.81% versus 94.00% in 2013–2018, and 97.48% versus 94.70% in 2019–2023 for DBD and DCD grafts, respectively. Across donor-ACLF strata, 1-year graft survival in the most recent era remained high in all groups, ranging from 94.58% to 97.51%, with the lowest estimates again observed among DCD recipients.

Effect-size analyses placed these differences in clearer clinical context. For DCD versus DBD, the absolute increase in 1-year graft failure was 1.66 percentage points (95% CI, 0.97–2.35) in the overall cohort, 2.94 percentage points (95% CI, 0.54–5.34) in 2004–2012, 2.68 percentage points (95% CI, 1.32–4.04) in 2013–2018, and 2.60 percentage points (95% CI, 1.78–3.42) in 2019–2023. By contrast, among DBD recipients, higher ACLF severity was associated with little to no absolute difference in 1-year graft failure: the risk difference for DBD with EST-ACLF-2/3 versus DBD with no ACLF/EST-ACLF-1 was –0.12 percentage points (95% CI, –0.44 to 0.20) overall, 0.71 percentage points (95% CI, 0.00–1.41) in 2004–2012, 0.27 percentage points (95% CI, –0.25–0.79) in 2013–2018, and –0.06 percentage points (95% CI, –0.47 to 0.35) in 2019–2023. None of these differences exceeded the prespecified MCID thresholds, which ranged from 7.73% to 12.42% across eras, indicating that the clinical magnitude of the observed differences was modest relative to the strong absolute 1-year outcomes.

Competing-risk analyses showed that death with a functioning graft occurred more frequently than graft failure overall and in every era (5.74% versus 4.26% overall, 7.34% versus 6.68% in 2004–2012, 5.65% versus 3.28% in 2013–2018, and 4.33% versus 2.75% in 2019–2023). In the Fine-Gray models, DCD strata consistently showed higher SHR of graft failure than the reference DBD with EST-ACLF-2/3 group, particularly DCD with no ACLF/EST-ACLF-1, with SHR 1.448 (95% CI 1.257–1.669) overall, SHR 1.417 (95% CI 1.027–1.957) in 2004–2012, SHR 1.904 (95% CI 1.425–2.546) in 2013–2018, and SHR 2.127 (95% CI 1.724–2.624) in 2019–2023. DCD with EST-ACLF-2/3 also showed elevated risk overall and in the earlier eras, although the estimate for 2019–2023 was no longer statistically significant (SHR 1.750, 95% CI 0.899–3.407).

Discussion

In this national retrospective analysis of 67,201 adult liver-only transplant recipients (62,510 DBD, 4,691 DCD) from the SRTR database, outcomes following DCD LT in patients with ACLF improved over time and became increasingly comparable to DBD LT. Among the most critically ill ACLF patients, 1-year DCD graft survival improved from 87.2% in Era 1 (2004–2012) to 96.0% in Era 3 (2019–2023), approaching the 97.5% 1-year graft survival seen for

DBD counterparts. Although the overall adjusted HR favored DBD grafts (HR 1.80, 95% CI 1.30–2.50; $p < 0.001$), this result is likely driven by the large sample size. Near 90% and above survival probabilities were observed even in the highest-risk DCD group in recent years. All absolute graft failure risk differences fell below MCID thresholds indicating no clinically meaningful differences between DCD and DBD grafts. These findings support the use of DCD grafts as a viable option in ACLF.

Several factors may explain why DCD outcomes in critically ill ACLF recipients have improved over time. Normothermic machine perfusion (NMP) for LT was first performed in 2012 [26] and has since been increasingly adopted, with a sharp increase between 2021 and 2022 [27]. NMP has increasingly been used in higher-risk recipient-donor combinations, indicating growing confidence in applying this technology to sicker patients [27]. Use of NMP for DCD donation was associated with a lower hazard of graft failure [28]. We were unable to formally account for the use of NMP, thus its impact on our outcomes may be underestimated. Future studies examining NMP's effect on DCD outcomes in ACLF are warranted, as is center level analysis to differentiate outcomes between low and high volume DCD programs.

The decision to allocate a DCD graft to a recipient with ACLF reflects complex clinical judgement involving graft scarcity, perceived recipient risk, center experience, and local allocation practices. Providers are guided by frameworks such as the International Liver Transplant Society consensus, which recommends caution when DCD livers are used in higher risk patients that meet specific criteria [29]. Consistent with these principles, DCD recipients in our study were systematically less ill at transplantation than their DBD counterparts with lower median MELD scores (17 vs. 24), less severe hepatic encephalopathy, and markedly lower rates of ventilator dependence (1.8% vs. 5.5%). This may reflect a pattern of preferential allocation of DCD grafts to more stable recipients. This is supported by single center studies employing rigorous donor-recipient matching that report no difference in mortality or graft loss at 3 years post-transplant, with DCD not emerging as a risk factor for patient or graft survival [30]. However, outcomes seem to differ when extended-criteria DCD donors are used which carry particularly poor outcomes, whereas non-extended-criteria DCD grafts achieve patient survival comparable to DBD transplantation [31]. We found that in the most recent era, the association between DCD donor type and 1-year graft failure persisted after accounting for recipient MELD and age. These findings underscore that recipient illness severity and donor organ quality must be considered when optimizing donor-recipient matching.

Among causes of graft failure, biliary tract complications accounted for a significantly greater proportion among DCD compared to DBD grafts (20% vs. 11%, $p < 0.001$). This is consistent with the known susceptibility of DCD grafts to ischemia-reperfusion injury and ischemic cholangiopathy, both consequences of the warm ischemic period [32, 33]. NMP mitigates these risks by restoring near-physiological perfusion prior to implantation, and its expanding use is likely a contributor to the era-over-era improvement [34, 35]. Even setting perfusion technology aside, accepting a DCD offer confers better overall survival for patients with advanced liver disease than

remaining on the waitlist, a pertinent consideration given the high waitlist mortality in ACLF [36].

In contrast to DCD grafts, DBD graft outcomes were stable across ACLF severity strata and did not significantly differ from one another in either adjusted or unadjusted analyses. This reinforces that DBD grafts remain the benchmark against which DCD performance is measured, and it also underscores that the principal driver of between-group differences in our analysis was the donor type rather than recipient illness severity alone.

Beyond donor type, donor diabetes (HR 1.30, 95% CI 1.18–1.44) and hypertension (HR 1.21, 95% CI 1.11–1.33) were independent predictors of graft failure. Both comorbidities are core components of the metabolic syndrome and are recognized indicators of hepatic microvascular compromise and reduced regenerative capacity [37]. Donor diabetes has been associated with increased graft failure risk, particularly in recipients with MASH [38]. Similarly, donor hypertension has been linked to reduced graft and patient survival, with both the presence and duration of hypertension implicated in worse outcomes [39]. Donor metabolic comorbidities should be accounted for when utilizing DCD grafts in ACLF.

Donor age was also associated with increased graft failure risk (HR 1.01, 95% CI 1.01–1.01). This is consistent with previous studies which show that DCD liver grafts from older donors have a higher incidence of primary nonfunction and initial poor function [40]. This likely reflects the decline in hepatic regenerative capacity with age [41]. Transplantation from younger DCD donors (under 50 years) has been associated with better graft survival than from older DBD donors (over 60 years), suggesting that careful age-based selection of DCD donors may allow for expansion of DCD utilization without compromising outcomes [42]. The effect of donor age on graft failure was no longer statistically significant in the most recent eras which may reflect either evolving allocation strategies or the selective acceptance of older donors with favorable graft profiles.

Competing-risk analyses provided additional context. DCD strata consistently showed higher SHR of graft failure than the reference DBD EST-ACLF-2/3 group, particularly DCD with no ACLF/EST-ACLF-1. That the non-critically ill DCD group consistently fared worse in graft failure is counterintuitive. This may reflect suboptimal donor–recipient matching in patients perceived as “safe” enough to tolerate a less optimal organ, inadvertently raising their graft failure risk. The loss of statistical significance in the most recent era is consistent with the Kaplan-Meier curves that showed 1-year graft survival becoming increasingly comparable to DBD outcomes over time.

Strengths of our study include the large sample size and national scope, providing robust statistical power and generalizability. Combining Cox-LASSO with clinical expert review yielded a parsimonious, interpretable model with acceptable discrimination (C-index 0.71), good calibration, negligible multicollinearity and only mild non-proportionality.

This analysis has some limitations. The restriction to US data limits generalizability to international populations. We are also limited by the retrospective design of national registry analysis that, in turn, offers the benefit of a large sample size. We did not assess graft survival beyond 1 year, so applicability to later outcomes remains uncertain. Additionally, unmeasured confounders, notably

the increasing adoption of NMP technologies likely contributed to the improvement in DCD outcomes [43]. However, we have controlled for other confounders. Lastly, the SRTR database does not provide information regarding antihypertensive or diabetic therapies of the donors, nor the characteristics of the liver graft. Nonetheless, the consistency of our findings across multiple statistical diagnostics, eras, and both adjusted and unadjusted analyses strengthens confidence in their validity [44].

Overall, 1-year graft survival after DCD LT in ACLF has improved substantially over time and is now approaching DBD outcomes. DCD grafts represent a viable means of expanding the donor pool and reducing waitlist mortality in this high-risk population, particularly as NMP technologies become more widely adopted. These findings underscore the importance of nuanced donor–recipient matching when considering DCD grafts in ACLF. Avoiding high-risk combinations, such as older DCD donors with metabolic comorbidities allocated to higher severity ACLF recipients is likely to optimize graft survival.

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.

Ethics statement

The study was deemed as exempt from review by the institutional review board at the University of British Columbia Clinical Research Ethics Board. The study followed the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines and was conducted in accordance with the Declaration of Helsinki.

Author contributions

YY: conceptualization, drafting manuscript, revising manuscript. TW: conceptualization, data analysis, revising manuscript. DC: conceptualization, supervision, revising manuscript. NT: revising manuscript. KL: revising manuscript. YL: revising manuscript. XC: revising manuscript. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontierspartnerships.org/articles/10.3389/ti.2026.16308/full#supplementary-material>

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Pre-transplant whole blood transcriptomic profiling identifies mRNAs linked to cirrhosis-associated immune dysfunction as candidate predictors of clinical outcomes after liver transplantation: an exploratory study

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Cirrhosis-associated immune dysfunction (CAID) contributes to poor outcomes after liver transplantation (LT), but pre-transplant immune predictors remain insufficiently defined. We investigated whether pre-transplant whole blood transcriptomic profiling was associated with post-LT outcomes in this exploratory ancillary study of the prospective EDMONHG cohort. Transcriptomic analysis of 26 immune-related genes was performed on 97 LT recipients. PCA and volcano plots identified candidate biomarkers; associations with outcomes were assessed using ROC analyses and Kaplan-Meier estimates with cohort medians as thresholds. PC1 (43.5% of variance) decreased progressively from cACLD to ALF ($p < 0.001$) and was lower in post-LT infected patients ($p = 0.044$). Within the first month, 34 patients (35%) developed infections; 7 (7.2%) died within 1 year. Three genes met predefined exploratory criteria ($q < 0.10$, $AUC > 0.65$) for infections: GNLY and IL7R were downregulated and IL10 upregulated. Low GNLY or high IL10 expression was associated with reduced 30-day infection-free survival ($p = 0.019$ and $p = 0.013$). IL10, CD177 and S100A9 showed associations with one-year survival,

though results should be treated as exploratory given the limited number of events. Pre-transplant transcriptomics captures CAID severity and identifies candidate gene signatures associated with post-LT outcomes. These hypothesis-generating findings warrant validation in larger multicenter cohorts.

KEYWORDS

liver transplantation, cirrhosis-associated immune dysfunction, transcriptomics, immune monitoring, infections

Introduction

Cirrhosis-associated immune dysfunction (CAID) is characterized by persistent systemic inflammation and progressive immune suppression, significantly contributing to increased morbidity and mortality in patients with cirrhosis [1]. Patients with Acute-on-Chronic Liver Failure (ACLF), who exhibit the most severe immune dysfunction, experience higher rates of infection and elevated mortality before liver transplantation (LT) [2, 3]. This higher risk of mortality and infection persists after LT compared with patients without ACLF [4]. The persistence of an excessive risk of death despite LT could suggest a potential link between pre-LT immune dysfunction and poor outcomes following LT. Several studies have reported associations between pre-transplant immune status and post-LT outcomes, including sepsis and mortality, using protein-level or cellular immune markers [5–7]. However, the relationship between pre-transplant immune dysfunction and its evolution or impact on post-transplant outcomes remains understudied and there are currently no tools available for immune monitoring in the context of LT.

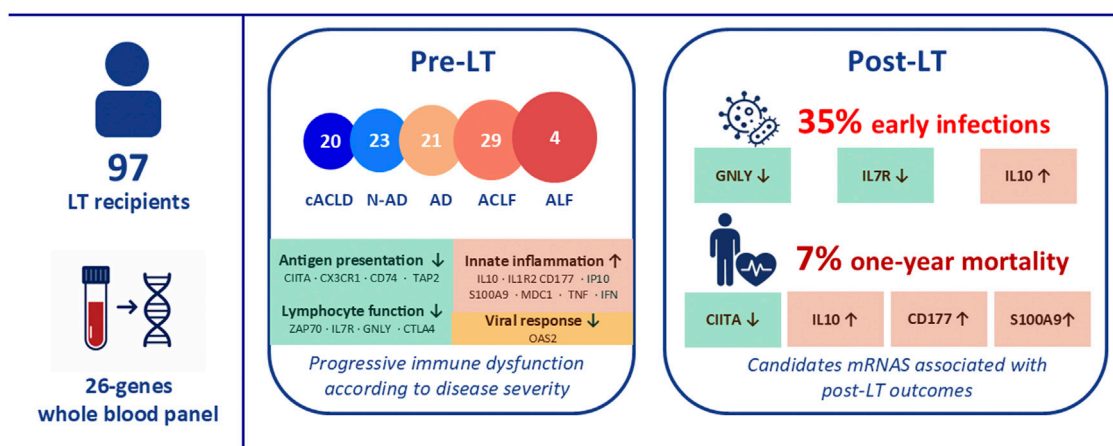
Recently, transcriptomic studies have contributed to decipher the mechanisms of CAID and systemic inflammation in end-stage liver disease. Weiss et al. characterized CAID features, notably neutrophil alterations, using transcriptomic analysis at different stages of cirrhosis including ACLF [8]. Gene scores developed from blood

RNA sequencing may be superior to clinical scores in reflecting the intensity of systemic inflammation in patients with acute decompensation of cirrhosis (AD) and ACLF [9]. Recent transcriptomic studies on sepsis have highlighted the potential of blood-based gene expression profiling to uncover immune signatures predictive of outcomes and to stratify patients based on their immune status. In particular, immune transcriptomic endotypes have been associated with differential risks of mortality and secondary infections in patients with septic shock, independently of clinical severity scores [10]. Given the close immunological parallels between septic shock and ACLF, both characterized by systemic inflammation and immune exhaustion, these findings support the relevance of transcriptomic approaches to better characterize and predict outcomes of cirrhosis-associated immune dysfunction.

We recently reported in the EdMonHG cohort that post-LT mHLA-DR trajectories were independently associated with early infections and one-year survival [11]. However, none of the immunological markers measured before LT, including mHLA-DR expression and lymphocyte counts, were associated with post-LT outcomes in that study, underscoring the need for more granular pre-LT immune characterization.

This motivated the design of an exploratory transcriptomic analysis as an ancillary study of the EdMonHG cohort, which pursued two objectives: first, to preliminarily characterize the spectrum of immune dysfunction across liver disease severity

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GRAPHICAL ABSTRACT

stages using a targeted 26-gene whole blood panel; and second, to explore whether specific pre-transplant transcriptomic immune signatures might be associated with post-LT outcomes, namely, early infections and one-year survival.

Materials and methods

Study population

This work represents an ancillary study of the prospective, single-center EdMonHG cohort ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03995537) identifier NCT03995537) [11]. The inclusion criteria were adult patients awaiting LT due to compensated Advanced Chronic Liver Disease (cACLD), decompensated ACLD (including acute decompensation (AD), non-acute chronic decompensation (N-AD) and acute-on-chronic liver failure (ACLF)), or acute liver failure (ALF). Exclusion criteria were ongoing immunosuppressive treatment (except corticosteroids), patients without underlying liver disease, and patients awaiting retransplantation or multiorgan transplantation.

Recipient, donor and perioperative variables

We systematically collected recipient demographic and clinical variables (age, sex, liver disease etiology, clinical presentation stage (cACLD, N-AD, AD, ACLF, ALF), clinical severity scores routinely used to assess pre-transplant disease severity in LT candidates: Model for End-stage Liver Disease (MELD) score, Sequential Organ Failure Assessment (SOFA) score, ACLF grade and number of organ failures according to the CLIF-ACLF definition, and hospitalization status at the time of LT. We also collected donor variables (age, sex, body mass index, donation type, and cause of death), and perioperative/surgical variables (intraoperative packed red blood cell transfusion requirements, warm and cold ischemia times, and hepaticojunostomy).

Blood collection and transcriptomic analyses

In line with the EdMonHG biobanking protocol, immune monitoring was performed every 3 months in cACLD and N-AD patients, and during admission for AD or ACLF patients. As a result, the median interval between the pre-LT sampling and transplantation was 9 days [IQR: 1–36]. T lymphocyte count and mHLA-DR expression were assessed in parallel at the same time point, using flow cytometry as previously described in the EdMonHG cohort [11].

For transcriptomic analyses, blood samples were drawn into PAXgene tubes for optimal RNA stabilization. After 2 h at room temperature, the samples were frozen at -80°C following the manufacturer's recommendations. We performed targeted transcriptomic analysis using RT-qPCR on a panel of 26 genes related to inflammation and immune response, the Immune Profiling Panel (IPP prototype, bioMérieux, Marcy l'Etoile, France). Of note, these 26 genes were selected based on previous work [10, 12]. This panel covered genes coding for soluble markers of the inflammatory response (pro- and anti-inflammatory),

membrane markers associated with innate and adaptive responses, alarmins and genes involved in the regulation of cell cycle or metabolism (Supplementary Figure 1). The mRNA expression level was determined using the FilmArray Torch System (bioMérieux) by injecting 100 μL of the PAXgene whole blood into the IPP prototype pouch. The gene expression data were normalized using reference housekeeping genes from the original publication detailing the approach [13]. The selection of these reference genes was based on previous studies conducted by our team and other groups [14–16].

Post liver-transplantation outcomes

The primary outcomes were the occurrence of significant early post-LT infections (within the first month following LT) and one-year survival post-LT. Post-operative infections were defined according to the American Society of Transplantation [17] (see definitions in Supplementary Materials) and only significant infections were recorded (excluding uncomplicated cystitis, colitis and catheter colonization). Two independent experts confirmed the cases of post-LT infections *a posteriori*, before performing transcriptomic assays.

Post-LT outcome variables, including early allograft dysfunction, biliary and vascular complications, and prolonged postoperative corticosteroid use, were also collected.

Statistics

The results were expressed as medians and interquartile ranges (IQRs) or as numbers and percentages (%). All 97 patients with available pre-transplant transcriptomic data were included; there was no missing data for the primary outcomes or transcriptomic variables.

To explore the overall structure of immune dysregulation, principal component analysis (PCA) was performed on the normalized expression values of all 26 transcriptomic markers, after centering and scaling each gene to unit variance (i.e., PCA was computed on the correlation rather than the covariance matrix), so that no individual gene's raw variance could disproportionately drive the principal components. PCA scores were compared across disease severity stages and according to post-LT outcomes using the Kruskal-Wallis and Wilcoxon rank-sum tests, respectively. Gene loadings on PC1 were examined to identify the main contributors to immune variance. Candidate biomarkers were identified through a two-step approach. For each gene included in the transcriptomic panel, normalized expression levels were compared between groups using Wilcoxon rank-sum tests for binary outcomes (post-LT infection and one-year survival) and Kruskal-Wallis tests for comparisons across liver disease severity stages and liver disease etiologies. To account for multiple testing, p-values were adjusted using the Benjamini-Hochberg false discovery rate (FDR) procedure, and both nominal p-values and adjusted q-values were reported. In parallel, receiver operating characteristic (ROC) analyses were performed and areas under the curve (AUCs) with 95% confidence intervals were calculated for each marker. Volcano plots summarized these analyses by representing the median difference in normalized expression on the x-axis and the $-\log_{10}(\text{p-value})$ on the y-axis, with dot size proportional to

the AUC. Genes fulfilling both $q < 0.10$ and $AUC > 0.65$ criteria were considered candidate biomarkers, highlighted in color on volcano plots, and selected for further analyses including boxplots of normalized expression, threshold-based survival analyses using Kaplan–Meier estimates with cohort median cut-offs, and calibration analyses. An AUC threshold of 0.65 was selected to enrich for markers with at least moderate discriminative ability in this exploratory study. Differences between groups in survival analyses were assessed using the log-rank test. Calibration plots for individual logistic regression models were generated to evaluate the predictive performance of candidate biomarkers. Calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test and generalized additive model (GAM) smoothing, in order to assess agreement between predicted probabilities and observed outcome rates.

Pre-transplant mHLA-DR expression and lymphocyte counts were compared across disease severity stages alongside transcriptomic markers, using the Kruskal–Wallis test, for contextual reference. As their associations with post-LT outcomes have been previously reported in this cohort [11], these markers were not included in the outcome analyses. Given that this was a single-center study with a limited number of outcome events, particularly for one-year mortality ($n = 7$), the analysis remained exploratory and no formal multivariable analysis could be performed.

R version 4.0.2 (R Core Team 2020, Vienna, Austria) and GraphPad Prism 6.0 (GraphPad Software, La Jolla California, USA) were used for all analyses. The significance level was set at $p < 0.05$ or $q < 0.10$ for the Benjamini–Hochberg test.

Guidelines

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by Institutional Review Board (Comité de Protection des Personnes Ile de France XI, approval number 19039-40433). Written informed consent was obtained from all participants prior to enrollment. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. This study was registered in the [ClinicalTrials.gov](https://www.clinicaltrials.gov) registry (NCT03995537, date: June 20, 2019).

Results

Clinical characteristics

A total of 130 patients were initially included in the EdMonHG cohort between February 2020 and May 2023. Among these patients, 99 underwent liver transplantation (LT), and 97 of these patients had available transcriptomic data and were therefore included in the current ancillary study.

LT recipients were predominantly male ($n = 78$, 80%), with a median age of 56 years [48–61]. At pre-LT, 73 patients had decompensated ACLD (23 with N-AD, 21 with AD, and 29 with ACLF), 20 patients had cACLD, and 4 patients were admitted for ALF. The most common underlying liver disease among ACLD patients was alcohol-related liver disease (ALD, $n = 68$, 73%), followed by viral infection ($n = 11$, 12% - see details in [Supplementary Materials](#)), autoimmunity ($n = 8$, 9%),

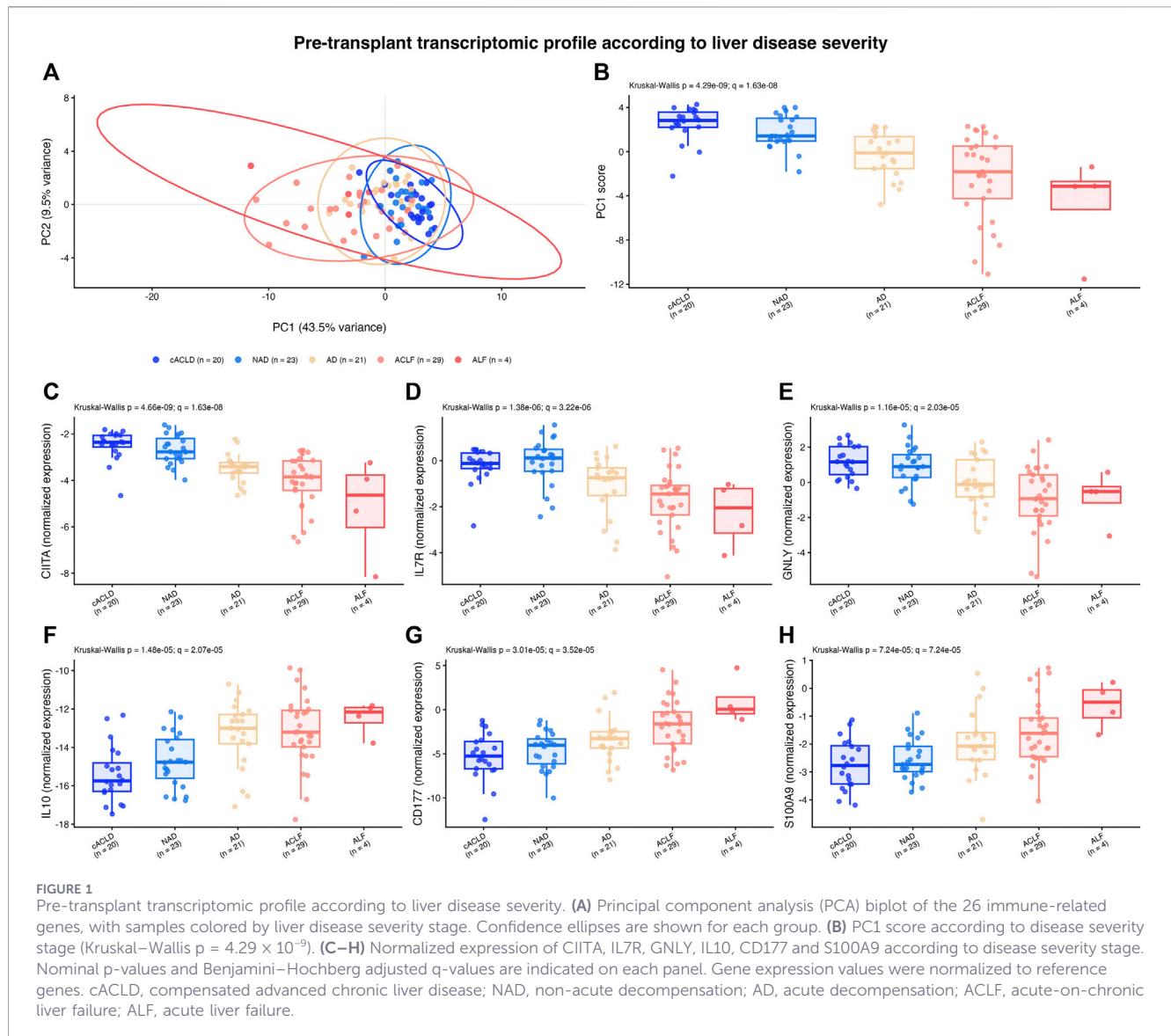
metabolic dysfunction-associated steatohepatitis (MASH) ($n = 3$, 3%), Wilson disease ($n = 2$, 2%), and progressive familial intrahepatic cholestasis ($n = 1$, 1%). The etiologies of ALF were acute HBV infection ($n = 2$), autoimmune hepatitis ($n = 1$) and posttraumatic ischemia ($n = 1$). Only three patients received pre-transplant corticosteroids. Among the ACLF patients, the median number of organ failures (OF) pre-LT was 2 [1–3], 7 (24%) patients presented with grade 1 ACLF, 16 (55%) with grade 2 ACLF and 6 patients (21%) with grade 3 ACLF. Coagulation failure (20/29), liver failure (19/29), and hemodynamic failure (10/29) were the most common organ failures. The median MELD score in the entire cohort pre-LT was 20 [14–28] and the median interval between pre-LT immune monitoring and LT was 9 days [1–36]. At the time of LT, 20 patients (20.6%) were hospitalized in the ICU, 12 (12.4%) in a hepatology ward, and 65 (67.0%) were outpatients.

Regarding donor and graft characteristics, donors were predominantly male ($n = 62$, 64%) with a median age of 66 years [51–72] and a median BMI of 25 kg/m² [23–28]. Causes of donor death were cerebrovascular ($n = 48$, 49%), traumatic ($n = 17$, 18%), anoxic ($n = 30$, 31%) and meningitis ($n = 2$, 2%). Of the total cohort, 17.5% ($n = 17$) were classified as Donation after Circulatory Death (DCD) donors. Median warm ischemia time was 37 min [27–51] and median cold ischemia time was 395 min [323–469]. Biliodigestive anastomosis was performed in 9 patients (9%).

Regarding perioperative and early post-transplant data, the median number of packed red blood cell units transfused intraoperatively was 2 [0–5]. Early allograft dysfunction (EAD) according to Olthoff criteria (see details of definition in [Supplementary Materials](#)) [18] occurred in 30 patients (31%). Biliary complications were observed in 14 patients (14%), vascular complications in 13 patients (13%), and prolonged corticosteroid therapy (>7 days) was required in 12 patients (12%).

Overall transcriptomic landscape: principal component analysis

To characterize the overall structure of immune gene expression in our cohort, we first performed PCA on the normalized expression values of all 26 transcriptomic markers. The first two principal components explained 43.5% and 9.5% of total variance, respectively ([Supplementary Figure 2](#)). PC1 loading analysis identified two gene clusters with opposing contributions. Genes contributing positively to PC1 (loadings >0.75) included markers of monocyte antigen presentation (CIITA, TAP2, CX3CR1), lymphocyte signaling (ZAP70, IL7R, CD3D), cytotoxic function (GNLY) and cell cycle regulation (CCNB1IP1). Conversely, genes contributing negatively to PC1 (loadings < -0.75) were predominantly associated with innate myeloid inflammatory and immunoregulatory responses, including the decoy interleukin-1 receptor IL1R2, a marker of suppressive myeloid activation, and the alarmin S100A9. PC2 explained a smaller proportion of total variance and was primarily driven by genes involved in innate inflammatory regulation and immune checkpoint signaling, including CD274 (PD-L1), C3AR1, and IL1RN (loadings >0.60). These genes are associated with inflammatory feedback regulation, complement-mediated innate immune activation, and counter-regulatory anti-inflammatory pathways.



Association between transcriptomic markers and pre-LT liver disease severity

On the PCA biplot, samples colored by disease severity showed a progressive spread along the PC1 axis from cACLD to ALF, with patients with more advanced disease shifting toward negative PC1 values (Figure 1A). PC1 score decreased progressively from cACLD to ALF (Kruskal–Wallis $p < 0.0001$, Figure 1B), indicating that the dominant axis of transcriptomic variability reflects the CAID severity continuum. Figures 1C–H illustrate representative genes from distinct immune functions, monocyte antigen presentation (CIITA), lymphocyte signaling (IL7R), cytotoxic function (GNLY), anti-inflammatory cytokines (IL10), neutrophil activation (CD177) and alarmin-related inflammation (S100A9), all showing significant progressive modulation across severity stages (all adjusted $q < 0.001$). Expression levels of all additional significantly modulated genes are shown in Supplementary Figure 3, alongside mHLA-DR expression and lymphocyte counts ($q < 0.001$ and $q <$

0.05 respectively). To assess whether the transcriptomic differences observed across severity stages could be explained by etiological heterogeneity, gene expression was compared across the three main underlying etiologies (ALD, viral, autoimmune). No significant differences were observed for any of the 26 genes after correction for multiple testing (all $q > 0.10$, Supplementary Table 1), although several genes reached nominal significance before adjustment. No etiology-specific transcriptomic differences could therefore be detected in this analysis; given the modest sample size, however, this exploratory comparison was not powered to formally exclude such differences.

Association between pre-LT immune markers and post-LT infections

Among 97 patients, 34 (35%) experienced at least one significant post-LT infection within the first month. The median time to diagnosis was 9 [6–14] days post-LT. The most frequent infections were intra-abdominal infections ($n = 19$), followed by

TABLE 1 Recipient's characteristics and severity score according to the occurrence of post-LT infections.

Recipient's characteristics	Post-LT infections n = 34	No post-LT infections n = 63	p
Age (years)	53 [45–60]	58 [50–61]	0.11
Sex (male)	30 (88.2)	48 (76.2)	0.25
Baseline severity scores			
Clinical presentation			0.06
cACLD	5 (14.7)	15 (23.8)	
N-AD	6 (17.6)	17 (27.0)	
AD	5 (14.7)	16 (25.4)	
ACLF	15 (44.1)	14 (22.2)	
ALF	3 (8.8)	1 (1.6)	
OF (ACLF/ALF)	18 (52.9)	15 (23.8)	0.008
Number of organ failures	1 [0–2]	0 [0–1]	0.04
MELD score	22 [16–36]	20 [13–26]	0.07
SOFA score	5 [2–8]	4 [3–6]	0.11
Hospitalisation status at LT			
ICU	13 (38.2)	7 (11.1)	0.004
Hepatology ward	5 (14.7)	7 (11.1)	
Outpatient	16 (47.1)	49 (77.8)	
Donors characteristics			
Age (years)	69 [51–74]	54 [51–71]	0.41
Sex (male)	17 (50.0)	45 (71.4)	0.06
BMI (kg/m ²)	25 [23–27]	25 [22–28]	0.98
DCD	2 (5.9)	15 (23.8)	0.05
Causes of donor death			0.12
Cerebrovascular	18 (52.9)	30 (47.6)	
Traumatic	7 (20.6)	10 (15.9)	
Anoxic	7 (20.6)	23 (36.5)	
Meningitis	2 (5.9)	0 (0)	
Surgery characteristics			
PRBC transfusion	4 [2–8]	2 [0–5]	0.005
Warm ischemia	37 [29–40]	37 [25–41]	0.73
Cold ischemia	398 [330–466]	393 [324–470]	0.71
Hepaticojejunostomy	3 (8.8)	6 (9.5)	>0.99
Outcome post-LT			
Biliary complications	8 (23.5)	6 (9.5)	0.06
Vascular complications	5 (14.7)	8 (12.7)	0.78
Early allograft dysfunction (EAD)	15 (44.1)	15 (23.8)	0.04
Prolonged postoperative steroids (>7 days)	3 (8.8)	9 (14.3)	0.44

LT, liver transplantation; BMI, body mass index; cACLD, compensated Advanced Chronic Liver Disease; N-AD, non-acute decompensation; AD, acute decompensation; ACLF, acute on chronic liver failure; ALF, acute liver failure; OF, organ failure; ICU, intensive care unit; MELD, Model for End-stage Liver Disease; SOFA, Sequential Organ Failure Assessment; DCD, donation after circulatory death; PRBC: packed red blood cells. Values are expressed as median [IQR] or n (%). Comparisons were performed using the Mann–Whitney U test or the Chi-square test, as appropriate. Bold values indicate statistical significance ($p < 0.05$).

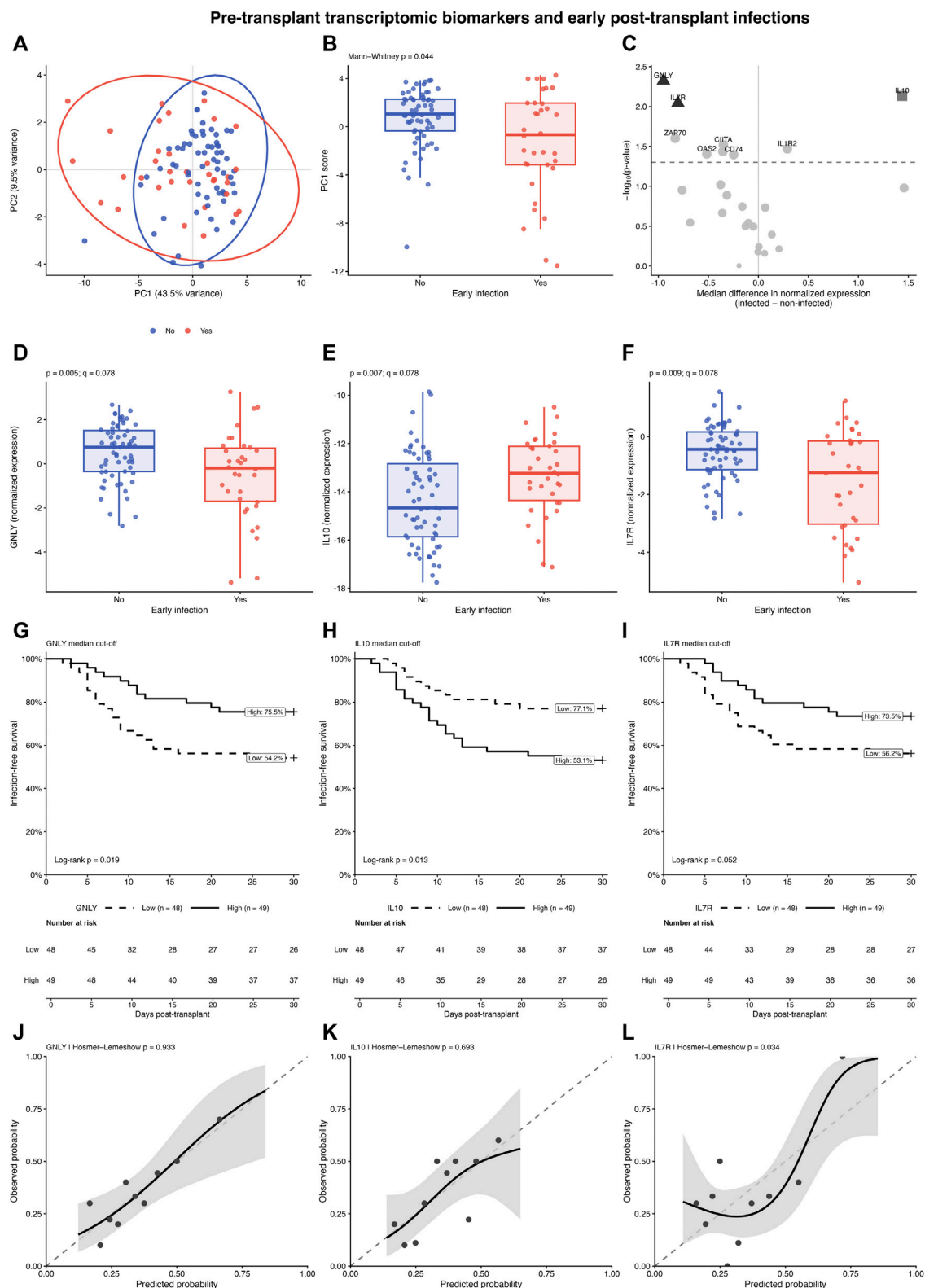


FIGURE 2

Pre-transplant transcriptomic biomarkers and early post-transplant infections. (A) PCA biplot colored according to early post-transplant infection status. Confidence ellipses are shown for each group. (B) PC1 score according to infection status (Wilcoxon rank-sum test $p = 0.044$). (C) Volcano plot representing the median difference in normalized expression between infected and non-infected patients (x-axis) and the $-\log_{10}(p\text{-value})$ (y-axis); point size represents the AUC. The dashed grey horizontal line indicates the nominal significance threshold ($p < 0.05$). Genes reaching adjusted significance ($q < 0.10$) are distinguished using distinct monochrome symbols: black triangles indicate genes underexpressed in infected patients, whereas dark grey squares indicate genes overexpressed in infected patients; non-significant genes are shown as light grey circles. (D–F) Normalized expression of

(Continued)

FIGURE 2 (Continued)

GNLY, IL10 and IL7R according to infection status. Nominal p-values and Benjamini–Hochberg adjusted q-values are indicated. (G–I) Kaplan–Meier 30-day infection-free survival curves according to cohort median expression of GNLY, IL10 and IL7R, respectively. Patients were dichotomized using cohort median expression values. Low-expression groups are shown with dashed black lines and high-expression groups with solid black lines. Thirty-day infection-free survival rates are indicated for each group; log-rank p-values are shown. (J–L) Calibration plots for individual logistic regression models using GNLY, IL10 and IL7R, respectively. The solid black curve represents a generalized additive model (GAM) smoother, the grey shaded area represents its 95% confidence interval, filled grey points represent observed event rates across Hosmer–Lemeshow groups, and the dashed grey line represents perfect calibration. Hosmer–Lemeshow p-values are indicated on each panel. Gene expression values were normalized to reference genes. GAM, generalized additive model; LT, liver transplantation.

pneumonia (n = 15), bacteremia (n = 2), fungal infections (n = 3) and viral infections (n = 2). Microbiological details are provided in [Supplementary Materials](#).

Regarding recipient characteristics, infected patients presented with a greater number of pre-LT organ failures (median 1 [0–2] vs. 0 [0–1], $p = 0.04$), and a higher rate of ICU admission at the time of LT (38% vs. 11%, $p = 0.004$); no significant differences were observed in MELD or SOFA scores ([Table 1](#)). Regarding donor and perioperative factors, intraoperative packed red blood cell transfusion requirements were significantly higher in infected patients (median 4 [2–8] vs. 2 [0–5] units, $p = 0.005$), EAD was more frequent (44.1% vs. 23.8%, $p = 0.04$), and a trend toward lower DCD utilization was observed (5.9% vs. 23.8%, $p = 0.05$, [Table 1](#)).

On the PCA biplot, samples from infected and non-infected patients showed overlapping distributions with partially separated confidence ellipses ([Figure 2A](#)). However, PC1 score was significantly lower in infected patients compared to non-infected patients ($p = 0.044$, uncorrected, [Figure 2B](#)), suggesting a possibly more pronounced pre-LT immune deficit in patients who subsequently developed infections (this comparison was not adjusted for multiple testing and should be interpreted as borderline).

Volcano plot analysis identified three genes reaching adjusted significance ($q < 0.10$ and $AUC > 0.65$): GNLY and IL7R were downregulated in infected patients, whereas IL10 was upregulated ([Figure 2C](#)). These genes were retained as candidate biomarkers for downstream analyses. For all 26 transcriptomic markers, univariate Wilcoxon rank-sum p-values, Benjamini–Hochberg adjusted q-values, and ROC-derived AUCs are reported in [Supplementary Table 2](#).

Individual boxplots confirmed differential expression of IL10, GNLY and IL7R between infected and non-infected patients ([Figures 2D–F](#)). ROC analyses demonstrated comparable discriminative performances for IL10, GNLY and IL7R, with AUCs of 0.67 [0.55–0.78], 0.67 [0.56–0.79], and 0.66 [0.54–0.79], respectively. MELD and SOFA scores did not reach significance for predicting early infection (AUC 0.61 [0.49–0.74], $p = 0.07$ and 0.60 [0.47–0.72], $p = 0.11$).

Kaplan–Meier analyses using cohort medians as thresholds demonstrated significantly reduced 30-day infection-free survival in patients with low GNLY expression (54% vs. 76%, $p = 0.019$, [Figure 2G](#)) and with high IL10 expression (53% vs. 77%, $p = 0.013$, [Figure 2H](#)). IL7R dichotomized at the median showed a borderline association with infection-free survival (56% vs. 73%, $p = 0.052$, [Figure 2I](#)).

Calibration analyses of univariable logistic regression models demonstrated good agreement between predicted probabilities and observed infection rates for GNLY (Hosmer–Lemeshow, $p = 0.93$) and IL10 ($p = 0.69$). In contrast, IL7R showed borderline calibration

($p = 0.03$), with a non-linear pattern on the calibration plot suggesting heterogeneity across predicted probability ranges ([Figures 2J–L](#)).

Association between immune markers and survival post-LT

Seven patients (7.2%) died within 1 year of LT; six deaths were infection-related and one resulted from refractory hemodynamic failure within 24 h post-LT. Regarding clinical characteristics, non-survivors tended to be younger, more frequently admitted to the ICU at the time of LT (57% vs. 18%), and had higher MELD (28 vs. 20) and SOFA scores (6 vs. 5); none of these differences reached statistical significance ([Table 2](#)). Among perioperative factors, intraoperative transfusion requirements were significantly higher in non-survivors (median 8 [5–9] vs. 2 [0–5] units, $p < 0.001$) and EAD was more frequent (71% vs. 28%, $p = 0.03$, [Table 2](#)).

On the PCA biplot, samples from survivors and non-survivors showed largely overlapping distributions ([Figure 3A](#)), and PC1 score did not differ significantly between groups ($p = 0.188$, [Figure 3B](#)). This binary comparison discards timing and censoring information and should therefore be interpreted with caution; it suggests, but does not establish, that the global immune signature captured by PC1 is less discriminant for one-year mortality than for early infections. Volcano plot analysis identified four genes meeting the predefined exploratory selection criteria ($q < 0.10$ and $AUC > 0.65$): CIITA was underexpressed in non-survivors, whereas IL10, CD177 and S100A9 were overexpressed ([Figure 3C](#)). AUC values, nominal p-values and Benjamini–Hochberg adjusted q-values for all 26 transcriptomic markers are reported in [Supplementary Table 3](#). These four genes were retained as candidate biomarkers for further exploratory analyses. Individual boxplots confirmed differential expression of CIITA, IL10, CD177 and S100A9 between survivors and non-survivors ([Figures 3D–G](#)). ROC curve analyses showed AUCs ranging from 0.79 to 0.85 for these candidate markers ([Supplementary Table 3](#)).

Given the limited number of deaths ($n = 7$), survival analyses were considered exploratory. Kaplan–Meier analyses using cohort median thresholds showed significantly lower one-year overall survival among patients with low CIITA expression (87.5% vs. 98.0%, $p = 0.049$), while similar trends were observed for high IL10, CD177 and S100A9 expression ([Supplementary Figure 4](#)).

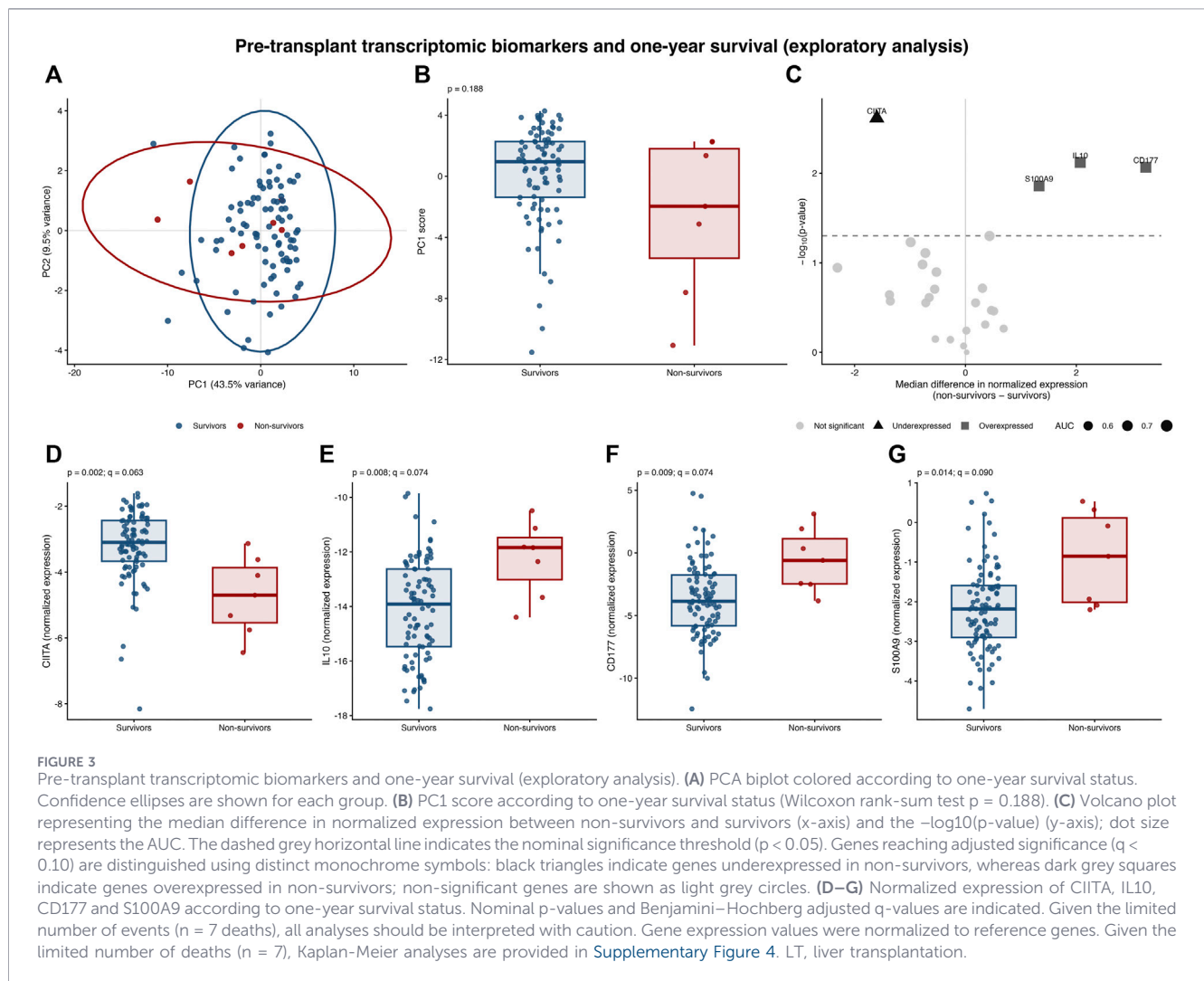
Discussion

In this exploratory prospective study of 97 LT recipients, pre-transplant whole blood transcriptomic profiling of

TABLE 2 Recipient's characteristics and severity score according to one-year survival post-LT.

Recipient's characteristics	Non-survivors n = 7	Survivors n = 90	p
Age (years)	45 [44–56]	56 [48–62]	0.06
Sex (male)	4 (57.1)	74 (82.2)	0.26
Baseline severity scores			
Clinical presentation			0.12
cACLD	0 (0.0)	20 (22.2)	
N-AD	0 (0.0)	23 (25.6)	
AD	3 (42.9)	18 (20.0)	
ACLF	3 (42.9)	26 (28.9)	
ALF	1 (14.2)	3 (3.3)	
OF (ACLF/ALF)	4 (57.1)	29 (32.2)	0.35
Number of organ failures	2 [0–4]	0 [0–2]	0.14
MELD score	28 [20–40]	20 [13–27]	0.08
SOFA score	6 [4–14]	5 [2–6]	0.11
Hospitalisation status at LT			
ICU	4 (57.1)	16 (17.8)	0.08
Hepatology ward	0 (0.0)	12 (13.3)	
Outpatient	3 (42.9)	62 (68.9)	
Donors characteristics			
Age (years)	67 [49–71]	66 [51–73]	0.81
Sex (male)	2 (28.6)	60 (66.7)	0.09
BMI (kg/m ²)	28 [24–35]	25 [22–28]	0.14
DCD	0 (0.0)	17 (18.9)	0.35
Causes of donor death			0.20
Cerebrovascular	4 (57.1)	44 (48.9)	
Traumatic	1 (14.3)	16 (17.8)	
Anoxic	1 (14.3)	29 (32.2)	
Meningitis	1 (14.3)	1 (1.1)	
Surgery characteristics			
PRBC transfusion	8 [5–9]	2 [0–5]	<0.001
Warm ischemia	40 [32–53]	37 [26–41]	0.29
Cold ischemia	400 [344–491]	394 [325–469]	0.75
Hepaticojunostomy	1 (14.3)	8 (8.9)	
Outcome post-LT			
Biliary complications	1 (14.3)	13 (14.4)	>0.99
Vascular complications	2 (28.6)	11 (12.2)	0.24
Early allograft dysfunction (EAD)	5 (71.4)	25 (27.8)	0.03
Prolonged postoperative steroids (>7 days)	0 (0.0)	12 (13.3)	0.59

LT, liver transplantation; cACLD, compensated Advanced Chronic Liver Disease; N-AD, non-acute decompensation; AD, acute decompensation; ACLF, acute on-chronic liver failure; ALF, acute liver failure; ICU, intensive care unit; OF, organ failure; MELD, Model for End-stage Liver Disease; SOFA, Sequential Organ Failure Assessment; DCD, donation after circulatory death; PRBC, packed red blood cells. Values are expressed as median [IQR] or n (%). Comparisons were performed using the Mann–Whitney U test or the Chi-square test, as appropriate. Bold values indicate statistical significance ($p < 0.05$).



26 immune-related genes appears to capture a progressive gradient of immune dysfunction across liver disease severity stages, consistent with the known features of CAID. Beyond this characterization, specific transcriptomic markers were associated with post-LT outcomes, early infections and, in a preliminary exploratory analysis, one-year survival. This suggests that immune profiling may capture prognostic information beyond disease severity alone, although whether it provides added value over clinical scores available prior to LT, which was not assessed here, is an interesting avenue for further research.

The present findings suggest that pre-transplant whole blood transcriptomic profiling of a 26 immune-related gene signature may represent a promising approach for characterizing CAID in patients with end-stage liver disease. In this study, the dominant axis of transcriptomic variability decreased progressively from cACLD to ALF, capturing the CAID severity continuum in an unsupervised manner. Loading analysis identified two opposing gene clusters: genes involved in monocyte antigen presentation and immune effector functions, including CIITA, CX3CR1, CD74, TAP2, ZAP70, IL7R and GNLY were progressively downregulated, while markers of innate myeloid activation and anti-inflammatory signaling, CD177, S100A9 and IL10, were upregulated with

increasing severity. This bidirectional pattern is consistent with the established features of CAID, characterized by simultaneous adaptive immune exhaustion and innate inflammatory dysregulation [1, 8, 9]. The magnitude of transcriptomic changes was comparable to that observed in this study for mHLA-DR across severity stages or in other immune alterations described previously [8, 19, 20], supporting the biological validity of the panel.

It is well established that patients with ACLF and ALF experience the highest rates of adverse post-transplant outcomes, including infections and mortality [4, 21]. However, conventional severity scores, such as the MELD and SOFA scores, primarily reflect pre-transplant disease severity in the recipient and have limited ability to predict post-LT infectious complications or guide individualized perioperative management. While underlying immunological dysfunctions (CAID) are well documented in cirrhotic patients [1, 8, 9], their association with post-transplant complications remains poorly investigated. Several studies have reported associations between pre-transplant immune status and post-LT outcomes using protein-level or cellular immune markers [5–7]. None of these biomarkers have been validated for use in clinical practice to guide personalized post-LT management strategies. In a previous report from our group, post-LT mHLA-DR

trajectories were independently associated with early infectious complications and one-year survival [11], suggesting that dynamic immune monitoring may hold prognostic relevance in this setting. Yet, conventional pre-LT immune markers, including mHLA-DR expression and lymphocyte counts, failed to predict post-LT outcomes in this previous study, underscoring the limitations of standard immunological parameters and the need for more comprehensive pre-transplant immune characterization. In this regard, whole blood transcriptomic profiling could be more effective than clinical scores at stratifying patients according to their prognosis in sepsis [22, 23], although its applicability in the context of LT remains unexplored.

According to Principal Component Analysis, the dominant axis of pre-LT transcriptomic variability showed only limited discrimination between patients who did and did not develop post-LT infections. Volcano plot analysis revealed that three main pre-LT transcriptomic markers (IL7R, IL-10 and GNLY) were dysregulated in patients who developed post-LT infections. Survival curves according to the median thresholds for each of these genes suggest that their pre-LT expression may identify patients at increased risk of early post-LT infections. Calibration analyses showed good agreement between predicted and observed infection probabilities for GNLY and IL10, whereas calibration was suboptimal for IL7R, suggesting that the predictive performance of individual genes within the signature is heterogeneous, and that the model's accuracy may rely more on the combined expression pattern of several genes than on the contribution of any single gene. In addition, the mRNA levels of three additional genes (CIITA, CD177 and S100A9) as well as IL-10 mRNA levels may be associated with one-year mortality following liver transplantation. These mRNA alterations closely mirrored those observed in sepsis-induced immunosuppression. CIITA, whose mRNA levels are reduced, encodes proteins involved in MHC class II expression, aligning with the well-described decrease in mHLA-DR expression in sepsis [24, 25]. Increased IL10 mRNA, a key immunosuppressive cytokine, has also been reported in sepsis along with elevated circulating IL-10 levels [26, 27]. Similarly, decreased IL7R mRNA expression reflects the findings in septic patients and is consistent with the profound lymphopenia observed in this population [28, 29], as IL-7 plays a critical role in promoting T-cell proliferation. Elevated CD177 is considered a marker of neutrophil immaturity, another hallmark of sepsis-induced immunosuppression [12, 30], whereas decreased GNLY expression reflects impaired cytotoxic functionality [31]. These findings, which closely align with the mechanisms of sepsis-induced immunosuppression, suggest that maladaptive immune reprogramming driven by progressive cirrhosis may persist even after LT. From a pathophysiological standpoint, further investigation is warranted to explore the potential causal link between pre-transplant immunosuppression and unfavorable post-transplant outcomes. From a clinical perspective, pre-LT immunological monitoring could facilitate the identification of patients who are at high risk of post-LT infection and pave the way for individualized post-transplant monitoring strategies. These preliminary findings require further validation through the recruitment of a larger cohort.

This study had several limitations. This is an exploratory study with a single-center design and modest sample size. This may have limited the generalizability of our results. In particular, the modest sample size and the limited number of outcome events precluded multivariable analyses adjusting marker–outcome associations for pre-transplant disease severity or other clinical confounders; consequently, this exploratory study cannot determine whether the identified transcriptomic markers add prognostic information beyond established clinical severity scores. Because candidate genes were selected in part on the basis of their AUC ($q < 0.10$ and $AUC > 0.65$), and the same AUCs are reported here as a measure of their performance, these estimates are likely optimistic and should be expected to be lower when evaluated in an independent validation cohort.

Thus, validation cohorts would be valuable to confirm the predictive value of these markers with stratification according to pre-LT disease severity (including ACLF grades), liver disease etiology and immunosuppressive regimens. In order to ascertain the additional value of pre-LT transcriptomic signatures, comparisons between validated post-LT prognosis scores - integrating donor and LT data - will also be necessary. Further studies on Acute Liver Failure may also be needed to confirm these results in this subgroup without underlying liver disease. Given the low number of patients and their similar clustering in PCA, we decided to analyze ACLF and ALF patients together, as they are both characterized by organ failure and similar features of innate immune dysfunction [32, 33]. Although the targeted transcriptomic panel used in this study is based on well-established immunological knowledge and is designed to provide a global overview of the immune response, encompassing genes involved in various stages of immune activation and regulation, it may not capture broader immune alterations. More comprehensive approaches, such as RNA sequencing, could offer additional insights and uncover novel pathways involved in post-transplant outcomes. The variable interval between the last pre-LT transcriptomic sample and transplantation (median 9 days [1–36]) reflects the constraints of a biobanking protocol designed for repeat immune monitoring across disease stages. In biologically dynamic populations such as ACLF, the immune status may evolve substantially over days. Thus, the interval between sampling day and LT date may result in a moderate distortion of the results. Sensitivity analyses restricted to samples collected within a shorter interval were not feasible given the sample size, and this temporal variability should be considered when interpreting our findings.

Overall, our results suggest that novel mRNA biomarkers associated with cirrhosis-associated immune dysfunction (CAID) may be valuable pre-LT tools to predict unfavorable outcomes following LT. Further studies will be necessary to confirm these preliminary results and explore the additional value of this immune assessment in clinical practice. Beyond the significance of these findings, which suggest that pre-transplant immune alterations may be linked to post-transplant clinical outcomes and warrant further investigation, this study also has important clinical implications. From a pragmatic perspective, integrating transcriptomic profiling into the pre-transplant evaluation process could markedly improve patient stratification and perioperative management. Specifically,

identifying patients at high risk for adverse outcomes may enable more personalized monitoring, targeted immunomodulatory strategies, and better-informed decisions regarding the timing and suitability of transplantation.

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 the Comité de Protection des Personnes Ile de France XI (approval number 19039-40433). 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

M-CD: conceptualization, methodology, resources, data curation, formal analysis, investigation, writing – original draft, writing – review and editing. EP: resources, investigation, writing – review and editing. AR: resources, investigation, writing – review and editing. TA: resources, investigation, writing – review and editing. MB: methodology, resources, investigation, writing – review and editing. EC: resources, data curation, writing – review and editing. SP: conceptualization, methodology, writing – review and editing. ECoz: methodology, resources, formal analysis, writing – review and editing. XM: resources, writing – review and editing. J-YM: resources, writing – review and editing. JD: resources, writing – review and editing. CG: resources, investigation, writing – review and editing. AB: resources, writing – review and editing. FA: resources, writing – review and editing. GM: conceptualization, methodology, resources, investigation, writing – original draft, writing – review and editing. FL: conceptualization, methodology, resources, investigation, writing – original draft, writing – review and editing. All authors contributed to the article and approved the submitted version.

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RT-qPCR (IPP prototype and FilmArray Torch System), carried out the analyses, and provided the raw data to M-CD, the first author of the article. The company had no role in the study design (EdMonHG), data analysis, interpretation of the results, or preparation of the manuscript.

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Conflict of interest

MB, EC, and EP were employees of the BioMérieux company, an in vitro diagnostic company. M-CD, MB, EP, and GM worked in a joint research unit (EA7426) co-funded by the Hospices Civils of Lyon and the BioMérieux company.

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.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontierspartnerships.org/articles/10.3389/ti.2026.16292/full#supplementary-material>

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Glossary

ACLF	acute-on-chronic liver failure
ACLD	advanced chronic liver disease
AD	acute decompensation
ALD	alcohol-related liver disease
ALF	acute liver failure
AUC	area under the curve
CAID	cirrhosis-associated immune dysfunction
CIITA	class II major histocompatibility complex transactivator
CLIF	chronic liver failure
cACLD	compensated advanced chronic liver disease
CD177	cluster of differentiation 177
CD74	cluster of differentiation 74
CX3CR1	C-X3-C motif chemokine receptor 1
DCD	donation after circulatory death
GAM	generalized additive model
GNLY	granulysin
HLA-DR	human leukocyte antigen–DR isotype
ICU	intensive care unit
IL7R	interleukin 7 receptor
IL10	interleukin 10
IPP	immune profiling panel
IQR	interquartile range
LT	liver transplantation
MASH	metabolic dysfunction-associated steatohepatitis
MELD	model for end-stage liver disease
mHLA-DR	monocytic human leukocyte antigen–DR isotype
N-AD	non-acute decompensation
OF	organ failure
OR	odds ratio
PCA	principal component analysis
qPCR	quantitative polymerase chain reaction
ROC	receiver operating characteristic
RT-qPCR	reverse transcription quantitative polymerase chain reaction
SOFA	sequential organ failure assessment
TAP2	transporter associated with antigen processing 2
TNF	tumor necrosis factor
ZAP70	zeta-chain associated protein kinase 70



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Kidney-alone transplantation in prior SLK candidates: a national registry analysis

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Outcomes of kidney-alone transplantation (KAT) in former simultaneous liver-kidney (SLK) transplant candidates after liver waitlist delisting are not well defined. Using Scientific Registry of Transplant Recipients (SRTR) data, we identified adult recipients who underwent KAT between 2005 and 2025 after prior SLK listing (RLD-KAT), which was matched 1:5 to primary KAT recipients without liver disease by age, transplant year, and diabetes status. Patient and graft survival were evaluated using the Kaplan-Meier method and multivariable Cox proportional hazards models. We identified 163 RLD-KAT recipients matched to 815 controls. Unadjusted Kaplan-Meier analyses demonstrated lower patient survival in RLD-KAT ($p = 0.020$), whereas death-censored and overall graft survival were similar ($p > 0.05$). In multivariable models, death-censored graft survival (HR 0.89; 95% CI 0.51–1.53), overall graft survival (HR 1.00; 95% CI 0.73–1.36), and patient survival (HR 1.07; 95% CI 0.76–1.5) did not differ significantly. Six RLD-KAT recipients (3.7%) subsequently underwent liver transplantation. Kidney-alone transplantation in prior SLK candidates was associated with acceptable patient and graft outcomes and a low incidence of subsequent liver transplantation.

KEYWORDS

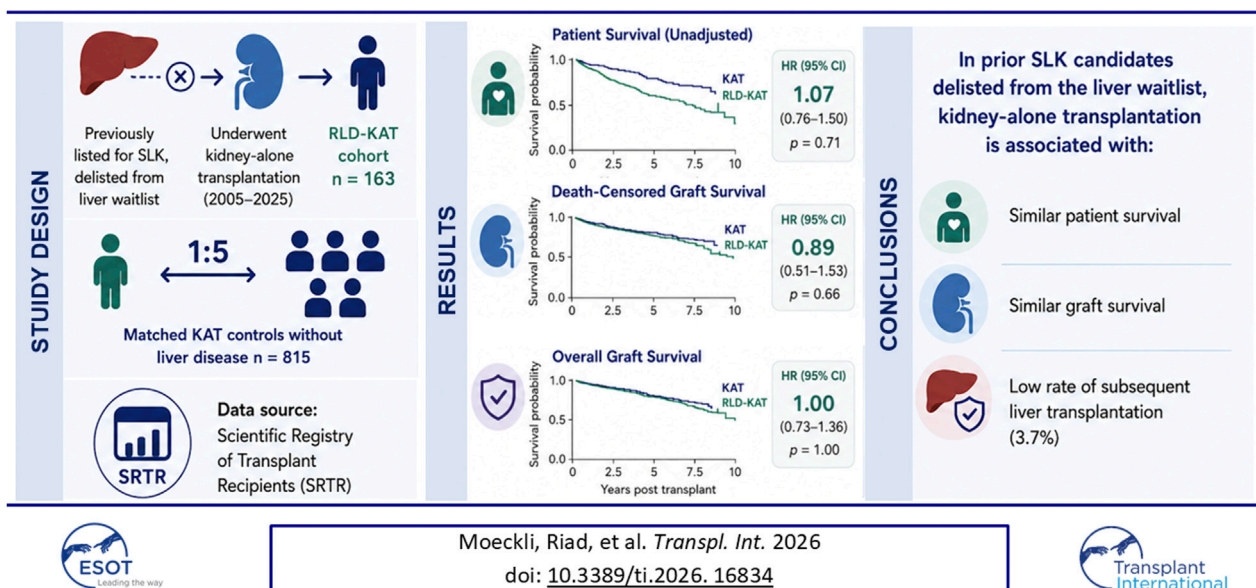
chronic liver diseases, cirrhosis, end stage renal disease, graft survival, kidney transplantation, simultaneous liver-kidney transplantation, compensated cirrhosis

Introduction

Chronic kidney disease (CKD) is increasingly common among liver transplant candidates, driven by shifts in liver disease epidemiology and rising rates of concurrent renal dysfunction [1, 2]. In the United States, alcohol-associated liver disease and metabolic dysfunction-associated steatohepatitis (MASH) have emerged as the leading indications for liver transplantation [3], both of which are strongly associated with CKD [2, 4]. This evolving landscape necessitates more nuanced decisions regarding organ allocation, particularly in balancing the use of simultaneous liver-kidney transplantation (SLK) versus kidney-alone transplantation (KAT).

In patients with compensated cirrhosis, early SLK listing practices were shaped by concerns that kidney transplantation alone could precipitate hepatic decompensation, leading to conservative strategies that favored dual-organ allocation [5–7]. This caution remains evident in the kidney transplant community, where hesitancy persists in offering KAT to patients with compensated cirrhosis, even when synthetic liver function appears preserved [8, 9]. Central

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concerns include the risk of post-transplant liver decompensation, progression to end-stage liver disease, and inadequate assessment of portal hypertension or ongoing hepatic injury [10].

In the United States, candidates are considered for simultaneous liver–kidney transplantation (SLK) only after meeting accepted indications for liver transplantation while also satisfying kidney-specific eligibility criteria established by the Organ Procurement and Transplantation Network (OPTN). Current OPTN policy defines SLK eligibility primarily by the severity and duration of kidney dysfunction, including prolonged dialysis dependence or sustained reductions in estimated glomerular filtration rate (eGFR), rather than by standardized measures of liver disease reversibility [11, 12].

While these criteria improved consistency in SLK allocation, they do not directly address the dynamic nature of liver disease or changes in transplant candidacy over time. Consequently, transplant decision-making often shifts to the kidney transplant community when candidates initially listed for SLK reach a point where liver transplantation is no longer pursued yet continue to require kidney transplantation. In this setting, uncertainty remains regarding the safety of proceeding with kidney-alone transplantation (KAT), particularly in the absence of standardized measures of hepatic stability or objective assessment of portal hypertension. Consequently, centers may vary in their willingness to proceed with

KAT. Although several single-center studies suggest that KAT may be feasible in carefully selected patients, long-term outcomes in this unique population remain poorly characterized [13–15].

Recently, our group examined national waitlist outcomes among more than 15,000 candidates listed for SLK transplantation using the SRTR. That study demonstrated that kidney-alone transplantation following SLK listing is uncommon, occurring in approximately 1%–1.5% of candidates, while approximately 15% were removed from the waitlist because transplantation was no longer considered necessary. These findings highlight the dynamic nature of transplant candidacy and suggest that a small but clinically important subgroup of candidates may ultimately proceed with kidney-alone transplantation. However, the long-term post-transplant outcomes of these recipients remain unknown [16].

This study leverages national SRTR data to evaluate outcomes in recipients who were initially listed for SLK but ultimately received KAT following liver waitlist delisting. By comparing these recipients with matched kidney-alone transplant recipients without liver disease, we characterize patient and graft survival, evaluate the subsequent need for liver transplantation, and provide evidence to inform transplant decision-making in this uncommon but clinically important population.

Materials and methods

Data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US,

Abbreviations: CKD, Chronic Kidney Disease; SLK, Simultaneous Liver–Kidney Transplantation; KAT, Kidney-Alone Transplantation; RLD-KAT, Recompensated Liver Disease Kidney-Alone Transplantation; MELD, Model for End-Stage Liver Disease; SRTR, Scientific Registry of Transplant Recipients; OPTN, Organ Procurement and Transplantation Network; HCV, Hepatitis C Virus; HBV, Hepatitis B Virus; BMI, Body Mass Index; HLA, Human Leukocyte Antigen; TIPSS, Transjugular Intrahepatic Portosystemic Shunt; eGFR, Estimated Glomerular Filtration Rate.

submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Data access for this study was obtained through the SRTR Data Access Portal under approved data-use agreements, and analyses were conducted in compliance with applicable ethical guidelines and regulatory requirements. This study was deemed exempt by the Mayo Clinic internal review board.

Study population

We analyzed all adult (≥ 18 years) kidney-alone transplant (KAT) recipients in the Scientific Registry of Transplant Recipients (SRTR) between 2005 and 2025. Recipients were identified using linked liver and kidney transplant records within the Scientific Registry of Transplant Recipients (SRTR). The study cohort consisted of adults with chronic liver disease who were initially listed for simultaneous liver–kidney transplantation (SLK) before their first kidney transplant, had no history of prior liver or kidney transplantation, and ultimately underwent kidney-alone transplantation (KAT). To preserve the temporal sequence between liver listing and kidney transplantation, only liver waitlist registrations preceding the first kidney transplant were considered.

Because SRTR does not capture physiologic markers of hepatic recovery, the cohort was characterized using liver waitlist status before kidney transplantation. Throughout the manuscript, this administratively defined cohort is referred to as recompensated liver disease kidney-alone transplantation (RLD-KAT) for simplicity. The acronym reflects the clinical pathway leading to kidney-alone transplantation rather than direct biologic evidence of hepatic recompensation. RLD-KAT recipients were then matched in a 1:5 ratio to primary kidney-alone transplant recipients without prior liver waitlist registration (hereafter referred to as the KAT cohort) using recipient age (± 5 years), kidney transplant year, and diabetes status.

Outcomes of interest

The primary outcome of the study was the patient and graft survival. Death-censored graft survival is defined as time from transplant to graft failure with death treated as a censoring event. Overall graft survival is defined as time from transplant to graft loss or patient death. Recipient survival is defined as time from transplant to death from any cause. Secondary outcomes included subsequent liver transplantation, repeat kidney transplantation, and cause-specific mortality where available.

Variables and definitions

Recipient characteristics include age, sex, race/ethnicity, body mass index (BMI), diabetes status, hepatitis B and C status, dialysis status and duration, serum creatinine, steroid maintenance, induction therapy, and other relevant comorbidities. Donor characteristics included donor age and sex, BMI, donor type, kidney donor risk index (KDRI) and human leukocyte antigen (HLA) mismatch. Transplant

characteristics include local organ availability, kidney cold ischemia time, and induction regimens.

For the RLD-KAT cohort, additional liver-related variables were collected to characterize the clinical trajectory after initial SLK listing, including liver disease etiology, MELD score at SLK listing, INR, ascites, encephalopathy, prior TIPS, liver waitlist removal or inactivation, documented liver waitlist removal reason, and the interval between liver waitlist status change and kidney transplantation, when available.

Statistical analyses

Recipients in the RLD-KAT cohort were matched to primary KAT recipients in a 1:5 ratio based on age (± 5 years), transplant year and diabetes status to ensure demographic comparability and reduce confounding by secular trends in transplant practice.

Descriptive statistics were used to summarize baseline characteristics. Continuous variables are presented as means with standard deviations or medians with interquartile ranges, depending on distribution. Categorical variables are summarized as counts and percentages. Group comparisons used chi-square or Fisher's exact tests for categorical variables and Student's t-tests or Wilcoxon rank-sum tests for continuous variables, as appropriate.

Liver waitlist removal status, removal reason, and timing of liver waitlist status changes were summarized descriptively to characterize the RLD-KAT cohort and were not incorporated into matching or survival models.

Survival outcomes, including death-censored graft survival, overall graft survival, and patient survival, were analyzed using the Kaplan–Meier method, with differences assessed using the log-rank test. Follow-up time was calculated from the date of kidney transplantation to the date of the outcome event or the last known follow-up.

To account for residual confounding, multivariable Cox proportional hazards models were constructed for each survival endpoint. Covariates included a priori-selected recipient (age, sex, ethnicity, BMI, diabetes, dialysis duration) and donor factors (donor age and donor type). Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. The proportional hazards assumption was evaluated using Schoenfeld residuals and visual inspection of scaled Schoenfeld plots; no major violations were detected. Missing data were minimal and handled using complete-case analysis. Statistical significance was defined as a two-sided p-value < 0.05 . All analyses were performed in R v4.4.1 [17].

Results

Baseline characteristics

Table 1 summarizes the characteristics of the RLD-KAT cohort and matched KAT controls. The mean age of both groups was identical (56.0 ± 10.3 years), and the matching strategy resulted in comparable sex distributions. Racial composition was also similar with the RLD-KAT group being predominantly white (64.4%), while the KAT group was slightly more racially diverse (59.8% white, $p = 0.306$). Comorbidity profiles were generally similar, including comparable rates of diabetes (34.9% in KAT vs. 35.2% in RLD-

TABLE 1 Baseline recipient characteristics by transplant type.

Characteristic	Missingness (%)	KAT (n = 815)	RLD-KAT (n = 163)	p-value
Recipient characteristics				
Age, years	0	56.0 (10.3)	56.0 (10.3)	0.99
Female sex, n (%)	0	325 (39.9%)	66 (40.5%)	0.88
Race/Ethnicity, n (%)	0			0.31
Black		259 (31.8%)	42 (25.8%)	
Other		69 (8.5%)	16 (9.8%)	
White		487 (59.8%)	105 (64.4%)	
BMI, kg/m ²	0	28.5 (5.3)	26.9 (5.05)	<0.001
Diabetes, n (%)	0.8	282 (34.9%)	57 (35.2%)	0.94
Hepatitis B positive, n (%)	1.5	14 (1.7%)	10 (6.3%)	<0.001
Hepatitis C positive, n (%)	2.2	43 (5.4%)	52 (32.7%)	<0.001
ESRD etiology	0.2			0.035
Diabetes		292 (29.9%)	40 (24.5%)	
Glomerulonephritis		174 (17.8%)	21 (12.9%)	
Polycystic kidney disease		113 (11.6%)	23 (14.1%)	
Other		397 (40.7%)	79 (28.5%)	
On dialysis, n (%)	0.3	669 (82.4%)	147 (90.2%)	0.014
Dialysis duration, years	0.7	3.4 (3.3)	5.1 (4.2)	<0.001
Kidney waitlist duration, years	0	1.9 (2.1)	2.6 (2.6)	0.001
Peripheral arterial disease	0.9	92 (11.4%)	25 (15.3%)	0.16
Donor characteristics				
Age, years	0	43.0 (14.7)	40.6 (13.2)	0.052
Female sex, n (%)	0	377 (46.3%)	80 (49.1%)	0.51
BMI, kg/m ²	0.5	28.1 (6.8)	28.8 (7.3)	0.20
Donation type	0			0.022
DBD		415 (50.9%)	99 (60.7%)	
DCD		169 (20.7%)	34 (20.9%)	
Living donor		231 (28.3%)	30 (18.4%)	
Estimated GFR	27.2	85.9 (41.1)	87.8 (36.6)	0.63
KDRI	28.8	1.23 (0.30)	1.19 (0.29)	0.11
Transplant characteristics				
Local organ, n (%)	0	351 (43.1%)	87 (53.4%)	0.016
Kidney cold ischemia time, h	1.6	14.4 (10.4)	15.5 (9.6)	0.25
HLA mismatch, n (%)	0.4			0.98
0		47 (5.8%)	10 (6.2%)	
1–3		175 (21.6%)	35 (21.6%)	
4–6		590 (72.7%)	117 (72.2%)	
Induction therapy, n (%)	7.6			0.034
Depletional		576 (76.3%)	96 (64.9%)	
Non-depletional		137 (18.1%)	41 (27.7%)	

(Continued)

TABLE 1 Continued

Characteristic	Missingness (%)	KAT (n = 815)	RLD-KAT (n = 163)	p-value
Mixed induction		27 (3.6%)	7 (4.7%)	
Steroids only		15 (2.0%)	4 (2.7%)	
Steroid maintenance, n (%)	1.2	559 (69.4%)	111 (68.9%)	0.901
Liver disease characteristics (RLD-KAT only)				
MELD score	0		20.5 (4.4)	NA
INR	0		1.13 (0.24)	N/A
Ascites	0		63 (38.9%)	N/A
Encephalopathy	0		34 (21.0%)	N/A
TIPS, n (%)	4.3		5 (3.1%)	NA
Etiology of liver disease, n (%)	0			NA
Alcohol			33 (20.2%)	
MASH			10 (6.1%)	
Cystic/Other			49 (30.1%)	
Autoimmune/Cholestatic (AIH, PSC, PBC)			6 (3.7%)	
Hepatitis C			49 (30.1%)	
Other (cryptogenic, metabolic, malignancy)			16 (9.8%)	
Liver waitlist characteristics (RLD-KAT only)				
Liver waitlist duration, years	1.2		2.97 (2.56)	NA
Time from liver waitlist inactivation or removal	19		2.11 (2.0)	NA
Removal cause (improved)	1.2		105 (65.2%)	NA

Values are presented as mean (SD) or number (%), unless otherwise specified. Liver disease and liver waitlist characteristics are reported only for the RLD-KAT cohort and are presented to characterize the clinical trajectory of recipients previously listed for simultaneous liver–kidney transplantation, rather than to define cohort eligibility.

Abbreviations: AIH, Autoimmune hepatitis; BMI, Body mass index; ESRD, End Stage Renal Disease; HLA, Human leukocyte antigen; KAT, Kidney-alone transplantation; LD, Living donor; MASH, Metabolic dysfunction–associated steatohepatitis; MELD, Model for End-Stage Liver Disease; PBC, Primary biliary cholangitis; PSC, Primary sclerosing cholangitis; RLD-KAT, Recompensated liver disease kidney-alone transplantation; TIPS, Transjugular intrahepatic portosystemic shunt. Bold values denote statistically significant differences between groups ($p < 0.05$).

KAT). Hepatitis C was more common among RLD-KAT recipients (32.7% vs. 5.4%), reflecting the underlying liver disease history.

RLD-KAT recipients had a lower body mass index (26.9 vs. 28.5 kg/m², $p < 0.001$), they were more likely to be on dialysis at the time of transplantation (90.2% vs. 82.4%, $p = 0.014$), with longer dialysis duration (5.1 vs. 3.4 years, $p < 0.001$) and longer waitlist time (2.6 vs. 1.9 years, $p = 0.001$). Among RLD-KAT recipients, the mean MELD score at initial SLK listing averaged 20.5 ± 4.4 , with last mean INR of 1.13 (0.24), documented ascites in 38.9%, encephalopathy in 21.0% and 5 patients (3.1%) had previous TIPS placement at the time of registration. Cystic disease (30.1%), Hepatitis C (30.1%) and alcohol-associated liver disease (20.2%) were the leading etiologies for initial SLK listing among RLD-KAT recipients. Liver waitlist removal due to clinical improvement was documented in 105 recipients (65.2%). The mean interval from liver waitlist inactivation or removal to kidney transplantation was 2.11 ± 2.0 years. Temporal trends in RLD-KAT over the study period are shown [Figure 1](#).

Donor characteristics were broadly comparable, although RLD-KAT recipients were less likely to receive living donor kidneys (18.4% vs. 28.3%) and more likely to receive donation after brain death organs (60.7% vs. 50.9%, $p = 0.022$). Donor kidney quality, as assessed by estimated GFR and KDRI, was similar between groups.

Primary outcomes

Outcomes following KAT and RLD KAT are reported in [Table 2](#). Kaplan–Meier analysis ([Figure 2](#)) did not show a significant difference in death-censored graft survival between RLD-KAT and matched KAT recipients (log-rank $p = 0.830$). In multivariable Cox regression adjusting for recipient demographics, diabetes, BMI, dialysis duration and donor factors, RLD-KAT was not associated with inferior graft outcomes (HR 0.89; 95% CI 0.51–1.53; $p = 0.670$).

Overall graft survival trajectories were likewise similar between groups ([Figure 3](#); log-rank $p = 0.089$). After adjustment, the hazard ratio for overall graft loss among RLD-KAT recipients (HR 1.00; 95% CI 0.73–1.36; $p = 0.980$) did not differ significantly from matched KAT recipients.

Recipient survival was lower in RLD-KAT than controls ([Figure 4](#); log-rank $p = 0.020$). However, in the adjusted model, RLD-KAT was not significantly associated with a higher risk of mortality (HR 1.07; 95% CI 0.76–1.5; $p = 0.710$).

In subgroup analyses stratified by underlying liver disease etiology, patient survival after KAT did not differ between RLD-KAT and matched KAT recipients across hepatitis C, alcohol-associated liver disease, polycystic liver disease, and MASH ([Supplementary Figure 1](#)).

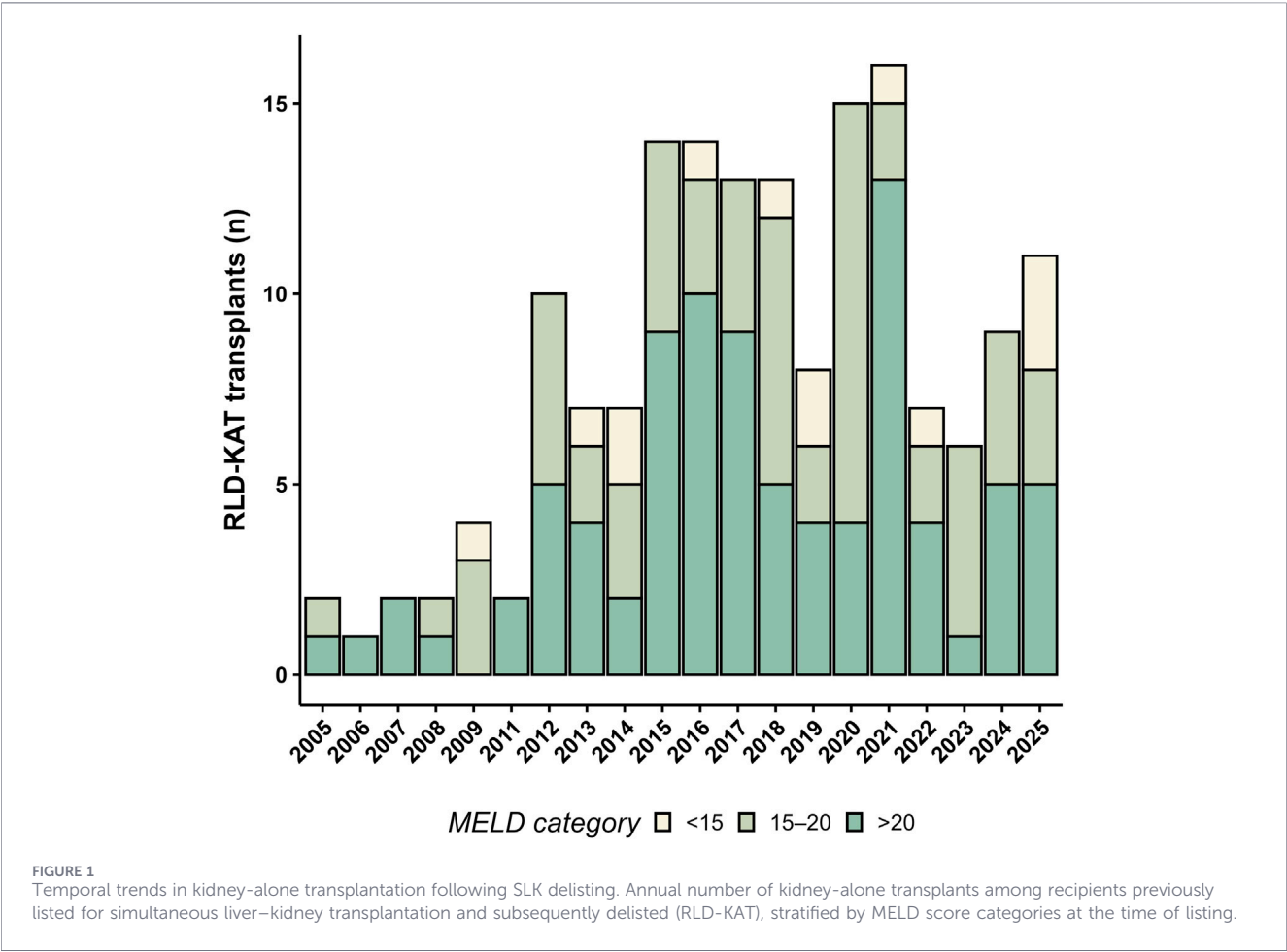


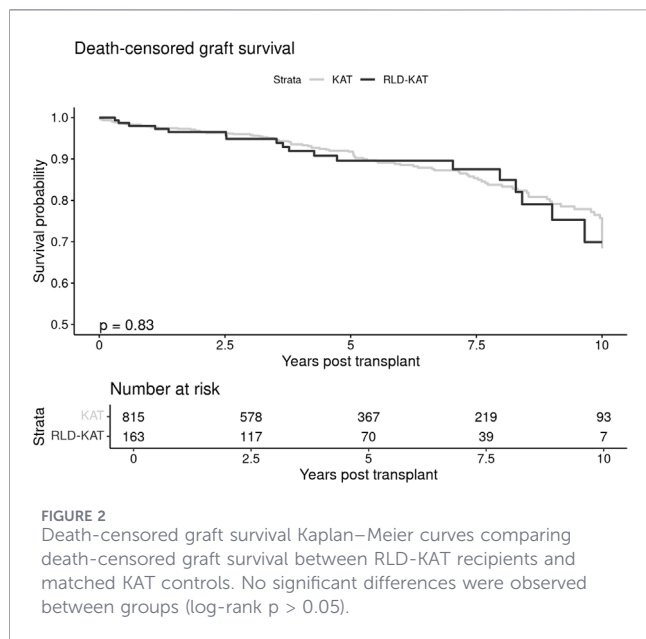
TABLE 2 Multivariable models for recipient and kidney graft survival.

Model	HR	95% C.I.	p-value
Death-censored kidney graft survival			
Kidney alone transplant	Reference		
RLD-KAT	0.89	(0.51, 1.53)	0.67
Overall kidney graft survival			
Kidney alone transplant	Reference		
RLD-KAT	1.00	(0.73, 1.36)	0.980
Recipient death			
Kidney alone transplant	Reference		
RLD-KAT	1.07	(0.76, 1.5)	0.710

Models were adjusted for recipients Age, Sex, Race, BMI, Diabetes, dialysis duration, Donor age and donor type.
Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; KAT, Kidney-alone transplantation; RLD-KAT, Recompensated liver disease kidney-alone transplantation.

Two additional sensitivity analyses were performed after stratifying recipients by waitlist removal status (“improved” versus all other causes). In the improved subgroup (n = 105), Kaplan–Meier analyses demonstrated no significant differences between RLD-KAT recipients and their matched KAT counterparts in recipient survival, death-censored graft

survival, or overall graft survival (all log-rank $p > 0.05$) (Supplementary Figure 2). In the remaining subgroup (n = 58), death-censored and overall graft survival also did not differ between groups (both log-rank $p > 0.05$). Although unadjusted recipient survival was lower among RLD-KAT recipients (log-rank $p = 0.005$), this association was attenuated after multivariable



adjustment and was no longer statistically significant (HR 1.58, 95% CI 0.89–2.79; $p = 0.12$), consistent with the findings of the primary analysis (Supplementary Figure 3).

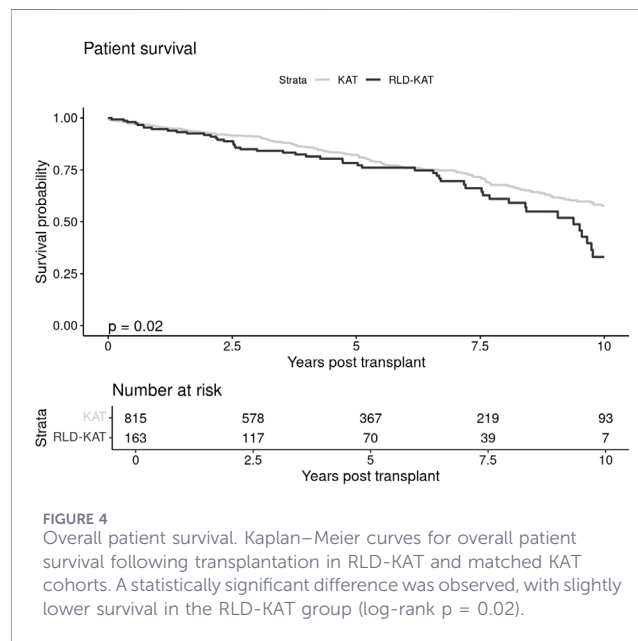
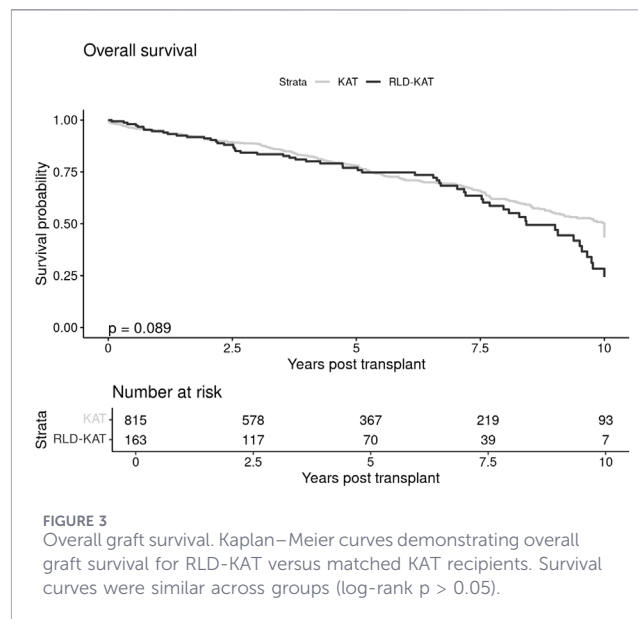
Secondary outcomes

Re-transplantation was rare in both groups (Table 3). Only seven (4.3%) RLD-KAT recipients required additional organ transplantation: one underwent repeat kidney transplantation, four received a subsequent liver transplant, and two ultimately required a combined SLK. These results suggest that progression to subsequent liver transplantation following kidney alone-transplantation was uncommon in this selected cohort.

Additionally, we examined the causes of death among decedents in the full cohort. Cause-of-death information was unavailable for a substantial proportion of decedents, limiting formal comparisons between groups. Among recipients with available data, the distribution of cause-specific mortality was similar between RLD-KAT and matched KAT recipients (Supplementary Table 1).

Discussion

In this national registry analysis, we evaluated outcomes of kidney-alone transplantation among recipients who were initially listed for SLK but ultimately underwent kidney-alone transplantation after liver transplantation was no longer pursued. These findings demonstrate that graft and patient survival in this administratively defined cohort are comparable to those of demographically matched primary KAT recipients. Across death-censored graft survival and overall graft survival, neither Kaplan–Meier analyses nor multivariable Cox models revealed significant differences between groups. While unadjusted Kaplan–Meier curves demonstrated lower patient survival in RLD-KAT recipients, this difference was attenuated and no longer statistically significant after multivariable adjustment.



These findings suggest that kidney-alone transplantation may be an appropriate strategy in carefully selected prior SLK candidates following liver waitlist delisting.

The separation observed in the unadjusted Kaplan–Meier survival curve likely reflects baseline differences between groups. Adjustment for clinically relevant variables attenuated the mortality signal, suggesting that the crude survival difference was driven by measured confounders rather than an independent effect of prior liver-kidney listing status. Given the modest sample size and the inherent selection of recipients in whom liver transplantations was no longer considered necessary, these findings should not be interpreted as demonstrating equivalence but rather as supportive of acceptable outcomes in a selected cohort.

The findings of this study align with real-world clinical practice within transplant hepatology and transplant surgery. Liver transplant

TABLE 3 Subsequent organ transplant by recipient group.

Characteristic	KAT (n = 815)	RLD-KAT (n = 163)
Not re-transplanted	795	156
Kidney transplant alone	20	1
Liver transplant alone	0	4
Simultaneous liver/Kidney transplant	0	2

Abbreviations: KAT, Kidney-alone transplantation; RLD-KAT, Recompensated liver disease kidney-alone transplantation.

teams may opt to discontinue pursuit of liver transplantation when hepatic recovery is sufficient, especially when synthetic function improves, portal hypertension stabilizes, MELD components normalize, or patients respond to interventions such as alcohol abstinence, antiviral therapy, or medical optimization [18–21]. In our cohort, 65.2% of recipients were removed from the liver waitlist because of documented clinical improvement. Although the SRTR does not capture the specific clinical factors underlying these decisions, our findings demonstrate that recipients who ultimately underwent kidney-alone transplantation after liver transplantation was no longer pursued had long-term outcomes comparable to standard KAT recipients. Notably, these outcomes were observed despite the RLD-KAT group having longer pre-transplant dialysis duration and a lower proportion of living donors (Table 1). Future work should aim to establish objective criteria, such as estimation of portal hypertension, fibrosis regression markers or biochemical recovery thresholds, that can better identify individuals who can safely transition from SLK consideration to KAT.

Recent work by Schmidt et al. further supports the concept of dynamic liver transplant candidacy. In a national SRTR analysis of more than 15,000 SLK-listed candidates, prior TIPS placement was associated with significantly lower one-year mortality and a 29% reduction in adjusted mortality overall [16]. These findings emphasize the importance of considering the evolving trajectory of hepatic candidacy, when determining whether SLK or KAT is the more appropriate strategy. Our results add a valuable post-transplant perspective to this evolving paradigm. Among carefully selected SLK candidate in whom liver transplantation was not pursued, long-term outcomes were comparable to those observed among matched KAT recipients. A notable finding is the durability of this treatment strategy. Only six patients (3.7%) in the RLD-KAT cohort required subsequent liver transplantation, four liver alone transplants and two SLK, suggesting that progression to liver transplantation after KAT was uncommon. Together, these findings support a more individualized approach to SLK vs. KAT decision-making. Transplant nephrologists and surgeons should consider KAT in carefully selected prior SLK candidates, as this approach appears both clinically safe and resource efficient.

Several smaller single center studies have demonstrated that kidney transplantation alone can be safe and effective in patients with well-compensated cirrhosis [13–15, 22]. For example, Nathani et al. reported favorable post-KAT outcomes in cirrhotic patients with preserved hepatic function in a single center study including 32 patients, with 19% of cirrhotic patients presenting with hepatic decompensation post KAT. In a multicenter retrospective study including 34 patients with compensated cirrhosis, Dodge et al.

demonstrated that kidney transplantation alone is feasible and associated with a five-year post-KTA incidence of hepatic decompensation of 23.5%, consistent with the natural history of disease progression in cirrhosis [23–25]. Our data complement and extend these findings by providing a national, matched cohort analysis with long-term follow-up. However, caution is warranted when generalizing our findings to all patients with compensated cirrhosis, as the RLD-KAT cohort represents a highly selected group of prior SLK candidates, and unmeasured factors such as degree of portal hypertension, presence of ascites, fibrosis, alcohol abstinence, or virologic control likely contributed to the outcomes.

A specific population warranting mention is patients with autosomal dominant polycystic kidney disease and coexisting polycystic liver disease. These individuals often present with massive hepatomegaly and progressive renal failure, and may be considered for SLK primarily to address symptom burden due to space constraints such as anorexia and abdominal distention, potentially leading to cachexia [26]. Hepatic synthetic function in this population is typically preserved, and liver disease rarely progresses to decompensation [27]. Our findings suggest that when renal dysfunction dominates the clinical picture, KAT may be an appropriate option even in patients previously listed for SLK, particularly with appropriate preoperative imaging and multidisciplinary planning (Supplementary Figure 1). Although our study was not designed specifically to evaluate this subgroup, these observations support careful patient selection and individualized decision-making regarding SLK versus KAT in polycystic liver disease.

The importance of this clinical question is likely to increase as the epidemiology and treatment of chronic liver disease continue to evolve. Alcohol-associated liver disease and MASH have become the leading indications for liver transplantation [3] and an increasing number of patients may experience meaningful improvement in liver function following sustained alcohol abstinence [18], antiviral therapy for chronic viral hepatitis [19, 20], optimization of portal hypertension [21], and emerging disease-modifying therapies for metabolic liver disease [28, 29]. As transplant candidacy becomes increasingly dynamic, multidisciplinary reassessment of both liver and kidney transplant needs will be key. Future studies should focus on developing objective clinical criteria incorporating portal hypertension, liver synthetic function, and disease trajectory to better identify candidates who may safely transition from SLK consideration to kidney-alone transplantation.

Nevertheless, several limitations merit acknowledgement. First, the SRTR lacks detailed clinical granularity regarding

liver disease recovery. Importantly, the exposure of interest in this study is administrative rather than physiologic. “Recompensation” in this analysis reflects transplant center listing decisions and liver waitlist status recorded within the SRTR rather than direct measures of portal hypertension, fibrosis regression, ascites history, abstinence durability, or virologic control. Furthermore, liver waitlist removal and documented reasons for removal were used to characterize the clinical pathway preceding kidney transplantation, rather than to ascertain cohort eligibility. Consequently, variability in transplant center practices regarding waitlist management may have influenced cohort characterization without affecting cohort ascertainment. As such, this study evaluates outcomes in candidates deemed stable enough that liver transplantation was not pursued, rather than the biologic reversal of cirrhosis. The findings, therefore, reflect selection practices and center-level decision-making as much as liver disease trajectory. Second, although we identified recipients who were initially listed for SLK and ultimately underwent kidney-alone transplantation, the SRTR database does not capture individuals who were referred for liver transplant evaluation but never listed. As a result, an important segment of patients with early or improving liver function is not represented. Third, despite matching and multivariable adjustments, unmeasured confounding remains possible, particularly given the extensive clinical selection and transplant center decision-making inherent to the RLD-KAT cohort. Additionally, because the SRTR does not capture the clinical rationale underlying initial SLK listing decisions, we cannot determine whether some candidates were listed conservatively before the trajectory of their liver disease became fully apparent. As disease-modifying therapies for alcohol-associated liver disease, viral hepatitis, and MASH continue to evolve, liver transplant candidacy may become increasingly dynamic, further emphasizing the need for objective criteria to identify candidates who can safely undergo kidney-alone transplantation.

Despite these limitations, the study provides valuable insights into the durability and outcomes of kidney-alone transplantation in carefully selected prior SLK candidates after liver transplantation was no longer pursued.

Conclusion

Kidney-alone transplantation in carefully selected candidates previously listed for SLK in whom liver transplantation was no longer pursued is associated with acceptable graft and patient survival and a low incidence of subsequent liver transplantation. These findings support careful individualized consideration of KAT over SLK in appropriately selected patients but should not be extrapolated to all patients with compensated cirrhosis or used to redefine SLK eligibility criteria. Rather, they provide reassurance regarding outcomes in this administratively defined, highly selected population.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Dataset not publicly available. Requests to access these datasets should be directed to srtr@srtr.org.

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

BM, KH, DS, and SR: Concept/design, Drafting article, Data analysis/interpretation, Critical revision of article, Approval of article. BS: Data analysis/interpretation, Critical revision of article, Approval of article. JO, ARC, TT, JH: Concept/design, Data analysis/interpretation, Critical revision of article, Approval of article. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontierspartnerships.org/articles/10.3389/ti.2026.16834/full#supplementary-material>

SUPPLEMENTARY FIGURE 1

Patient survival after kidney-alone transplantation stratified by underlying liver disease etiology Kaplan–Meier estimates of patient survival following kidney-alone transplantation (KAT) comparing recipients without liver disease (KAT, black) and recipients with recompensated liver disease initially listed for simultaneous liver–kidney transplantation (RLD–KAT, gray). Survival is shown stratified by underlying liver disease etiology for the RLD–KAT

group, including hepatitis C, alcohol-associated liver disease, polycystic liver disease, and metabolic dysfunction–associated steatohepatitis (MASH). No statistically significant differences in survival were observed between cohorts across all etiologies (log-rank p values shown).

SUPPLEMENTARY FIGURE 2

Kaplan–Meier curves for recipients removed because of clinical improvement. Kaplan–Meier curves comparing death-censored graft survival (top), overall graft survival (middle), and recipient survival (bottom) between RLD–KAT recipients with documented liver waitlist removal due to clinical improvement (n = 105) and their matched KAT controls. No significant differences were observed for death-censored graft survival, overall graft survival, or recipient survival (all log-rank p > 0.05), consistent with the primary analysis.

SUPPLEMENTARY FIGURE 3

Kaplan–Meier curves for recipients removed because of other reasons. Kaplan–Meier curves comparing death-censored graft survival (top), overall graft survival (middle), and recipient survival (bottom) between RLD–KAT recipients removed from the liver waitlist for reasons other than documented clinical improvement (n = 58) and their matched KAT controls. Death-censored graft survival and overall graft survival did not differ significantly between groups (both log-rank p > 0.05). Although unadjusted recipient survival was lower among RLD–KAT recipients (log-rank p = 0.005), this association was attenuated after multivariable adjustment and was no longer statistically significant (HR 1.58, 95% CI 0.89–2.79; p = 0.12), consistent with the primary analysis.

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ABO incompatible LRD kidney transplantation should be offered to children: results from a 33-year comparative OPTN study

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ABOi transplantation is a growing practice with excellent clinical outcomes. Some paediatric transplant programmes are reluctant to offer ABOi transplantation and list children on a DD waiting list. However, there are no studies directly comparing the outcomes between pediatric ABOi LD kidney transplants (LDKTx) and ABOc DD transplants (DDKTx). Data were retrieved on all pediatric kidney transplants from 1987–2020, from the United Network for Organ Sharing. Propensity score matching was used to select a control group of ABOc transplant recipients. Long term outcomes were compared between ABOi and ABOc kidney transplants and between ABOi LDKTx and ABOc DDKTx. Data were compared using chi-square test, t-test and Kaplan-Meier survival analysis. Overall, there were 70 pediatric ABOi kidney transplants meeting the study criteria. There was no significant difference in allograft ($p = 0.42$) and patient survival ($p = 0.58$) between ABOi and ABOc transplants. ABOi LDKTx had significantly lower incidence of delayed allograft function and better long-term allograft survival than ABOc DDKTx ($p < 0.01$, $p = 0.01$). ABOi transplantation has excellent long-term outcomes. ABOi LDKTx lead to better long-term outcomes than ABOc DDKTx. We recommend that ABOi transplantation from a LD should be considered prior to listing children for transplantation from a DD.

KEYWORDS

ABO incompatible, kidney transplant, living donor, pediatric, registry

Introduction

Shortage of organs is a major issue in pediatric renal transplantation globally. An increasing number of children with kidney failure are surviving infancy and presenting as potential kidney transplant candidates. This has created an increasing demand for donor kidneys which is reflected by the increase in pediatric patients on the waiting list (34.3% increase over 10 years) as well as an increase in the average waiting time (the number of patients waiting >1 year for a transplant increased from 55.2% to 59.7% in 10 years [1]). Despite an increasing number of children requiring a transplant, the incidence of both living and deceased donor kidney transplants have decreased by 16% and 16.1% respectively in the last 10 years [1].

The best treatment for a child with kidney failure is a pre-emptive kidney transplant from a living donor [2, 3]. Pediatric patients carry a high likelihood of requiring subsequent transplants throughout their life, so it is important that their first transplant functions for as long as possible.

ABO Incompatible LRD Kidney Transplantation Should be Offered to Children: Results from a 33-year Comparative OPTN study

Methods	Results		
	Delayed Allograft Function	Allograft Survival	Patient Survival
- USA National Registry (OPTN) - All paediatric kidney transplants 1987-2020	ABO incompatible	ABO incompatible	ABO incompatible
	ABO compatible	ABO compatible	ABO compatible
 ABO Incompatible n=70 ABO Compatible n=23,695	Living Donor ABO incompatible	Living Donor ABO incompatible	Living Donor ABO incompatible
	Deceased Donor ABO compatible	Deceased Donor ABO compatible	Deceased Donor ABO compatible

Living donor ABO incompatible transplantation has excellent outcomes and should be considered prior to listing for deceased donor transplant.



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GRAPHICAL ABSTRACT

Traditionally, the options for a child that has a potential living donor who is blood group incompatible, included: being listed for a deceased donor transplant or to enter a paired exchange programme. Unfortunately, paired exchange programmes are not available in all countries, and still only comprise a minority of transplants—in 2023 in the USA, only 22 children received transplants through a paired exchange programme (2.7% of overall transplant activity) [1].

A third option, which is increasingly being used, is a blood group incompatible kidney transplant. Historically, ABO incompatible (ABOi) transplants have been associated with an increased risk of rejection, infection, post-transplant lymphoproliferative disorder (PTLD) and increased graft loss [4]. Due to these risks, ABOi transplants were previously reserved for a very small subset of patients. However, there have been modern advances, largely led by Japan, in safer and more effective desensitisation techniques such as the use of B-cell depleting agents like Rituximab, and the use of immunoadsorption [5–7]. This has in turn led to improved outcomes for patients receiving ABOi transplants [5, 8] and is a potential alternative for children requiring kidney transplants who do not have a blood group compatible living donor.

While there has been an increasing amount of encouraging evidence in case reports and registry analysis from Japan [9], there is to our knowledge, no large-scale data on the outcomes of pediatric ABOi kidney transplants from another country. Therefore, our aim was to compare the short- and long-term outcomes of all pediatric ABOi kidney transplants in the USA to a propensity score matched (PSM) cohort of children receiving ABO compatible (ABOc) kidney transplants.

Furthermore, in order to try and increase the donor pool for pediatric recipients, and to equip clinicians with useful knowledge for clinical practice, we also aimed to provide evidence that may be directly applicable in clinical practice for the common clinical scenario

described above in which patients have a potential living donor who is blood group incompatible. Therefore, we also carried out a sub-set analysis directly comparing the short- and long-term outcomes of ABOi kidney transplants from living donors to a PSM cohort of patients receiving ABOc kidney transplants from deceased donors.

Materials and methods

The OPTN database is an online registry that contains all data pertaining to patient waiting lists, living and deceased organ donation, organ matching and organ transplants that have taken place in the USA since 1st October 1987 [10]. Data are added to the database at the point of listing a patient for transplant, at the point of donation and is updated at 6 months, 1-year and annually post-transplant with recipient outcome data. This database is the largest registry containing data on pediatric kidney transplants. It was chosen for this study as it would be able to provide the largest sample size for analysis. Ethical approval was not required for this study. Patient data is required as per the U.S. federal law to be included in the OPTN registry at the time of listing/donation; only de-identified data was provided so no written consent was required.

OPTN registry data for all kidney transplants in recipients under the age of 18 years in the U.S. from October 1987 until September 2020 were requested. Data retrieved from the registry included donor and recipient demographics, number of prior transplants, dialysis status at transplantation, blood group compatibility, number of HLA mismatches (at HLA-A, HLA-B and HLA-DR), primary allograft non-function, delayed allograft function, allograft survival and patient survival time. All patients' post-transplant follow up data that were used for analysis were based on their latest data submitted to the registry in January 2021. Missing data was assumed to be missing completely at random. For each patient we only analysed data for the first kidney transplant.

TABLE 1 Number and proportion of patients receiving ABO incompatible transplants by each donor to recipient blood group combination for all ABOi transplants and for ABOi from living donor transplants.

Donor blood type to recipient blood type	Number (all ABOi) (n = 70)	Proportion (all ABOi)	Number (ABOi-LD) (n = 50)	Proportion (ABOi-LD)
A to B	3	4.3%	2	4%
A2 to B	7	10%	3	6%
A to O	21	30%	13	26%
A2 to O	10	14.3%	9	18%
AB to A	3	4.3%	2	4%
AB to B	5	7.1%	4	8%
A2B to b	4	5.7%	2	4%
AB to O	1	1.4%	0	0%
B To O	10	14.3%	9	18%
B To A	6	8.6%	6	12%

All statistical analysis was carried out with IBM Statistical Package for Social Sciences (SPSS) Version 28 [11]. Propensity score matching was used to identify a control group of patients who received ABOc transplants. Propensity score matching controlled for donor type, dialysis status pre-transplant, recipient sex, recipient age, recipient ethnicity, underlying renal disease, and number of HLA mismatches. This provided a control group for comparison which was equal to the ABOi group in terms of age, sex, ethnicity, underlying disease, dialysis exposure, and HLA mismatch. Baseline demographics of all patients receiving ABOc transplants were described, as well as the baseline demographics of the PSM control group. Analysis of all post-transplant outcomes including Kaplan-Meier survival curves for allograft and patient survival was done comparing the ABOi group to the PSM ABOc group. The data in this study was not normally distributed and therefore medians and interquartile ranges were reported to describe all numerical data, frequencies and percentages were used to describe categorical data. Mann-Whitney U Test, Chi-Square Tests and Kruskal-Wallis was used for significance testing to compare groups of patients. Patient and allograft survival at 1, 3, 5 and 10 years post-transplant was estimated using Kaplan-Meier analysis and log-rank testing was used to assess comparisons. P-values, with a threshold of significance of $p < 0.05$ are displayed as a measure of significance. When data were used for multiple comparisons Bonferroni corrections were implemented.

A sub-set analysis was carried out comparing ABOi transplants from living donors to ABOc transplants from deceased donors. For this subset analysis a new PSM control group of patients receiving ABOc transplants from deceased donors was created which controlled for dialysis status pre-transplant, recipient sex, recipient age, recipient ethnicity, underlying renal disease, and number of HLA mismatches.

Results

Overall, there were 23,695 pediatric ABOc kidney transplants and 70 pediatric ABOi kidney transplants. Donor and recipient

blood groups of the ABOi transplants can be seen in Table 1. Although A2 to B and A2B to B transplants are widely accepted to have equivocal outcomes to traditional ABOc transplants (where anti-A titres are acceptable), these were included in this study as ABOi transplants due to the limited existing data in paediatrics. Furthermore, we do not have data on how those listed as group “A” where serotyped, i.e., if they were tested and confirmed to be A, or whether subtype was not tested and they were assumed to be A1. Nevertheless, in this cohort, A2 transplants only made up 30% of all ABOi transplants.

The median recipient age did not differ significantly between the two groups – 14 (9.0–16.0) years in ABOi, and 14 (9.0–16.0) years, in the ABOc-PSM group ($p = 0.48$). Patient ethnicity, sex, underlying renal disease, transplant year, donor type, HLA match and dialysis status for the ABOi group, the ABOc group and PSM ABOc group can be seen in Table 2.

Post-transplant outcomes

The median follow up time post-transplant for the ABOi group was 6.3 years (3.0–12.1 years). There was no significant difference in the incidence of delayed allograft function (DGF) between ABOi and ABOc transplants: $n = 4$, 5.7% in ABOi and $n = 16$, 8.0% in ABOc ($p = 0.89$). The same findings were seen in the incidence of primary non-function: $n = 1$, 1.4% in ABOi and $n = 1$, 0.5% in ABOc ($p = 0.77$). There were no cases of renal vein thrombosis in ABOi transplants whilst in the ABOc group five children had thrombosis (2.5%, $p = 0.60$).

There was no significant difference in both allograft and patient survival between ABOi and ABOc transplants. 1, 3, 5 and 10 years allograft and patient survival is summarized in Table 3 and survival curves can be seen in Figures 1A,B. Patient and allograft survival across different eras of transplantation are summarized in Table 4 and Figures 2A,B.

Further sub-set analysis was carried out to compare the outcomes between A, A2, B and AB incompatible transplants and found no significant difference in allograft survival ($p = 0.43$) nor patient survival ($p = 0.71$).

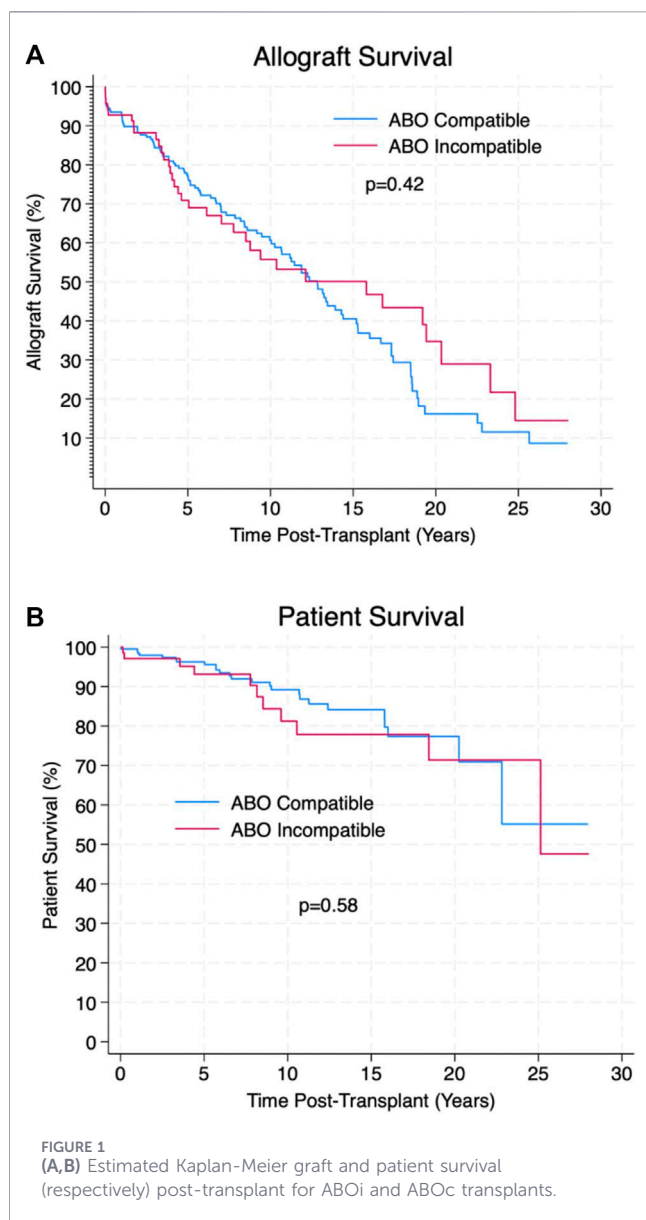
TABLE 2 Number and proportions of ABO incompatible and compatible transplants for different ethnicities, sex, underlying renal disease, eras, donor types and HLA matches. Favorable HLA match = 0, 1, 2 or 3 mismatches; unfavorable HLA match = 4, 5 or 6 mismatches. Patients with no data on ethnicity, sex, renal disease, era, dialysis status or HLA matching were excluded from analysis for their respective category.

Demographic	Sub-group	ABO incompatible (n = 70) (%)	ABO compatible (N = 23,695) (%)	P-value	ABO compatible – PSM group (n = 200) (%)	P-value
Ethnicity	White	45 (64.3)	13,153 (55.6)	0.21	125 (62.5)	0.64
	Black	15 (21.4)	4,274 (18.0)		34 (17.0)	
	Hispanic	6 (8.6)	4,982 (21.0)		29 (14.5)	
	Asian	1 (1.4)	712 (3.0)		5 (2.5)	
	Other/Mixed	3 (4.3)	574 (2.4)		7 (3.5)	
Sex	Male	42 (60.0)	14,004 (59.1)	0.87	113 (56.5)	0.25
	Female	28 (40.0)	9,691 (40.9)		87 (43.5)	
Renal disease	Cystic	2 (6.9)	1,044 (7.6)	<0.01	4 (4.8)	0.99
	Obstructive/Reflux	6 (20.7)	3,221 (23.5)		21 (25.3)	
	Glomerulo-nephritis	9 (31.0)	4,424 (32.3)		27 (32.5)	
	Hypertension/Vascular	1 (3.5)	647 (4.7)		4 (4.8)	
	Hereditary/Metabolic	2 (6.9)	812 (5.9)		3 (3.6)	
	Hypoplasia/Dysplasia	6 (20.7)	2,472 (18.1)		19 (22.9)	
	Other	3 (10.3)	1,078 (7.9)	-	5 (6.0)	
Era	<1990	10 (14.3)	1,409 (6.0)	-	6 (3.0)	-
	1990–1999	24 (34.3)	6,643 (28.0)	-	79 (39.5)	-
	2000–2009	21 (30.0)	7,819 (33.0)	-	78 (39.0)	-
	2010–2019	14 (20.0)	7,372 (31.1)	-	36 (18.0)	-
	2020 >	1 (1.4)	452 (1.9)	-	1 (0.5)	-
Donor type	Living	50 (71.4)	10,588 (44.7)	<0.01	136 (68.0)	0.28
	DBD	19 (27.1)	12,754 (53.8)		64 (32.0)	
	DCD	1 (1.5)	353 (1.5)		0 (0.0)	
HLA match	Favorable	47 (69.1)	11,646 (49.9)	<0.01	142 (71.0)	0.76
	Unfavorable	21 (30.9)	11,714 (50.1)		58 (29.0)	
Dialysis status	Pre-emptive	21 (30.0)	5,500 (23.2)	0.17	60 (30.0)	1.0
	On dialysis	49 (70.0)	18,195 (76.8)		40 (70.0)	

Bold values indicate statistical significance.

TABLE 3 Overall estimated Kaplan-Meier graft and patient survival for ABOi and ABOc (PSM group) transplants at 1, 3, 5 and 10 years post-transplant. The ABOc group refers to the propensity-score-matched group.

Survival	Patient group	1 year	3 years	5 years	10 years	P-value
Allograft survival	ABOi (n = 70)	93%	88%	69%	56%	0.42
	Number at risk	63	54	38	23	
	ABOc (n = 200)	93%	84%	77%	60%	
	Number at risk	179	152	123	69	
Patient survival	ABOi (n = 70)	97%	97%	93%	81%	0.58
	Number at risk	65	54	42	25	
	ABOc (n = 200)	99%	97%	96%	89%	
	Number at risk	193	172	147	83	



Impact of donor type

Outcomes were also compared between patients who received ABOi transplants from living donors ($n = 50$) and a PSM group of patients who received ABOc transplants from deceased donors ($n = 144$).

Patient receiving ABOi transplants from living donors experienced significantly less DGF than patients receiving ABOc transplants from deceased donors— $n = 1$, 2% vs. $n = 23$, 16.0% ($p < 0.01$). However, there was no significant difference in incidence of primary non-function— $n = 1$, 2% in ABOi transplants from living donors and $n = 4$, 2.8% in ABOc transplants from deceased donors ($p = 0.76$).

Analysis showed that patients receiving ABOi transplants from living donors had significantly better allograft survival than patients receiving ABOc transplants from deceased donors, although there was no difference in patient survival between the two groups. 1, 3, 5, and 10 years allograft and patient survival for these patients is

summarized in Table 5 and survival curves can be seen in Figures 3A,B. The same trend continued after 10 years as seen in Figures 3A,B.

A further sub-analysis was carried out to analyse just living donor transplants to assess whether controlling for donor type would reveal a difference in outcomes from ABOi transplants. This found there was no significant difference in the incidence of DGF ($p = 0.13$), incidence of primary non-function ($p = 0.46$), allograft survival ($p = 0.42$) nor patient survival ($p = 0.55$).

Discussion

We present the first study analysing the outcomes of all ABOi pediatric kidney transplants to date in one of the countries with the largest transplant programme—the USA and the first to analyse a direct comparison between ABOi kidney transplants from living donors and ABOc kidney transplants from deceased donors. We show that ABOi pediatric kidney transplants have equitable short and long-term outcomes to ABOc pediatric kidney transplants. We also show that on direct comparison, ABOi transplants from living donors have lower incidence of delayed allograft function and better allograft survival than ABOc transplants from deceased donors.

Our findings are consistent with those reported in the literature. A Japanese study of Kidney Transplant Registry showed that there was no difference in graft survival or patient survival between ABOi and ABOc in 102 pediatric ABOi kidney transplants [5]. Encouragingly, this study also found no difference in infectious complications between ABOi and ABOc recipients [5]. Additionally, a UK study with 11 patients showed no difference between ABOi and ABOc with respect to graft function and acute rejection [7]. Another study with 52 patients had similar allograft and patient survival rates to our study and also did not show any difference compared to ABOc transplants [12]. They also showed that ABOi transplants did have higher incidence of acute rejection, however, after the addition of Mycophenolate to the standard immunosuppression regime for these patients, this improved significantly [12].

Recently there have been changes in the way that ABOi transplants have been facilitated with a lot of variation in desensitisation techniques. Previously, patients underwent splenectomies prior to transplant in addition to plasmapheresis which posed higher risks. Currently the accepted strategy used by many centers involves plasmapheresis or immunoadsorption pre-operatively to reduce antibody titres. Many centers aim to reduce titres to $<1/8$ [5, 7, 12, 13], however one study has also shown that reducing antibody titres to $<1/32$ led to good outcomes [9]. Current evidence has found that using this strategy has not led to any increase in infectious complications [6].

Unfortunately our study did not have data on the immunosuppression used so we cannot comment on whether these patients had escalated immunosuppression, however, there are some case reports of safe ABOi transplantation with good outcomes without any additional desensitization in patients who have antibody titres of $<1/8$ at baseline [6, 7]. Another case report

TABLE 4 Estimated Kaplan-Meier graft and patient survival for patients receiving ABOi transplants ABOi transplants across different timepoints at 1, 3, 5 and 10 years post-transplant. The ABOc group refers to the propensity-score-matched group.

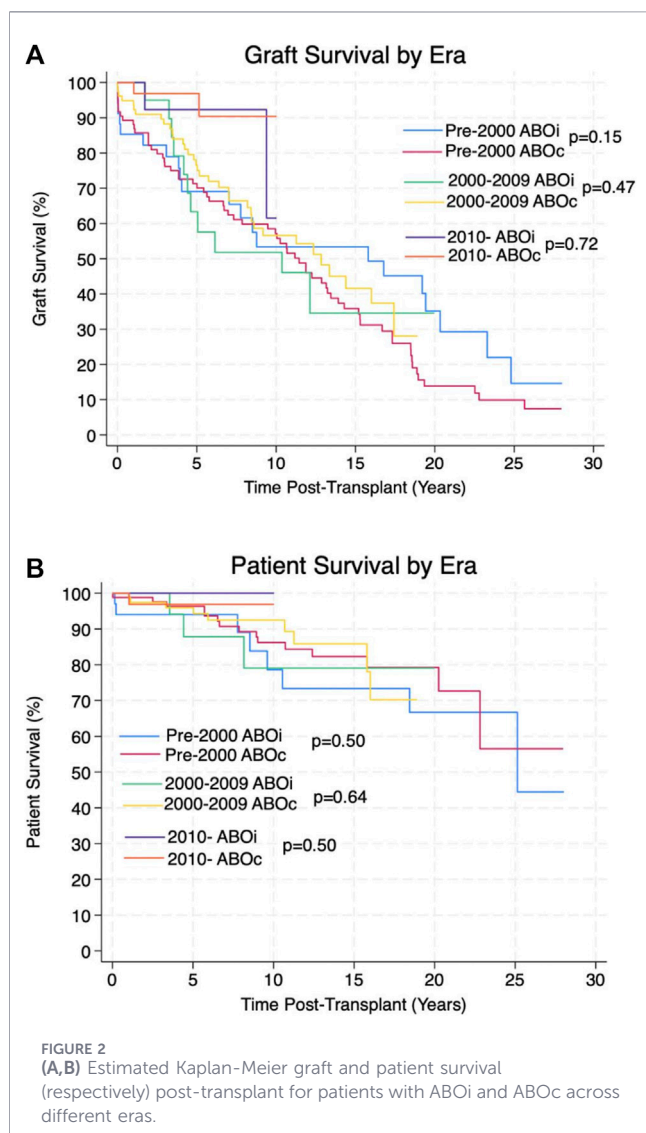
Survival	Era		1 year	3 years	5 years	10 years	P-value
Graft Survival	Pre-2000	ABOi (n = 34)	85%	82%	69%	53%	0.15
		Number at Risk	29	26	20	13	
		ABOc (n = 85)	87%	75%	70%	57%	
		Number at Risk	74	64	57	42	
	2000–2009	ABOi (n = 21)	95%	90%	58%	46%	0.47
		Number at Risk	20	18	11	9	
		ABOc (n = 78)	94%	88%	77%	57%	
		Number at Risk	73	64	51	26	
	2010 - current	ABOi (n = 15)	100%	92%	92%	61%	0.10
		Number at Risk	14	10	7	1	
		ABOc (n = 37)	100%	97%	90%	90%	
		Number at Risk	33	24	15	1	
Patient Survival	Pre-2000	ABOi (n = 34)	94%	94%	94%	73%	0.50
		Number at Risk	31	26	23	15	
		ABOc (n = 85)	99%	98%	96%	86%	
		Number at Risk	84	79	73	51	
	2000–2009	ABOi (n = 21)	100%	100%	88%	79%	0.54
		Number at Risk	20	18	12	9	
		ABOc (n = 78)	99%	97%	96%	92%	
		Number at Risk	77	69	59	31	
	2010 - current	ABOi (n = 15)	100%	100%	100%	100%	0.50
		Number at Risk	14	10	7	1	
		ABOc (n = 37)	100%	97%	97%	97%	
		Number at Risk	33	24	15	1	

from South Africa discussed a patient with titres $<1/8$ who was safely transplanted with standard immunosuppression and only one dose of Rituximab prior to transplant which shows that ABOi transplantation may be possible even in some middle-/low-income settings [14]. This suggests that patients with antibody titres $<1/8$ may potentially also be considered for ABOi transplantation from deceased donors, as no additional pre-transplant desensitisation may be needed. No study simulated a kidney allocation scheme that would allow children on the deceased donor waiting list with antibody titres of $<1/16$ to be allocated ABOi transplants and found that this strategy could potentially reduce waiting times and lead to a 2.2% increase in transplants while also increasing the number of children receiving transplants with 0 HLA mismatches at A, B and DR [15]. However, it is also important to note that reporting titre measuring methods is crucial as there is significant variability in the methods leading to a lack of standardization and significant variability in results [16]. We would encourage that further published studies describe the methods used for titre measurement and where possible that

these be standardised (with for example, new assays based on single-antigen bead technology [17]) for the purpose of making transplant decisions.

Another advantage of ABOi transplants from living donors is the benefit of planned surgery which can occur in a more controlled environment. For example, when transplanting children with inherited metabolic disorders, ensuring clinical stability prior to transplant is crucial [18], so planning for a living donor ABOi transplant over a deceased donor ABOc transplant allows the clinical team more control and can ensure the patient is transplanted in optimal circumstances.

An alternative to ABOi transplantation is the use of paired donation schemes. There is significant evidence that paired donation and non-paired living donation provides the same outcomes, although this approach continues to be underutilized in the USA in comparison to other countries [19–21]. Paired donation is an additional opportunity for patients to benefit from living donation. Given the perceived risk and the thus far limited evidence and somewhat limited use of ABOi transplantation in children, paired



exchange schemes provide an excellent opportunity. Unfortunately, there is only a limited number of centres in the USA that participate in the scheme so this does limit the potential opportunities it may provide and effort should be focused on expanding the scheme to more centers [19]. Where patients have blood group incompatible living donors and lack of access to a paired scheme, ABOi transplantation should be considered prior to deceased donation.

Our study has several advantages including a large sample size of 70 ABOi paediatric transplants over a 30 year period with a median follow up of 6 years. While 70 ABOi transplants may not be a large sample size compared to some adult studies and may limit some of the statistical conclusions, it is one of the largest sample sizes to date within paediatrics. Encouragingly, when outcomes were stratified by era of transplantation to try and control for changes in practice in transplantation over time, our results continued to show the same findings—that ABOi transplants had equitable outcomes to ABOc transplants. Furthermore, using propensity score matching allows this study to control for many potential confounders such as year

of transplantation, age, dialysis status, underlying disease, HLA matching etc. and allows the results attributed to the ABO compatibility to be more reliable.

Our study is limited by having no data on pre-transplant antibody titres, titre-measurement methods, centre variability in titre level acceptability (particularly for A2-incompatible transplants) nor cPRA or which desensitization techniques used. This adds significant variability to the degree of mismatch between the transplants and also variability between desensitisation protocols which can make long-term outcomes more difficult to generalize. ABOi transplants typically are done with different induction therapies compared to ABOc; our registry data does not hold this data. Therefore we were not able to control for this in the propensity score matching, nor present data on how this theoretical difference in immunosuppression may have influenced transplant and patient outcomes. Our lack of data on these is an important factor to consider when interpreting our results. We also do not have data on the incidence of rejection or infectious complications. Nevertheless, as our results do not show a difference in long-term allograft and patient survival between ABOi and ABOc transplants; any potential differences in rejection or infectious complications are not significant enough to impact long-term outcomes which is very reassuring. While using registry data allows us to have a large enough sample size to carry out analysis on outcomes, it does also mean that our data is limited by what variables are held by the registry and relies on the accuracy of the data that is submitted to the registry. For example, we only have data on HLA matching at HLA-A, HLA-B and HLA-DR; it is possible that mismatches at other loci which may have impacts on outcomes could be confounding the results. Additionally we also did not have data on cPRA of the two cohorts either.

Another important consideration is that OPTN largely relies on the lectin method to determine ABO, whereas there are now new molecular methods to determine ABO more accurately [22]. The lectin method is particularly less accurate in infants and neonates [23] so there's a possibility that some of the reported ABO types for the younger recipients and donors is not accurate and so some of the transplants reports as ABOi are not incompatible and equally some reported as compatible may in fact be ABOi. Unfortunately, we do not have data on how frequently ABO mistyping occurs due to using serotyping as opposed to phenotyping in the OPTN. Some studies have found that discrepancies in ABO compatibility between sero- and genotyping can occur in up to 42% of patients so it is crucial that further research is carried out using the more up to date molecular methods of ABO classification.

Due to the difficulty in accurately identifying A subgroups, amongst other factors, there has been limited uptake in A2-incompatible transplants. The positive outcomes of A2-incompatible transplants have been described in adults, and there appears to be an increased acceptability of this type of incompatible transplants [24]. However, studies have shown that when using more advanced genotyping methods, up to 55% of patients believed to be A1 may actually be A2, and using more up to date molecular ABO classifications methods

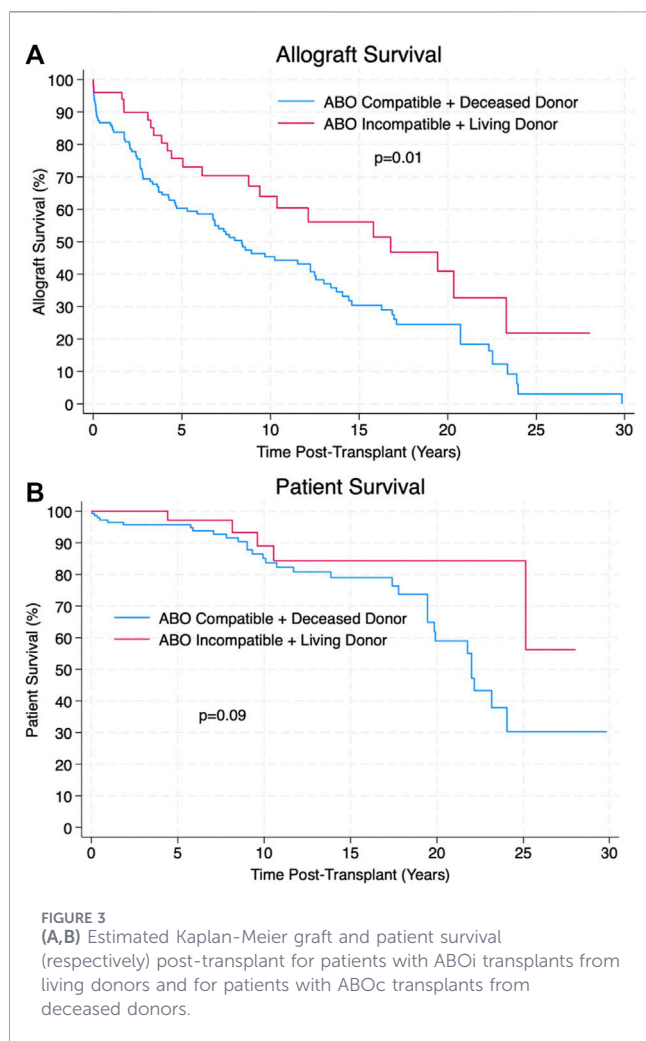


TABLE 5 Estimated Kaplan-Meier graft and patient survival for patients receiving ABOi transplants from living donors, ABOc transplants from deceased donors (PSM Group) and ABOc transplants from living donors (PSM Group) at 1, 3, 5 and 10 years post-transplant.

Survival	Patient group	1 year	3 years	5 years	10 years	P-value
Graft Survival	ABOi – Living Donor (n = 50)	96%	90%	73%	64%	ABOi-LD vs. ABOc-DD $p = 0.01$ ABOi-LD vs. ABOc-LD $p = 0.42$
	Number at Risk	47	40	29	19	
	ABOc – Deceased donor (n = 64)	86%	69%	59%	44%	
	Number at Risk	54	46	39	20	
	ABOc – Living donor (n = 136)	94%	86%	76%	65%	
	Number at Risk	125	106	84	49	
Patient survival	ABOi – Living donor (n = 50)	100%	100%	97%	89%	ABOi-LD vs. ABOc-DD $p = 0.09$ ABOi-LD vs. ABOc-LD $p = 0.55$
	Number at Risk	48	40	31	20	
	ABOc – Deceased donor (n = 64)	97%	96%	96%	84%	
	Number at Risk	62	52	45	27	
	ABOc – Living donor (n = 136)	99%	98%	95%	90%	
	Number at Risk	132	120	102	56	

may facilitate more transplants [17]. It is crucial that these newer methods should be brought into every day clinical practice and inform transplant decisions.

Furthermore, we also do not have data on which centers carried out these transplants and so it is possible that there are some “center effects” contributing to the difference in outcomes that we were not able to control for in the propensity matching. However, we do recommend that as ABOi transplantation becomes more common practice, it should initially be carried out at or in collaboration with centers who have experience in immunologically complex transplantation.

Conclusion

In conclusion, our registry analysis and propensity score matched study spanning over 30 years, has found that pediatric ABOi kidney transplants can have excellent outcomes that do not differ significantly from ABOc kidney transplants. More importantly, we also show that ABOi transplants from living donors showed better long-term outcomes than ABOc transplants from deceased donors. While we cannot comment on induction therapies and immunosuppression, rejection or infections, and the lack of this data should be kept in mind when interpreting our results, long-term graft and patient survival does not differ significantly which suggests that these transplants are a viable option that should be considered for children requiring transplantation.

In patients who have a potential living donor who is blood group incompatible and either do not have access to or have not been successfully paired in an exchange programme, one may consider proceeding with ABOi transplantation prior to listing for deceased donor transplantation. However,

we recommend that these transplants should initially be done in collaboration with high-volume centres who have experience in immunologically complex transplants. Prospective studies comparing ABOi transplantation with paired exchange transplants and deceased donor transplants are necessary to further support the evidence given in our study and determine the best approach for these patients.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: <https://www.hrsa.gov/optn/data/data-reports>.

Ethics statement

Ethical approval was not required for this study. Patient data is required as per the U.S. federal law to be included in the OPTN registry at the time of listing/donation; only de-identified data was provided so no written consent was required.

Author contributions

AP, IL, PC, NK, and JS participated in research design. AP, PC, and JS participated in the writing of the paper. AP and PC participated in the data analysis. JS supervised the research project. All authors contributed to the article and approved the submitted version.

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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.

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Findings and significance of early follow-up biopsies after treatment of acute rejection in kidney transplant recipients

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Treatment resistant acute rejection after kidney transplantation is linked to inferior outcomes, yet many centers do not routinely perform follow-up biopsies. The optimal timing of such biopsies remains uncertain. We evaluated findings from follow-up biopsies performed ≤ 45 days after treatment of acute rejection and assessed their association with long-term outcomes. Adult kidney transplants performed from 01/2014 to 07/2024 were included ($n = 2,420$). Acute rejections were classified according to Banff criteria. T-cell-mediated rejection, including borderline TCMR changes, was treated with pulse steroids; antibody-mediated rejection was treated with steroids, intravenous immunoglobulin, and plasma exchange. Findings from follow-up biopsies taken ≤ 45 days after treatment of early acute rejection were correlated with graft outcomes. Of 383 patients (16%) with acute rejection within 3 months post-transplant, 221 underwent a follow-up biopsy ≤ 45 days. Of these, 50% were taken by protocol and 50% because of clinical reasons. In 164 cases (74%), rejection changes had resolved. At 1-year, median creatinine was 1.3 mg/dL in those without rejection, 1.6 mg/dL in patients with persistent changes, and 1.5 mg/dL in those with resolved changes. Persistent histologic rejection within 45 days was associated with inferior long-term graft survival.

KEYWORDS

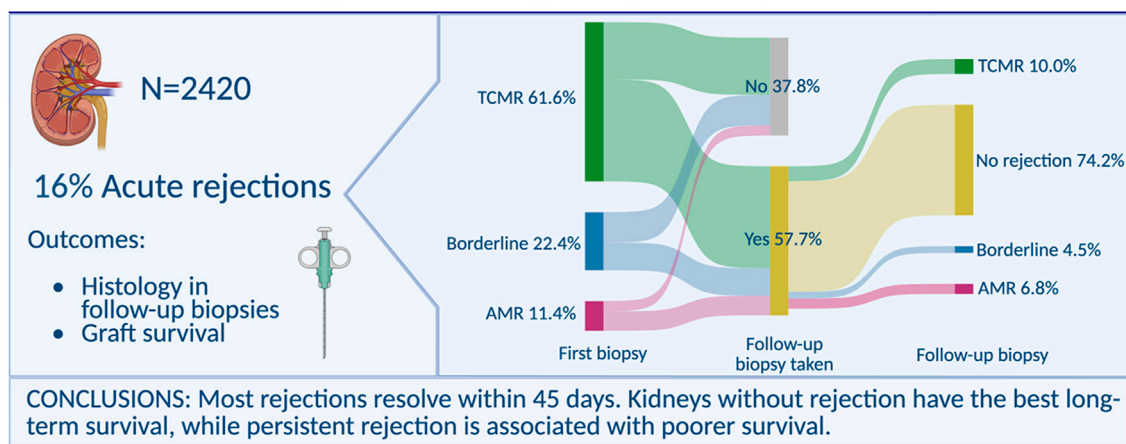
acute rejection, follow-up biopsies, histology, kidney transplantation, outcomes

Introduction

Up to 20% of patients experience rejection of the kidney allograft during the first weeks after transplantation [1–3]. The Banff classification of Transplant Pathology is used for reporting kidney transplant biopsies. Acute rejection is classified mainly into two different categories: T-cell-mediated rejection (TCMR), which is more common, and antibody-mediated rejection (AMR), which can be more difficult to treat [4]. Both types of rejection are associated with worse long-term graft survival [4–6]. Furthermore, borderline TCMRs are seen as a mild version of TCMR, but the views on the clinical significance of borderline TCMRs and their possible treatment differ [7, 8]. The Banff system was established in 1991 and has since undergone multiple updates, especially regarding AMR [2, 9].

To detect early rejection, a biopsy is recommended within the first few weeks post-transplantation in cases of early graft dysfunction or delayed graft function (DGF) [10]. Weekly biopsies have been recommended until kidney function is achieved, but later studies

Findings and Significance of Early Follow-up Biopsies After Treatment of Acute Rejection in Kidney Transplant Recipients



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GRAPHICAL ABSTRACT

have shown that often one biopsy may be enough since the diagnosis seldom changes in subsequent biopsies [11, 12].

Follow-up biopsies after treating rejection are not always routinely taken but might offer valuable information to guide immunosuppressive therapy after rejection, helping clinicians to balance the need to detect persistent rejection early enough for effective intervention while avoiding unnecessary early biopsies that could lead to excessive immunosuppression.

There is no clear consensus for an optimal timing of a follow-up biopsy, although 3 months has been suggested [13].

At our institution, follow-up biopsies are usually taken 2–6 weeks post-treatment of acute rejection. We analyzed findings of these follow-up biopsies taken ≤ 45 days after treatment of acute biopsy-confirmed rejection and correlated the findings with long-term outcomes. We hypothesized that persistent rejection findings are associated with worse long-term outcomes.

Methods and materials

Study population and data collection

This is a retrospective observational registry analysis studying the results of follow-up biopsies after treatment of acute rejection and their association with long-term outcomes. The study population comprised all consecutive adult (>18 years) kidney transplantations performed at Helsinki University Hospital, Finland, from January 2014 to July 2024. All transplantations were complement dependent cytotoxicity crossmatch negative,

examined with donor splenocytes between 2006 and 2015 and peripheral T- and B-cells thereafter. The donor pool consisted of living donors, brain-dead donors, and donors after circulatory death, and also included HLA-incompatible (when at least moderate donor specific antibodies existed pre-transplantation) and ABO-incompatible transplantations. The exclusion criteria were primary nonfunction and graft loss or death within 30 days after transplantation. Patients with missing data were excluded from relevant analyses.

Patient data were sourced from electronic medical records and the Finnish Kidney Transplant Registry, a legally mandated national registry for the follow-up of kidney transplant patients. Patients were followed until death, graft loss, or 31 December 2024.

One Lambda Labscreen® mixed and single antigen beads with Luminex® were used for pretransplant HLA antibody screening and identification using the HLA Fusion software (One Lambda Inc., Canoga Park, CA). DSAs were measured centrally. Donor HLA typing was performed in intermediate resolution, complemented with haplotype analyses. Median fluorescence intensity values over 1000 were considered positive. Posttransplant DSAs were not routinely monitored, but taken at rejection diagnostics at clinician's discretion. The number of patients with pretransplant DSA are presented in Table 1. The individual MFI levels of all the DSAs were unfortunately not available for the purposes of this study.

Calculated panel reactive antibodies were calculated by comparing the known distribution of HLA antigens of Finns to the patient's HLA antibody profile.

Delayed graft function was defined as the need for dialysis during the first post-transplant week.

This study was approved by the institutional review board of Helsinki University Hospital (HUS/23/2024). The clinical and research activities being reported are consistent with the Principal of Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Abbreviations: AMR, antibody-mediated rejection; DSA, donor-specific antibodies; HLA, human leukocyte antigen; HLA-MM, human leukocyte antigen mismatch; TCMR, T-cell mediated rejection.

TABLE 1 Characteristics of study population based on rejection occurrence.

Variable	Resolved rejection within 45 days ¹ N = 164	Persistent rejection within 45 days ¹ N = 47	No rejection ¹ N = 1988	p-value ²
Recipient age (years)	54 (43.64)	55 (38.64)	57 (45.65)	0.16
Recipient sex				0.32
Female	57 (35%)	13 (28%)	744 (37%)	
Male	107 (65%)	34 (72%)	1,244 (63%)	
Previous kidney transplant	40 (24%)	10 (21%)	248 (12%)	<0.001*
Donor type				0.07
Living donor	13 (8%)	3 (6%)	245 (12%)	
Brain-dead donor	149 (91%)	43 (91%)	1,659 (83%)	
Circulatory death donor	2 (1%)	1 (2%)	84 (4%)	
ABO-incompatible donation	0 (0%)	0 (0%)	29 (1%)	0.30
Donor sex				0.15
Female	89 (54%)	20 (43%)	931 (47%)	
Male	75 (46%)	27 (57%)	1,057 (53%)	
Donor age (years)	63 (52.68)	62 (45.70)	60 (49.67)	0.16
First biopsy diagnosis				0.04*
AMR	20 (12%)	8 (17%)	Not applicable	
Borderline TCMR	37 (23%)	3 (6%)	Not applicable	
TCMR	107 (65%)	36 (77%)	Not applicable	
Delayed graft function	75 (46%)	20 (43%)	316 (16%)	<0.001*
Cold ischemia time (hours)	17 (12.21)	15 (11.18)	15 (9.19)	0.001*
DSAs present at time of transplantation ³	27 (16%)	10 (21%)	0 (0%)	<0.001
Peak panel reactive antibodies >30% ⁴	52 (32%)	19 (40%)	458 (23%)	0.002*
HLA AB mismatch	2 (2.3)	2 (2.3)	2 (2.3)	0.093
HLA DR mismatch	1 (1.1)	1 (1.1)	1 (0.1)	<0.001*
Follow up time (months)	63 (30.93)	52 (13.73)	54 (26.86)	0.09
Serum creatinine 1 year post transplantation mg/dL ⁵	1.56 (1.28, 2.06)	1.61 (1.40.1.96)	1.30 (1.06.1.61)	<0.001*
Change in serum creatinine between rejection diagnosis and 1 year post transplantation mg/dL ⁶	-2.15 (-4.6, -0.78)	-1.91 (-3.64, -1.1)	Not applicable	0.97

¹n (%); Median (IQR).²Fisher's exact test; Pearson's Chi-squared test; Kruskal-Wallis rank sum test.

Missing n.

³891.⁴10.⁵821.⁶20.

*p-value statistically significant, <0.05.

AMR, antibody mediated rejection; TCMR, T-cell mediated rejection; DSAs, donor specific antibodies; HLA, human leukocyte antibodies.

Immunosuppression and rejections

Corticosteroids were used as induction therapy for all kidney recipients. In addition, basiliximab or anti-thymocyte globulin was administered to patients with immunologic risk factors. Post-transplant maintenance immunosuppression comprised corticosteroids, mycophenolate, and a calcineurin inhibitor (tacrolimus or cyclosporine A). In 2014–2019, Tacrolimus was

chosen in immunologically higher-risk patients and in all patients after 2019. From 2023 onwards, virtual crossmatch was done prior to kidney allocation on all patients, and donor-specific antibodies (DSA)-positive transplantations were generally avoided.

All biopsies were paraffin-embedded. Histopathologic changes described were scored by experienced renal pathologists using the Banff scoring system at the time, and the histopathological analyses were not reassessed for this study. TCMR, including borderline

TCMR changes, were treated with pulse corticosteroids, and AMR typically with corticosteroids, intravenous immunoglobulin, and plasma exchange. Anti-thymocyte globulin was used in 10 cases to treat steroid resistant TCMR. Cases of probable AMR, which were treated as AMR, were defined as AMR for the purposes of this study.

Statistical analyses

Borderline TCMR changes were considered rejection in the main analysis. In sensitivity analysis, borderline TCMR changes in follow-up biopsies after treated TCMR were considered as a resolved rejection. In addition, survival analyses were repeated excluding borderline changes from the rejection cohort.

Categorical variables are described as the number of cases and percentages. Continuous variables are described as median and interquartile range, as the distributions within the dataset were not normal. Kruskal-Wallis rank sum test was used to assess statistical significance for differences in the continuous variables, Fisher's exact test was used for categorical data with small sample sizes, and Pearson's Chi-squared test was used for categorical data with larger sample sizes. Histograms and Sankey diagrams were used to graphically describe the rates of acute rejection and follow-up biopsy findings.

Graft survival was analyzed using Kaplan-Meier survival curves with both death with functioning graft and graft loss as outcomes. Sensitivity analyses were done with only death-censored graft survival. Differences between the groups were analyzed with the log-rank test. Two-sided *p*-values <0.05 were considered statistically significant.

Risk factors for persistent rejection were studied using multivariable logistic regression analysis. Variables for the regression analysis were chosen based on known risk factors for acute rejection, as well as clinical interest. Graft function was not included in the main model due to possible confounding, but was included in supplemental models. Possible multicollinearity was studied using the variance inflation factor.

Patients with missing data were excluded from relevant analyses. In survival analyses, patients who died or lost their graft within 30 days of transplantation were excluded (*n* = 9).

Statistical analyses were performed using R (R Core Team, 2024), R Studio (Posit Software, 2025), and the R packages dplyr, tidyverse, readxl, ggplot2, patchwork, gtsummary, rms, broom, survival, survminer, and stats.

Results

A total of 2,420 kidneys were transplanted during the study period. Patients with primary non-function (*n* = 49) and follow-up time <30 days after transplantation (*n* = 9), were excluded.

Among 2,362 patients, 383 (16%) experienced acute rejection within the first 3 months post-transplant. Of these, 236 (61%) were TCMR, 44 (11%) AMR, and 86 (22%) borderline TCMR; 17 (4%) had missing detailed biopsy data. Within 45 days post-rejection, 221 (58%) of the patients with acute rejection had at least one follow-up biopsy taken. In 74% (*n* = 164), the rejection changes had already resolved (Figures 1A,B). Persisting rejection changes consisted of 6.8% AMR (*n* = 15), 4.5% borderline TCMR (*n* = 10), and 10.0% TCMR (*n* = 22). 4.5% (*n* = 10) of the follow-up biopsies were inadequate or unclear (Figure 2). In clinical practice, if TCMR was downgraded to borderline

TCMR rejection in the follow-up biopsy, the rejection was considered resolved, and no new rejection therapy was started.

Basic characteristics of included patients are shown in Table 1. Patients with previous kidney transplantation had a higher risk of acute rejection during the first 3 months. The presence of DSAs at the time of transplantation and a peak panel reactive antibodies >30 was associated with acute rejection, with the highest rates observed in the group with persistent rejection changes within 45 days. Patients with acute rejection had a significantly higher creatinine at 1 year post-transplantation, with the highest levels in those with persistent rejection changes within 45 days, compared to those with no rejection. There was no clinically or statistically significant difference in serum creatinine change from initial rejection diagnosis to 1 year post transplant, between those who had resolved rejection and persistent rejection (Table 1).

In Kaplan-Meier survival estimates, the survival of patients with persistent rejection within 45 days was significantly worse than those who had resolved rejection or no acute rejection (Figure 3). The survival rates at 1, 3, and 7 years were 87%, 68%, and 54%, respectively, for patients with persistent rejection; 93%, 87%, and 66% for those with resolved rejection; and 97%, 91%, and 76% for those with no acute rejection. The best survival was observed in patients with no rejection changes during the first 3 months (*p* < 0.001, Figure 3). These trends could also be observed in death-censored survival analysis, with less prominent but still significant differences in survival (Supplementary Figure S1). Patients with no follow-up biopsy taken after treatment of acute rejection had similar survival as those with resolved rejection changes within 45 days (Supplementary Figure S2). The patient characteristics based on the availability of follow-up biopsy are presented in Supplementary Table S1. Follow-up biopsies were more commonly performed in patients with delayed graft function, whereas an initial diagnosis of borderline TCMR rejection less often led to a follow-up biopsy compared to AMR or TCMR.

In sensitivity analyses with borderline TCMR considered resolved if following TCMR, similar trends in survival were observed as in the main analyses, but the survival estimates of patients with persistent rejection within 45 days were more inferior (Supplementary Figures S3, S4). Furthermore, inferior survival was observed in all TCMR grades including Borderline TCMR with persistent rejection changes (Supplementary Figure S5).

The indication for the follow-up biopsy was available for 210 of the 221 patients with acute rejection. Of these biopsies, 50% were performed according to protocol, and 50% were performed for clinical indications, such as rising serum creatinine or failure of serum creatinine to decline. In Kaplan-Meier survival analyses, the survival of patients with clinical indications for follow-up biopsy had the worst survival (Supplementary Figures S6, S7).

In multivariable logistic regression analysis, patients with borderline TCMR rejection had a lower risk for persistent rejection findings within 45 days (OR 0.22, 95% CI 0.05–0.69, *p* = 0.03). No other risk factors were identified (Table 2). In supplemental analyses with graft function included no differences in risk could be observed (Supplementary Table S2). In a subgroup of patients with delayed graft function, there were no differences in risk (Supplementary Table S3). In a subgroup of patients with early function (Supplementary Table S4), male recipients and male donors were associated with a higher risk of persistent rejection.

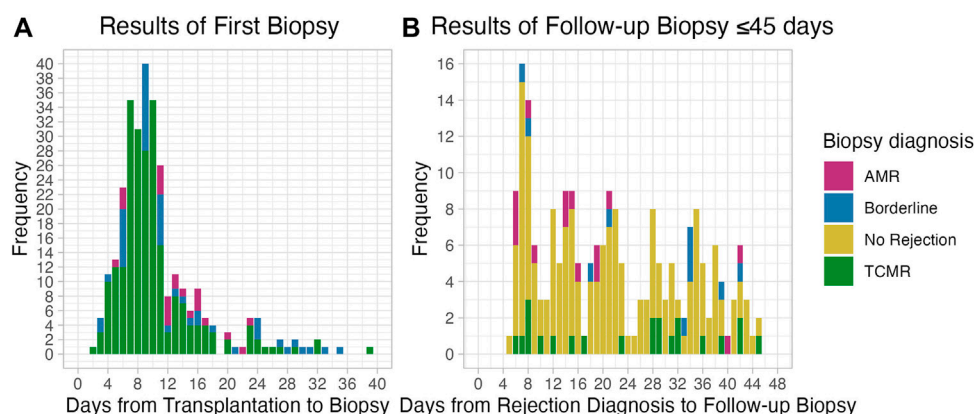


FIGURE 1
(A,B) Biopsy diagnoses of first biopsy (A) and results of follow-up biopsy ≤ 45 days (B).

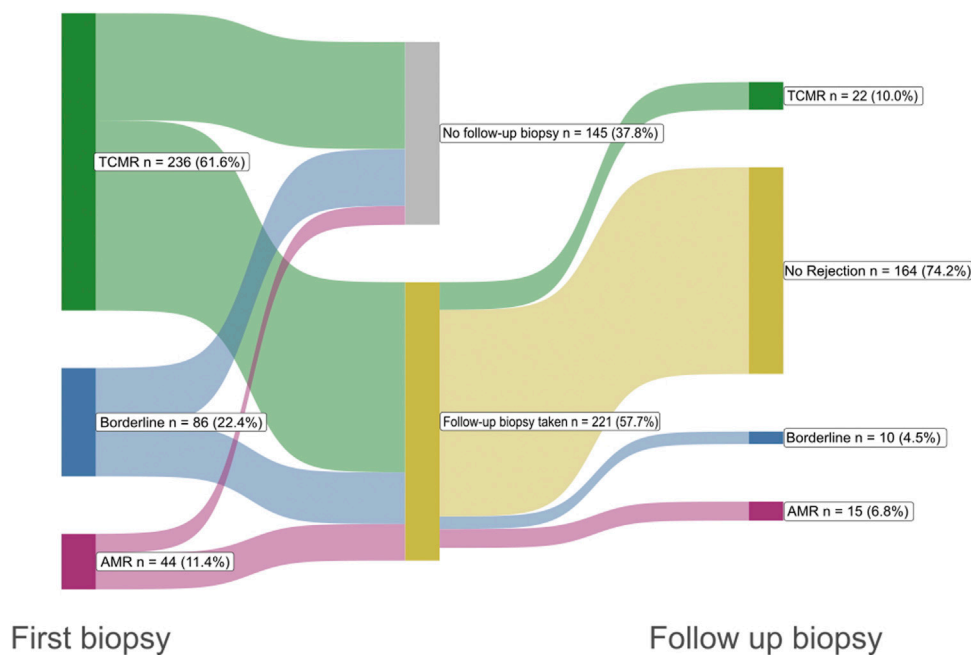


FIGURE 2
Sankey diagram on the evolution of biopsy diagnosis from rejection diagnosis to follow up.

Patients with borderline TCMR rejection had a lower risk of persistent rejection. The risk was also lower for patients with a previous kidney transplant. Patients with previous transplants were generally younger in this subgroup.

The rejection grades in the initial and follow-up biopsies are presented in Table 3. In this cohort, 26 cases presented with an isolated v-lesion. Of these, 5 were in recipients from living donors and 3 in recipients from DCD. The changes in lesion scores from baseline to follow-up biopsy are presented in Supplementary Table S5. Generally, lesion scores remained the same or increased in persisting rejections. Also the activity lesion, which was calculated as described by Vaulet et al [14], increased or remained the same more often in persisting rejections.

Discussion

In this retrospective study on the findings of follow-up biopsies after treating acute rejection in kidney transplantation, we found that most rejection findings were resolved within 45 days. There are no recent guidelines on when and if a follow-up biopsy after treated rejection should be taken. KDIGO guidelines on transplant recipient care in 2009 recommend a follow-up biopsy if creatinine does not return to baseline level after treated rejection [10]. However, treating remaining histological rejection changes, even in patients with recovered kidney function, might be beneficial for kidney allograft survival [15]. Following our study, we conclude that follow-up biopsies could be performed earlier than the suggested 3-month mark.

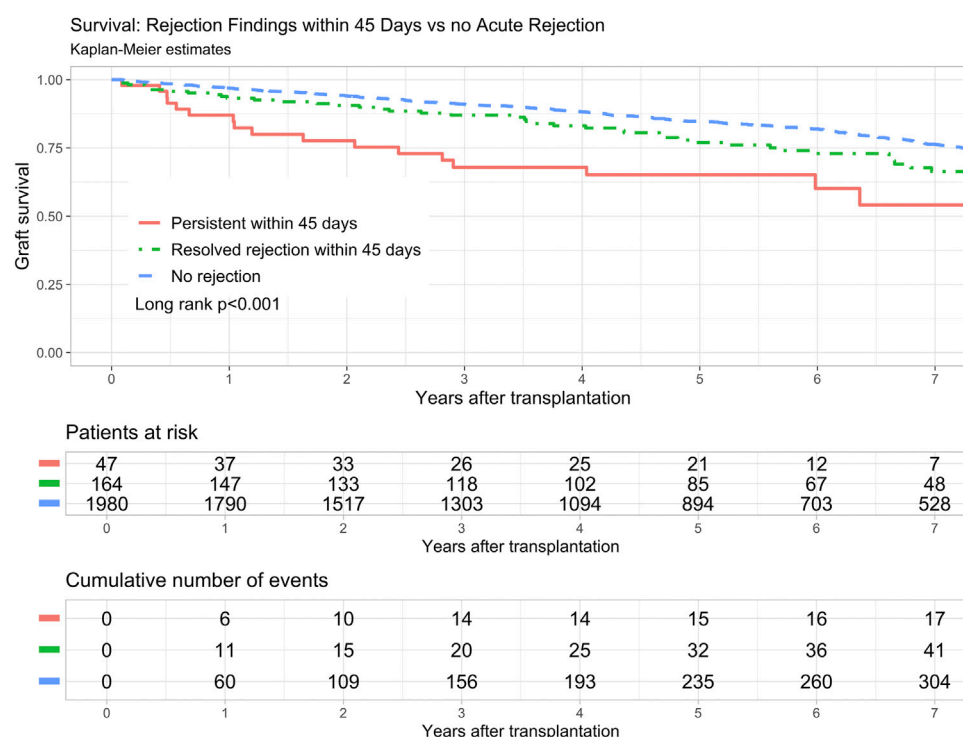


FIGURE 3
Survival estimates based on rejection findings within 45 days, graft survival.

Rejection is common after kidney transplantation despite improvements in immunosuppressive medication over the past decades [16]. The rate varies across studies between 15 to over 20 percent [17]. The rejection rate in this study population, comprising all kidney transplantations at our institution over 10 years, is well in line with reports from other centers.

Paris Transplant Group reports that at a 3-month posttreatment biopsy, 13.3% of patients showed persisting TCMR changes [13]. In another study, 79% of patients had a complete response to rejection treatment histologically when treated with corticosteroids or with corticosteroids and ATG (17/163 patients) [15]. They gave further treatment to all but one of the patients ($n = 34$) with remaining histological rejection regardless of kidney function and reached complete response in an additional 27 patients. A Canadian study presented worse graft survival in persistent TCMR, when follow-up biopsies were taken within 6 months post-rejection treatment, with a study population having persisting or subsequent TCMR in 64% of cases [18]. In our study, where a follow-up biopsy was taken earlier, 10% of patients had persisting TCMR changes. Additionally 4.5% had borderline TCMR changes not warranting additional treatment. Thus, changes classified as TCMR had cleared earlier than previously reported. This opens an opportunity to intervene earlier to improve kidney function in more patients. Patients with persisting rejection within 45 days post-treatment had worse graft survival. We included patients who had rejection within the first three months post-transplantation, but most of the rejections were discovered at a median time of 9 days since transplantation.

In our study, we found that graft survival in those with rejection, and especially those with persistent rejection, is worse than in

patients with no rejection. Persistent rejection changes are associated with the formation of fibrosis and loss of graft function, which essentially leads to graft loss in the long term [19]. In addition to risk of graft loss, acute rejections can also be associated with worse patient survival. Return to dialysis worsens patient outcomes by increasing the risk for both cardiovascular disease and cachexia [20, 21]. Immunosuppression increases the risk of cancer. A Finnish population registry study comprising over 6500 solid organ transplant recipients showed that heart transplant recipients are at the highest risk of developing cancer [22]. Heart transplant recipients receive higher doses of maintenance immunosuppression compared to kidney transplant recipients and often receive anti-thymocyte globulin/anti-human T-lymphocyte immunoglobulin induction. Immunosuppression also causes higher rates of infection, with around 50% of kidney transplant recipients experiencing some kind of infection during the first year after transplantation [23]. The higher immunosuppression doses and the adverse effects associated with these could also partly explain why those with persistent rejection after kidney transplantation have worse survival.

At our center, borderline TCMRs in a first biopsy are treated as TCMR, with corticosteroids. Practices for the treatment of borderline TCMR changes vary [24]. It has been suggested that treating subclinical borderline TCMR might not be beneficial, but treatment if the biopsy was taken on clinical indications (i.e., impaired kidney function) has been associated with improved kidney function [8]. In sensitivity analyses, we observed similar results, supporting the treatment of borderline TCMRs. On a similar note, the dichotomous view of rejections being

TABLE 2 Multivariable logistic regression analysis of factors associated with persistent rejection within 45 days.

Characteristic	OR	95% CI	p-value
Recipient sex: Male	2.30	0.99, 5.88	0.054
Recipient age (years)	1.01	0.97, 1.05	0.6
Peak PRA over 30: Yes	1.90	0.69, 5.24	0.2
Donor sex: Male	1.50	0.73, 3.14	0.3
Donor age (years)	0.97	0.94, 1.01	0.11
Previous kidney transplant	0.43	0.13, 1.29	0.14
HLA AB mismatch	0.90	0.62, 1.33	0.6
HLA DR mismatch	0.84	0.42, 1.68	0.6
First rejection diagnosis			0.037*
TCMR	—	—	
AMR	1.02	0.29, 3.49	
Borderline TCMR	0.23	0.05, 0.74	
Cold ischemia time (hours)	0.96	0.86, 0.99	0.03
Donor specific antibodies at time of transplantation	1.61	0.47, 5.52	0.4
Donor type			0.3
DBD	—	—	
DCD	0.37	0.01, 4.65	
LD	0.33	0.05, 1.61	

*p-value statistically significant, <0.05.

PRA, panel reactive antibodies; HLA, human leukocyte antibodies; TCMR, T-cell mediated rejection; AMR, antibody mediated rejection; DBD, donation after brain-death; DCD, donation after circulatory determination of death; LD, living donor.

TABLE 3 Rejection grades.

Rejection type	First biopsy, N	First follow-up biopsy, N	Second follow-up biopsy, N	Third follow-up biopsy, N
AMR	44	18	6	4
Borderline TCMR	86	13	4	4
TCMR IA	60	8	1	NA
TCMR IB	12	2	2	NA
TCMR IIA	126	30	7	NA
TCMR IIB	38	6	2	1
No rejection	NA	168	47	13
Inadequate	NA	8	4	2

TCMR, T-cell mediated rejection; AMR, antibody mediated rejection.

either TCMR or AMR has been questioned. A recent review by Callemeyn et al provides insight into the current evidence on the serology, histology, and prognosis of different rejection phenotypes, highlighting the gap in the current dichotomous classification [25]. In our study population, 26 cases presented with an isolated v-lesion TCMR. Their number remains so low, that subgroup analyses were not deemed justified.

This study consists of a large number of kidney transplant recipients. There are some limitations to consider, the retrospective nature of the study being one of them. In Finland,

the follow-up of kidney transplant recipients is done by nephrologists in local hospitals around the country. These hospitals are required to report kidney graft and patient data to the National Transplant Registry. However, this does not always include data on biopsies taken regionally. Furthermore, a follow-up biopsy was not taken in all patients. In survival analysis, patients with missing follow-up biopsy post-rejection had similar survival as those with resolved rejection. Half of the follow-up biopsies taken were by protocol, and the survival of these patients was similar to those with missing follow-up biopsy. If a persistent rejection was

found in the biopsy taken by protocol, the survival was slightly worse than those with resolved rejection findings, but the number of cases was low in this group.

As the immunosuppression regimen did not include induction therapy in the majority of patients, these results may not apply to all kidney transplant patients. But on the other hand, despite the induction-free therapy, most rejection changes had resolved within 45 days.

In conclusion, in our current study, the majority of rejections are resolved within 45 days after rejection. Early follow-up biopsies could allow earlier intervention in case of persistent rejection. Long-term survival is significantly better in kidneys with no rejection, while persistent rejection is associated with worse outcomes.

Data availability statement

The datasets presented in this article are not readily available because The individual-level data is not available due to national regulations and laws in Finland regarding the sharing of individual-level patient data. Aggregate-level data can be shared based on a reasonable request. Requests to access the datasets should be directed to amanda.ahlmark@helsinki.fi.

Ethics statement

This study was approved by the institutional review board of Helsinki University Hospital (HUS/23/2024). The clinical and research activities being reported are consistent with the Principal of Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Author contributions

Data collection – AA, KA, IH, and JL. Statistical analyses – AA. Manuscript original draft – AA, KA, and IH. Manuscript review and editing – AA, KA, IH, VS, JL, AR-S, and ML. All authors contributed to the article and approved the submitted version.

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Conflict of interest

IH holds research grants from Hansa Biopharma and Neovii and has received consultancy fees from AstraZeneca, Hansa Biopharma, Takeda, and MSD. JL has received consultancy fees from Hansa Biopharma. KA has received consulting fees from Hansa Biopharma and Astellas. AR-S has received consulting fees from SOBI.

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.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontierspartnerships.org/articles/10.3389/ti.2026.16296/full#supplementary-material>

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Impact of tacrolimus peak concentration on kidney graft outcomes

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Low tacrolimus (Tac) trough concentration-to-dose ratio (C₀/D ratio) identifies kidney transplant patients with high level of Tac metabolism and is associated with poorer outcomes. We hypothesized that fast metabolism is associated with higher maximal Tac blood concentration (C_{max}) and that Tac C_{max} has a detrimental effect by itself. We retrospectively selected consecutive kidney transplant patients who (i) were treated by Tac, (ii) had systematic pharmacokinetic evaluation at 3- and 12-month posttransplant, and (iii) with a minimal follow-up of 5 years. Association between Tac C_{max}/C₀ with traditional transplant outcomes was analysed. 519 patients with a median follow-up of 8 years were included. Fast metabolizers displayed significantly higher median C_{max} (20 vs. 17 ng/mL p < 0.001). Death-censored graft survival (DCGS) was significantly lower for patients with the highest C_{max}/C₀ values (Log rank, p = 0.05). In multivariate cox analysis, higher C_{max}/C₀ was independently associated with DCGS (HR = 1.37 [1.01; 1.87], p = 0.043). Our data support the hypothesis that exposure to high C_{max} is detrimental and that fast metabolizers exhibit higher Tac C_{max} even in situations where Tac C₀ is not elevated. Tac formulations prone to mitigate pharmacokinetic peak could thus be particularly beneficial to fast metabolizers and should be evaluated in this indication.

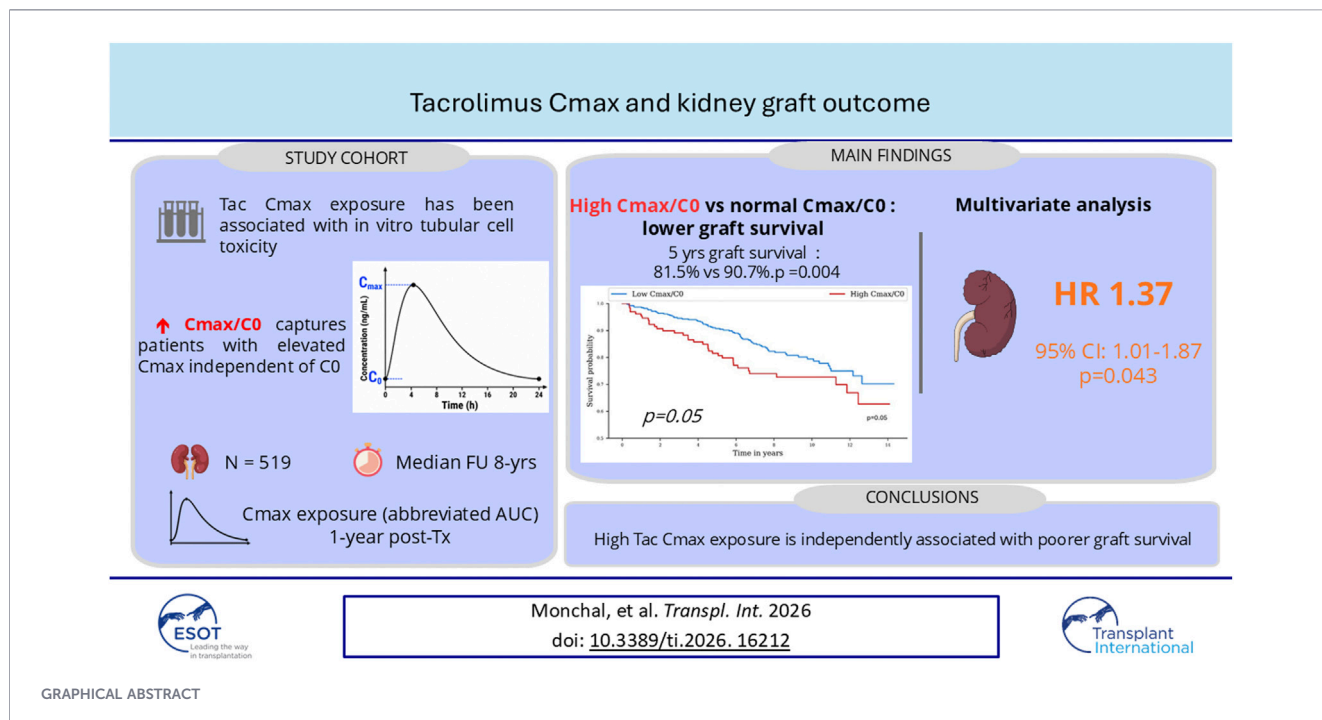
KEYWORDS

kidney transplantation, tacrolimus, pharmacokinetics, tacrolimus concentration-to-dose ratio, tacrolimus exposure, graft survival

Background

The calcineurin inhibitor tacrolimus (Tac), when combined with mycophenolate mofetil and glucocorticoids, constitutes the standard immunosuppressive regimen for kidney transplant recipients [1, 2]. Tac is characterised by a narrow therapeutic index: low exposure is associated with higher risk of rejection [3] whereas overexposure leads to acute toxicity [4, 5] as well as to chronic graft injury [6]. In addition, Tac metabolism is subject to substantial intra- and inter-individual variability [7]. In practice, this translates into the necessity to carefully and regularly monitor Tac exposure in transplanted patients. Tac trough level (C₀), being well correlated with 24 h-Tac Area Under Curve (AUC), is usually considered as a valid and clinically useful proxy for Tac exposure [8] even though direct evaluation of Tac AUC is recommended in specific situations [9, 10].

With the aim to better capture the clinical impact of Tac metabolism, a novel metric has recently emerged, the ratio between Tac C₀ and Tac daily dose, also known as C₀/D ratio [11]. Low C₀/D ratio (usually below 1.05) identified so-called “fast metabolizer” patients who require higher Tac dose to achieve the desired C₀ [11–13]. Retrospectively, the fast metabolizer status has been associated with lower graft function at 2 and 5 years post-



transplantation [8], lower graft survival [12], increased risk of rejection [14], higher incidence of BK nephropathy [15] and histological lesions of interstitial fibrosis/tubular atrophy [16].

While a low C0/D ratio is linked to poorer outcome in kidney transplantation, the precise determinants driving this effect remain largely elusive. In this regard, a detrimental role of Tac maximal concentration (Cmax) could be discussed. Fast metabolizers receive higher doses of tacrolimus and might be exposed to higher Cmax levels (for the same C0) than non-fast metabolizers. This was actually reported in patients with the CYP3A5*1 allele, an allele that confers accelerated Tac metabolism [17, 18]. In the same line, Thölking and colleagues have observed higher C2 Tac blood concentrations in fast metabolizer patients, along with higher renal tubular cells toxicity [19].

While those data suggest a detrimental role of Tac Cmax, no study has specifically assessed the link between exposure to elevated Tac Cmax and graft outcome. We thus sought to retrospectively investigate the association between Tac Cmax, C0/D ratio and graft outcome in a cohort of kidney transplant patients who had Tac abbreviated pharmacokinetics as part of their routine follow-up.

Patients and methods

Study population

We conducted a retrospective analysis, considering all patients who underwent kidney transplantation between December 2008 and December 2016 at Saint Etienne University Hospital, France, with a minimum follow-up period of 5 years. Outcome data were collected up to December 31, 2021.

This study was formally approved and registered by our local ethics committee “Terre d’Ethique” under reference number IRBN902023/CHUSTE.

Patients under the age of 18 or who had lost their graft within the first 3 months post-transplantation or who received cyclosporine as a maintenance regimen were not included in the analysis. Tac-treated patients were considered eligible for the analysis regardless of the formulation used. Induction therapy was selected based on the immunologic risk profile of the recipient. Maintenance therapy primarily consisted in tacrolimus, mycophenolate mofetil, and steroids. Tacrolimus dosing commenced at 0.1 mg/kg/day, targeting a trough level of 8–12 ng/mL during the initial month, 6–10 ng/mL for the first 3 months, and 4–8 ng/mL thereafter.

Data, collected from medical records, were recipient’s age, gender, weight and height, underlying nephropathy, dialysis status, history of previous kidney transplants, medical history, donor’s age, gender, donor type, expanded criteria donor status, medical history, and morphological data. In addition, type of induction therapy, HLA mismatch in A, B, and DR loci, PRA and pre-existing donor-specific antibodies (DSA), ABO incompatibility, ischemia times, use of machine perfusion, and occurrence of delayed graft function were collected.

Measurement of tacrolimus serum concentration

In our department, patients routinely undergo tacrolimus pharmacokinetic (PK) evaluation at month 3 and month 12 and every year post-transplant. PK evaluation consists in a 4 time-points measurements: before the morning dose of Tac (C0), and 30, 90 min and 180 min after Tac taking. Tac blood concentration was evaluated using HPLC-MS-MS. Analyses were performed on a Waters Acquity H-Class UPLC system coupled to a Waters Xevo TQD triple quadrupole mass spectrometer (Waters, Saint-Quentin-en-Yvelines, France). The analytical method was fully validated according to the U.S. Food and Drug Administration Bioanalytical

Method Validation Guidance for Industry. Furthermore, the tacrolimus assay is accredited by the French Accreditation Committee (COFRAC) in accordance with the ISO 15189 standard for medical laboratories.

For the present analysis, we used the median of M3 and M12 PK values. C_{max} was defined by the maximum concentration measured at 90 or 180 min, a time period likely to capture Tac peak concentrations irrespective of its formulations [8].

Two different ratios were considered: the classical C₀/D ratio in order to identify fast metabolizers (C₀/D < 1.05) and the C_{max}/C₀ (i.e., Tac peak over trough level) in order to identify patients exposed to elevated peaks despite adequate C₀.

Clinical outcomes

The primary endpoint was death-censored graft survival. Secondary endpoints were patient survival, onset of *de novo* DSA, acute or chronic rejection, histologically proven CNV nephrotoxicity, BK virus associated nephropathy, infectious, cardiovascular, metabolic and carcinologic complications.

Statistical analysis

All statistical analyses were performed using the R statistical software (R core team 2019) or Easymedstat (version 3.29; www.easymedstat.com). Data were expressed as mean ± SD if normally distributed or median (Q1; Q3) otherwise. Categorical variables were presented as frequency and percentages. Pairwise comparison repeated-measures analyses were performed with Friedman's test. If the null hypothesis of Friedman's test was rejected, post-hoc pairwise analyses were performed with Nemenyi's test (alpha risk was set to 5%). Comparison of baselines characteristics was done using unpaired Student's t-test, Welch t-test or Mann-Whitney U test for continuous parameters, and chi-squared or Fisher's exact test for categorical parameters (alpha risk was set to 5% and two-tailed tests were used). Kaplan-Meier method was used to estimate survival probabilities with their pointwise 95% confidence intervals. The Logrank non-parametric test for comparison of survival distributions was used to compare survival differences between groups (alpha risk was set to 5.0%). Cloglog fixed point method was used to compare survival probabilities between groups at different time points. Survival models were built by Cox methodology, to estimate the association between C_{max}/C₀ with several survival endpoints (patient survival, graft survival, death censored graft survival, survival without acute rejection, chronic rejection...). A multivariate Cox model was built in a forward manner, retaining variables associated with death-censored graft survival at a $p < 0.10$.

Results

Population characteristics

Between December 2008 and December 2016, a total of 559 kidney transplantations were performed at the University Hospital of Saint Etienne, France. Among these patients, 519 met the inclusion criteria and were retained for the analysis. Table 1 displays the characteristics of the study population

categorized on the C₀/D ratio. Median C₀/D ratio was 1.54 (Q1 1.06; Q3 2.16), with 24% of patients classified as fast metabolizers (C₀/D < 1.05). Fast metabolizers were notably younger ($p = 0.004$) and less likely to have received expanded criteria donor (ECD) grafts ($p = 0.01$). There was no significant difference observed in the immunosuppressive regimen between groups with the vast majority of patients receiving corticosteroids, mycophenolate mofetil, and extended-release tacrolimus formulation (ADVAGRAFTM was the unique extended-release tacrolimus formulation used in this study). Pharmacokinetic profiles did not differ significantly according to tacrolimus formulation, [Supplementary Table S1](#).

Tacrolimus pharmacokinetics

Table 2 provides a summary of Tac PK parameters. Fast metabolizers exhibited lower C₀ [6.8 (Q1 5.8; Q3 7.9) vs. 7.9 (Q1 6.8; Q3 9.2); $p < 0.001$], while receiving higher doses of Tac [8.5 (Q1 7.5; Q3 10) vs. 4.5 (Q1 3.5; Q3 5.5); $p < 0.001$], resulting in a lower C₀/D ratio ($p < 0.001$). Interestingly, C_{max} was significantly higher in patients classified as fast metabolizers [20.0 (Q1 16.0; Q3 25.4) vs. 17.1 (Q1 13.5; Q3 20.6); $p < 0.001$]. Tac C_{max}/C₀ ratio was 2.29 (Q1 1.93; Q3 2.81) in the entire cohort and was notably higher for fast metabolizer patients [2.96 (Q1 2.44; Q3 3.53) vs. 2.16 (Q1 1.84; Q3 2.58); $p < 0.001$]. We considered the cut-off value of 2.81 (corresponding to the third quartile) to distinguish patients with low (<2.81) and high (>2.81) C_{max}/C₀ values. Using this cut-off, 56.4% of fast metabolizers exhibited an elevated C_{max}/C₀ as compared to 15.0% for slow- or normal metabolizer patients ($p < 0.001$) (Figure 1; Table 2).

Survival analysis

Over the study period, there were a total of 114 deaths and 111 death-censored graft losses. Kaplan-Meier curves for death-censored graft and patient survival according to C_{max}/C₀ ratio ±2.81 are displayed in Figure 2. Death-censored graft survival (Figure 2A) and patient overall survival (Figure 2B) were significantly lower in patients with a C_{max}/C₀ ratio >2.81 ($p = 0.05$ and $p = 0.02$, respectively). At 5 years, death-censored graft survival was 90.7 (95% CI: 87.9–93.7) in the low C_{max}/C₀ group compared to 81.5% (95% CI: 75.0–88.7) in the high C_{max}/C₀ group ($p = 0.004$). Overall survival was 5.8% lower in the high C_{max}/C₀ group, with rates of 86.7% (95% CI: 81.0–92.8) versus 92.5% (95% CI: 0.90–0.95), respectively ($p = 0.04$).

In univariate Cox regression model, higher C_{max}/C₀ ratio was significantly associated with reduced death-censored graft survival (HR 1.26 [95% CI: 1.004–1.57]; $p = 0.046$) Table 3. In multivariate analysis, after adjusting for age, diabetes, preemptive status, ECD status and cPRA, the association between C_{max}/C₀ ratio and lower death-censored graft survival remained significant (HR 1.37 [95% CI: 1.01–1.87]; $p = 0.043$).

Association between C_{max}/C₀ and other clinical outcomes

Table 4 summarizes the association between C_{max}/C₀ and other clinical outcomes in univariate Cox regression model. Higher C_{max}/

TABLE 1 Comparison of baseline characteristics and pharmacokinetic parameters according to metabolization status.

Characteristics	Fast metabolizers C0/D ratio <1.05 N = 126	Slow metabolizers C0/D ratio ≥1.05 N = 393	p value
Demographics (recipient)			
Age (years)	52.2 ± 13.7	56.1 ± 13.5	0.004
Gender (male)	73 (57.9)	262 (66.67)	0.094
Pre-transplant comorbidities			
Hypertension	95 (75.4)	348 (88.6)	<0.001
Diabetes	26 (20.6)	6 (15.5)	0.23
Donor			
Age (years)	55.4 ± 14.2	56.8 ± 5.9	0.122
Donor type			0.188
Living donor	19 (15.1)	40 (10.3)	
Brain dead donor	107 (84.9)	353 (89.7)	
Expanded criteria donor	43 (34.13)	185 (47.8)	0.01
Immunology			
PRA >20%	13 (10)	65 (16)	0.16
Induction therapy			0.716
ATG	32 (25.4)	94 (24.0)	
Anti IL-2 receptor	94 (74.6)	294 (75)	
Other	0	4 (1)	
Immunosuppressive drugs (1year)			
Corticosteroid	90 (71)	268 (68)	0.308
Mycophenolate mofetil	108 (86)	351 (89)	0.538
Tacrolimus			0.623
IR-tacrolimus	23 (18)	83 (21)	
ER-tacrolimus	94 (74)	288 (73)	

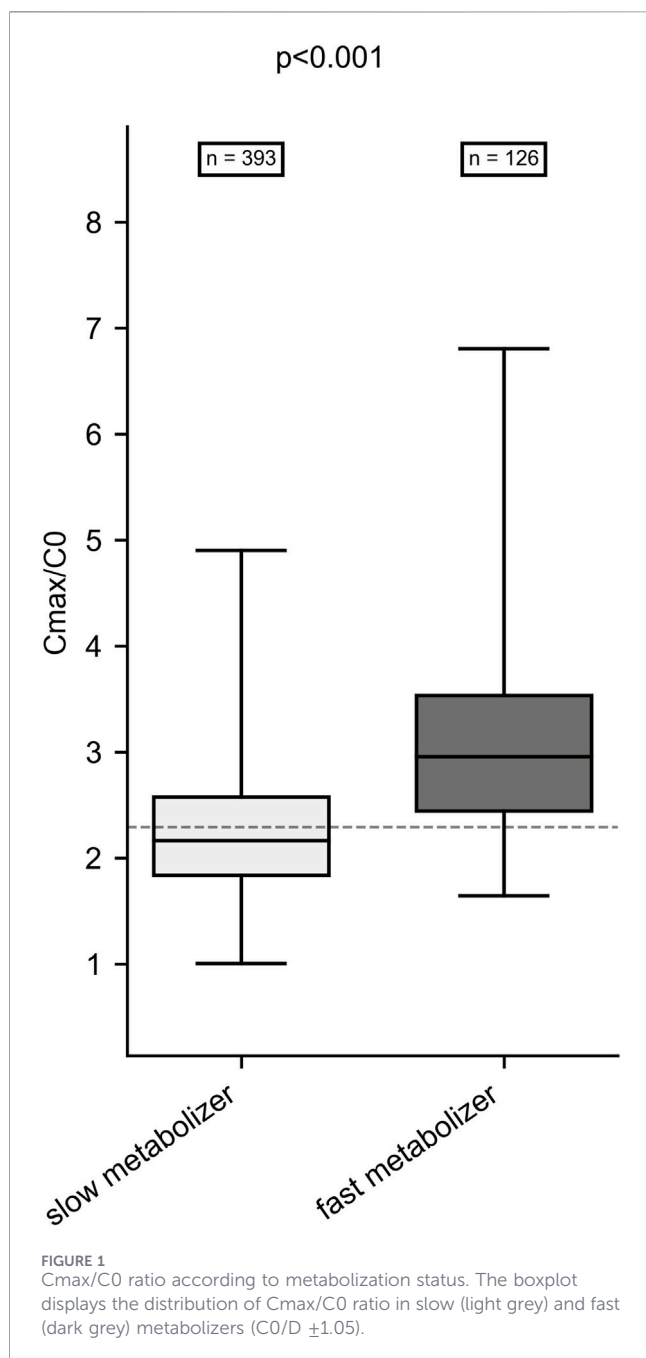
TABLE 2 Pharmacokinetic parameters.

Variables	Fast metabolizers C0/D ratio <1.05 N = 126	Slow metabolizers C0/D ratio ≥1.05 N = 393	p value
C0 (ng/mL)	6.8 (5.8–7.9)	7.9 (6.8–9.2)	<0.001
Dose (mg)	8.5 (7.5–10)	4.5 (3.5–5.5)	<0.001
C0/D	0.84 (0.7–0.95)	1.80 (1.41–2.40)	<0.001
Cmax (ng/mL)	20.0 (16.0–25.4)	17.1 (13.5–20.6)	<0.001
Cmax/C0	2.96 (2.44–3.53)	2.16 (1.84–2.58)	<0.001
Cmax/C0 >2.81	71 (56.4%)	59 (15.01%)	<0.001

C0 was associated with a higher risk of BK nephropathy (HR 1.52 [1.05–2.21], $p = 0.0284$). This relationship was not found with other viral infections. High Cmax/C0 ratio was not associated with the occurrence of acute rejections episodes neither the risk of developing *de novo* DSA formation. No significant relationship was observed between Cmax/C0 ratio and histological evidence of CNI-induced nephrotoxicity.

Discussion

In this study, we took advantage that Tac PK monitoring is routinely realized in our centre, to evaluate a possible detrimental effect of high Cmax exposure on transplant long term outcome. The main result of our study is that high Cmax exposure is significantly associated to decreased graft survival and that this



detrimental effect is at least partially independent of Tac C0 and even of Tac AUC.

In the present study, we have first observed - consistently with previous reports- that fast metabolizers transplant patients exhibit significantly higher Cmax compared to slow/normal metabolizers [19]. It was thus tempting to speculate that elevated Cmax was responsible, at least partially, for the poor transplant outcome observed in recipients with low C0/D ratio, keeping in mind that several experimental and clinical data support a model of Tac Cmax induced nephrotoxicity [19]. However, as others previously reported, we were not able to identify a direct association between Cmax and transplant outcome. We believe that this apparent discrepancy can be explained by the fact that high Cmax actually reflects two

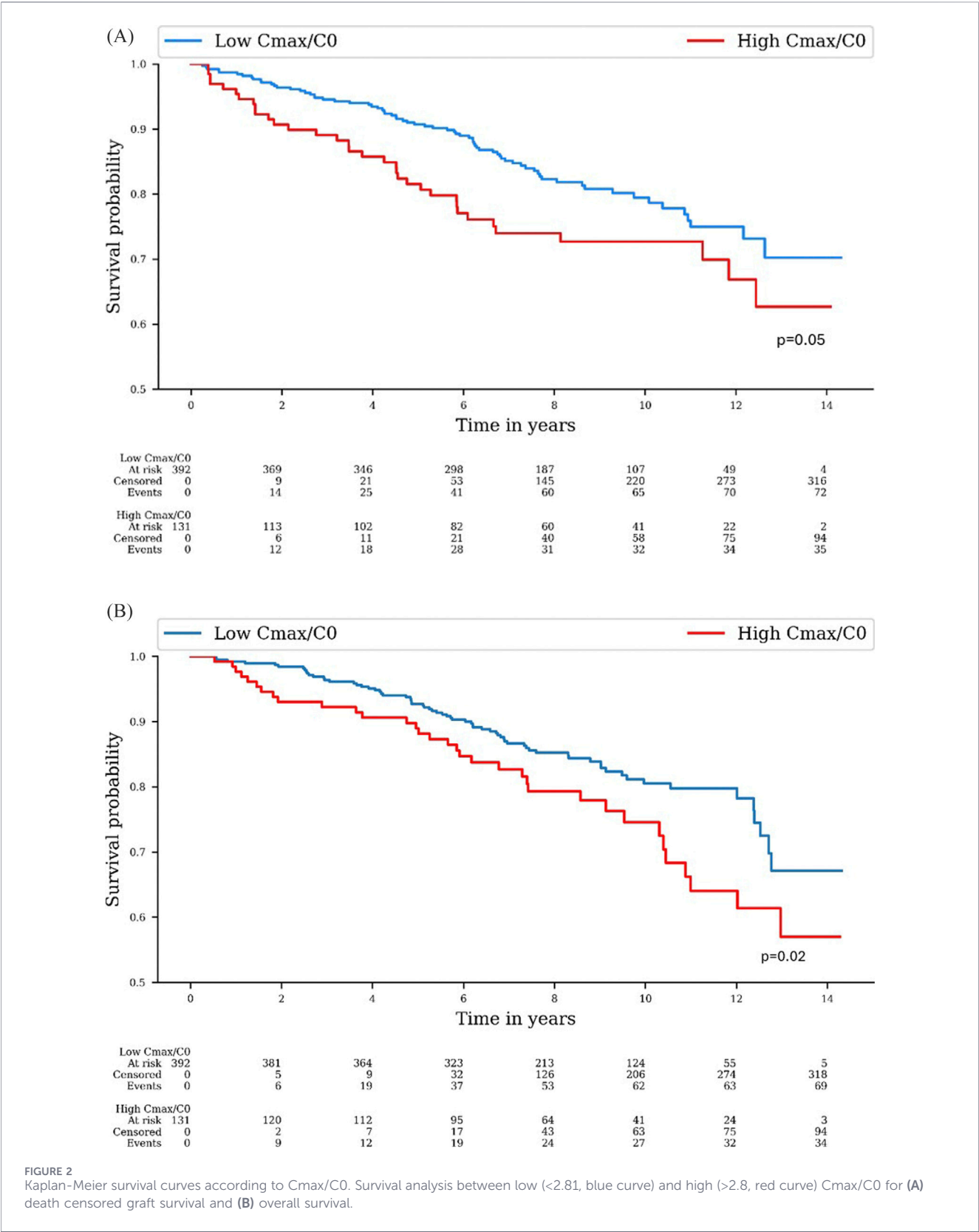
different clinical situations. First, a scenario in which Tac overexposure is concomitant to high C0. In this scenario, exposition to high Cmax is obvious and likely to be rapidly corrected by decreasing Tac dosing. Second, a scenario in which elevated Cmax coexists with an apparently “normal” Tac C0 (i.e., within the expected range and thus falsely reassuring). In this scenario, elevated Cmax is *bona fide* not detectable and is likely to remain uncorrected. In consequence, testing the hypothesis of a direct toxicity of Tac Cmax may require to preferentially select the subpopulation of patients with a “high Cmax-normal C0” profile.

By re-expressing Cmax as Cmax/C0 ratio, we intended to better decipher the clinical impact of elevated Cmax, the hypothesis being that higher Cmax/C0 ratio confers higher risk. We did observe a statistically significant and independent association between Cmax/C0 and graft survival. In our cohort, an elevated Cmax/C0 clearly appears to be a marker of poor outcome suggesting that Tac Cmax overexposure could be deleterious (with a positive trend irrespective of the C0/D ratio, [Supplementary Figure S3](#)). While patients with high Cmax/C0 did not have more histological lesions related to Tac nephrotoxicity, they were significantly more likely to develop BK-associated nephropathy. The exact mechanisms underlying Cmax toxicity will however need to be thoroughly explored in larger and more appropriately designed studies.

Tac PK varies according to Tac formulation [8, 18, 20] and may impact Cmax/C0 ratio. In our study, we did not find any difference in Cmax alone or Cmax/C0 between different Tac formulations but the large majority of our patients (almost 75%) received conventional extended released-Tac. It is known that patients under the LCP formulation have significantly lower Cmax (−31%) especially when they expressed CYP3A5 fast metabolizer alleles [16]. In a retrospective proof of concept study [21], when patients were switched from intermediate release- to LCP formulation early after transplantation, fast metabolizers patients showed a noticeable and persistent increase of eGFR (+4.15 (mL/min/1.73 m²) whereas eGFR in slow metabolizers remained stable. While this was not directly evaluated in the present study, our data suggest that a lower Cmax exposure following the switch to LCP Tac might have played a role in renal graft function improvement. This speculation will need to be formally tested in a prospective and controlled manner, especially given that LCP-formulation has so far not demonstrated any consistent benefit over conventional extended-released formulation of Tac.

Interestingly, Tac Cmax/C0 and Tac AUC were poorly correlated ([Supplementary Figure S1](#)). Additionally, we did not observe a significant association between high Tac AUC and graft survival ([Supplementary Figure S2](#)). Together, those observations suggest that the detrimental effect of high Cmax/C0 is at least partially independent of Tac AUC.

Beyond the impact of Cmax, accumulation of Tac metabolites are also potential factors that could negatively influence graft outcome, especially in fast metabolizers [22, 23]. The increased Tac dosing which is required in fast



metabolizers could result in intra renal metabolites accumulation responsible for cellular damages. This hypothesis is currently being explored in the TIPS study (ClinicalTrials.gov Identifier: NCT04526431).

Cmax value was defined in our study as the higher Tac concentration analysed between 2 predefined time points, namely, 90 and 180 min. Strictly speaking, this does not correspond to the real Cmax which would require

TABLE 3 Univariate and multivariate Cox regression model to predict death-censored graft survival. Multivariate model was built in a forward manner, retaining variables associated with death-censored graft survival at a $p < 0.10$.

Variables	Univariate		Multivariate	
	HR (IC 95%)	<i>p</i> value	HR (IC 95%)	<i>p</i> value
Age	1.03 (1.014–1.047)	<0.001	1.03 (1.00–1.06)	0.042
Gender	1.105 (0.5–1.62)	0.61		
Body Mass index	1.02 (0.98–1.06)	0.33		
Cold ischemia	1 (0.99–1.02)	0.16		
PRA	1.007 (1–1.014)	0.048	1.00 (1.00–1.01)	0.019
Induction treatment	1.45 (0.99–2.1)	0.053		
Diabetes (recipient)	2.34 (1.54–3.57)	<0.001	2.44 (1.41–4.23)	0.001
Living donation	0.76 (0.38–1.50)	0.43		
Preemptive transplantation	0.44 (0.21–0.94)	0.03	0.93 (0.42–2.08)	0.86
ECD donor	2.6 (1.76–3.83)	<0.001	1.54 (0.86–2.77)	0.14
Cmax/C0	1.26 (1.004–1.57)	0.046	1.37 (1.01–1.87)	0.043

ECD, Expanded Criteria Donor; PRA, Panel Reactive Antibody.

TABLE 4 Association between Cmax/C0 and other clinical outcomes in univariate Cox regression model.

Outcome	HR (IC95%)	P value
Early outcomes		
Acute rejection	1.193 (0.972–1.464)	0.091
BK nephropathy	1.518 (1.045–2.20)	0.029
CMV infection	1.168 (0.877–1.554)	0.288
Other viral infection	1.28 (0.837–1.97)	0.257
Infectious event	1.16 (0.93–1.45)	0.185
Late outcomes		
Graft loss	1.163 (0.976–1.388)	0.092
Death	1.163 (0.944–1.474)	0.146
Death censored graft loss	1.258 (1.004–1.574)	0.046
Chronic rejection	0.932 (0.631–1.378)	0.726
DSA <i>de novo</i>	1.044 (0.823–1.324)	0.723
Histological toxicity	1.144 (0.879–1.488)	0.317
Cancer occurrence	0.952 (0.776–1.167)	0.635
NODAT	0.71 (0.5–1.02)	0.067
Cardiovascular event	0.70 (0.570–1.039)	0.088

a full PK analysis, a procedure hardly implementable in clinical practice. However, considering the PK profile of Tac [8, 24], we can reasonably assume that Cmax values determined from our abbreviated PK were close to the real Cmax. Of note, the pharmacokinetic status of each patient

was determined from the median Tac concentrations measured at month 3 and month 12. We acknowledge that this relies on the assumption that the pharmacokinetic status is stable over this time-period, which was actually verified for a majority (81%) but not for all our patients.

Our study has other limitations, the first being its retrospective, monocentric nature. The absence of a systematic protocol biopsies policy in our centre may have also accounted for the low rate of histologically documented calcineurin inhibitor toxicity and our inability to demonstrate the histological impact of Tac overexposure that is usually expected [16]. Additionally, physicians had access to Cmax values which could have influenced subsequent prescriptions in adjusting Tac dosing. Finally, Tac PK results did not include AUC measurements. Tac AUC is considered the most reliable parameter to assess Tac exposure [9].

To the best of our knowledge, our study is the first one to have analysed the relationship between metabolization status and Tac peak concentration in regard with transplant outcome. Of note, all Tac measurements were done in the same laboratory at university hospital of Saint Etienne using a HPLC-MS-MS method, limiting biases due to the dosage technique. Another strength of our study lies in its relatively long median follow-up time of 8 years.

In conclusion, our data suggest that high Tac Cmax exposure is independently associated with poorer graft survival and support the hypothesis that fast metabolizers exhibit higher Tac Cmax even in situations where Tac C0 is not elevated.

Tac formulations prone to mitigate pharmacokinetic peak could thus be particularly beneficial to fast metabolizers kidney transplant patients and should be thoroughly evaluated in this indication.

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 Local ethics committee “Terre d’Ethique” reference number IRBN902023/CHUSTE. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants’ legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

QM contributed to data acquisition, performed the statistical analyses, and drafted the manuscript with the assistance of GC. NM contributed to additional statistical analyses. CM supervised and directed the study. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontierspartnerships.org/articles/10.3389/ti.2026.16212/full#supplementary-material>

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Secondary thrombotic microangiopathy following lung transplantation: a multicenter European cohort study

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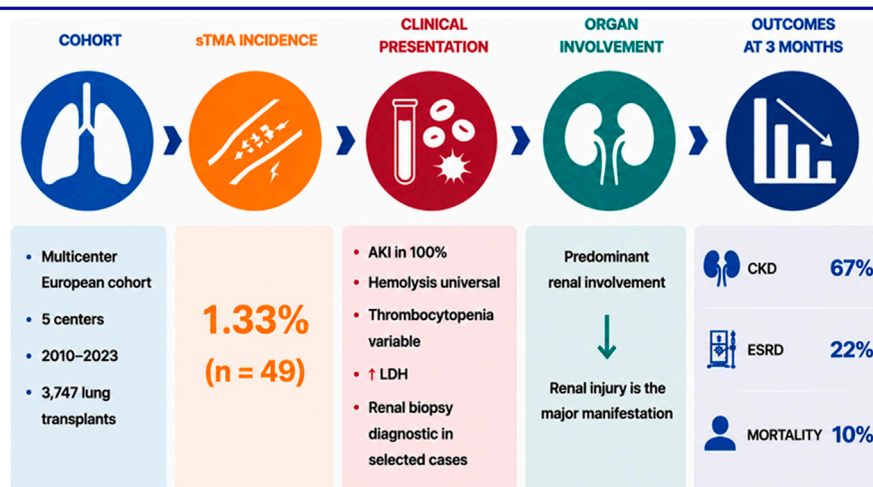
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Secondary thrombotic microangiopathy (sTMA) is a rare but severe complication after lung transplantation. We performed a multicenter retrospective cohort study including adult lung transplant recipients diagnosed with *de novo* sTMA between 2010 and 2023 across five European transplant centers. The primary outcome was incidence of sTMA, with secondary outcomes including clinical presentation, treatment strategies, renal outcomes, and survival. Among 3,747 lung transplantations, 49 cases of sTMA were identified, corresponding to an incidence of 1.33%. Median time to diagnosis was 312 days (IQR 93–546), with 53% occurring within the first post-transplant year. All patients presented with acute kidney injury and laboratory signs of hemolysis, neurological complications were observed in 8%. Therapeutic approaches included plasma exchange (46.9%), anti-C5 therapy (24.5%), and sequential plasma exchange followed by complement inhibition (10.2%). At follow-up, 65.3% developed chronic kidney disease, 20.4% progressed to end-stage renal disease, and 10.2% died during the acute episode. No significant association between treatment modality and renal or survival outcomes was observed. sTMA after lung transplantation is infrequent but associated with substantial renal morbidity and mortality. Early recognition through assessment of hemolysis and kidney injury, supported by renal biopsy in selected cases, may facilitate timely diagnosis and management.

KEYWORDS

clinical outcomes, European lung transplant centers, lung transplantation, multicenter cohort, secondary thrombotic microangiopathy

Secondary Thrombotic Microangiopathy Following Lung Transplantation: A Multicenter European Cohort Study



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GRAPHICAL ABSTRACT

Introduction

Thrombotic microangiopathy (TMA) is a rare but potentially life-threatening complication characterized by microvascular endothelial injury, leading to a triad of hemolytic anemia, thrombocytopenia, and organ damage, primarily affecting the kidneys and central nervous system [1].

Secondary thrombotic microangiopathy (sTMA) refers to TMA occurring in association with an identifiable trigger, such as transplantation, infection, malignancy, autoimmune disease, or drug exposure. Although complement activation may contribute to endothelial injury in selected cases, sTMA is generally distinguished from primary complement-mediated TMA by the presence of an underlying precipitating condition [2]. While sTMA has been extensively studied in these populations, its occurrence following lung transplantation (LuTX) remains poorly understood. Although some studies have estimated the incidence of sTMA in lung transplant recipients to be between 2% and 7%, the true prevalence and underlying mechanisms remain unclear [3–7].

Several risk factors for sTMA development after LuTX have been identified, including endothelial injury during surgery, ischemia-reperfusion injury, and the use of immunosuppressive agents such as calcineurin inhibitors and mTOR inhibitors. Despite these identified risks, the precise pathophysiology of sTMA in lung transplant recipients is still under investigation. Notably, not all cases of sTMA present with systemic hemolysis, which can make diagnosis challenging, particularly when renal injury occurs without the typical hematologic features. Furthermore, early identification and treatment options remain underexplored, with therapies such as plasmapheresis and complement inhibition showing mixed results in transplant populations [8–10], [10–12].

In recent years, a few small case series have shed light on the clinical characteristics and outcomes of sTMA following lung transplantation. However, these reports have been limited by small sample sizes and single-center designs. A recent study with approximately 80 patients represents one of the larger efforts to understand sTMA in LuTX recipients [13], yet this remains a rare and underexplored complication [4]. To date, no multicenter studies have systematically examined the incidence, risk factors, and clinical outcomes of sTMA after lung transplantation across different European centers.

This study aims to fill this gap by conducting a multicenter, retrospective cohort analysis of adult lung transplant recipients diagnosed with sTMA across five major European transplant centers. By evaluating the incidence, risk factors, treatment strategies, and renal outcomes in a larger cohort, we aim to provide more robust data that could inform diagnostic and therapeutic strategies for this rare but potentially severe complication of lung transplantation [4–6, 8–12, 14].

Abbreviations: ACR, Acute Cellular Rejection; ADAMTS13, A Disintegrin and Metalloproteinase with Thrombospondin Motif 13; CMV, Cytomegalovirus; CLAD, Chronic Lung Allograft Dysfunction; CFH, Complement Factor H; CFI, Complement Factor I; DSA, Donor-Specific Antibodies; ECU, Eculizumab; eGFR, Estimated Glomerular Filtration Rate; ESRD, End-Stage Renal Disease; IS, Immunosuppression; LDH, Lactate Dehydrogenase; LuTX, Lung Transplantation; MMF, Mycophenolate Mofetil; MFI, Mean Fluorescence Intensity; mTOR, Mammalian Target of Rapamycin; PE, Plasma Exchange; PRA, Panel Reactive Antibody; sTMA, Secondary Thrombotic Microangiopathy; TMA, Thrombotic Microangiopathy; TTP, Thrombotic Thrombocytopenic Purpura.

Patients and methods

We conducted a multicenter, retrospective cohort study across five major European lung transplantation (LuTX) centers. The study included adult patients who underwent lung transplantation between 2010 and 2023 and were diagnosed with *de-novo* secondary thrombotic microangiopathy (sTMA).

Inclusion and exclusion criteria

Adult patients (≥ 18 years) who underwent lung transplantation between 2010 and 2023 at the participating centers and developed *de-novo* secondary thrombotic microangiopathy (sTMA) were included in the study. Diagnosis of sTMA was based on clinical, laboratory, and histopathological criteria, with a focus on renal involvement. Diagnostic criteria included hemolysis, thrombocytopenia, organ damage, elevated lactate dehydrogenase (LDH) levels, reduced platelet counts, and ADAMTS13 activity (when available), with renal biopsy used to support diagnosis where available.

Exclusion criteria were: (1) patients with primary TMA (e.g., typical or atypical hemolytic uremic syndrome [HUS] or thrombotic thrombocytopenic purpura [TTP]) diagnosed before lung transplantation; (2) patients with incomplete data on transplant-related variables, post-transplant complications, or those lost to follow-up.

Data collection

Data were collected from five major European lung transplantation centers between June and November 2024. A total of 20 centers were initially contacted via email and telephone to inquire about the diagnosis of secondary thrombotic microangiopathy (sTMA) in lung transplant recipients. Five centers provided anonymized case-level data, which were subsequently included in the analysis. A full list of the contacted centers and all definitions are available in [Supplementary Material](#).

For each sTMA case, detailed clinical data were gathered using a standardized case report form, which was completed with the assistance of local transplant teams. The data collected included demographic information, transplant-related factors, immunosuppressive therapy details, infection history, and post-transplant complications ([Supplementary Table S1](#)).

Study outcomes

The primary outcome of the study was the incidence of sTMA in lung transplant recipients across the participating centers. Secondary outcomes included, identification of risk factors associated with the development of sTMA, with particular focus on immunosuppressive regimens, infection history, and post-transplant complications. Clinical outcomes following diagnosis, including progression to chronic kidney disease (CKD), end-stage renal disease (ESRD), and mortality after the end of the TMA episode (i.e., hospital discharge, normalization of laboratory parameters, death) or after 3 months, whichever came first. Evaluation of the impact of different immunosuppressive therapies on the onset and progression of sTMA. Assessment of

TABLE 1 Patient characteristics.

Characteristic	All patients
Patient number, n	49
Female, n	24 (49%)
Mean age at transplant, years	54 (± 11.2)
Median time from TX to TMA, days	312 (IQR 93–546)
CMV high risk, n	13 (27%)
Lung disease leading to transplant	
COPD, n	27 (55%)
ILD/fibrosis, n	12 (24%)
Cystic fibrosis, n	4 (8%)
Alpha 1 AT, n	3 (6%)
Other, n	3 (6%)
Induction therapy	
Alemtuzumab, n	15 (30.6%)
Anti-thymocyte globulin, n	11 (22.4%)
Basiliximab, n	10 (20.4%)
None, n	8 (16.3%)
Unknown, n	5 (10.2%)
Immunosuppression regimen	
Tacrolimus-based, n	33 (67%)
Cyclosporine-based, n	13 (26%)
Tacrolimus + mTOR inhibitor, n	3 (6%)*

Abbreviations: anti C5 treatment, eculizumab or ravulizumab; TX, transplantation; TMA, thrombotic microangiopathy; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; AT, antitrypsin; mTOR, mammalian target of rapamycin.

*Included in tacrolimus-based group.

renal recovery following the TMA episode, as well as the presence of neurological involvement at presentation.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics, transplant-related variables, and clinical features at the time of sTMA diagnosis. Continuous variables are presented as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR), depending on data distribution, while categorical variables are reported as absolute numbers and percentages.

Chi-square tests were used to compare categorical variables between groups.

The primary outcome was a composite endpoint defined as chronic kidney disease (CKD) stage 5 or death at 3 months, dichotomized as poor outcome (CKD stage 5 or death) versus favourable outcome (CKD stages 1–4).

To assess associations between clinical variables and the primary outcome, binary, multivariate logistic regression was performed. Covariates included age, sex, KDIGO acute kidney injury (AKI), requirement of renal replacement therapy during the index episode, and eculizumab treatment status.

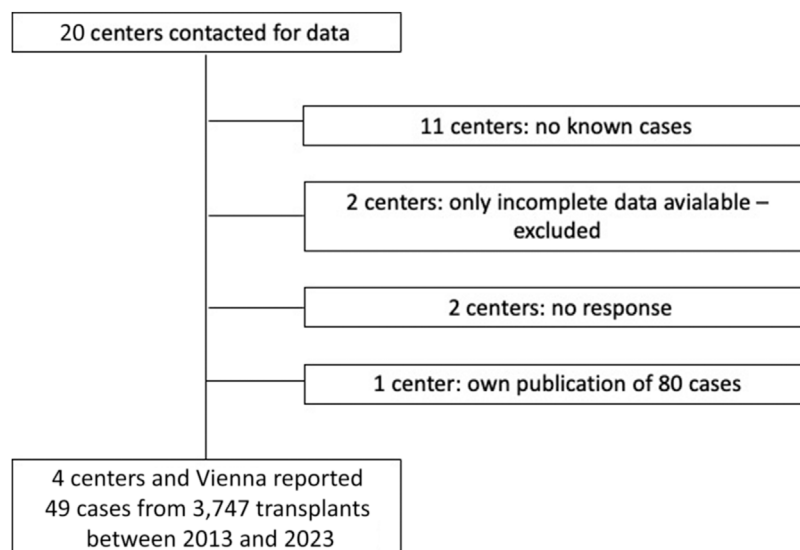


FIGURE 1
Flow chart on center disposition.

Results are reported as odds ratios (OR) with corresponding 95% confidence intervals (CI). Statistical significance was defined as a two-sided p-value <0.05.

All statistical analyses were conducted using JASP 0.96, and a two-sided p-value of <0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Ethics Committee of the Medical University of Vienna (reference number 1361/2014). All procedures were carried out in accordance with the STROBE guidelines for observational research.¹

Results

A total of 49 patients with a diagnosis of secondary thrombotic microangiopathy (sTMA) were identified across the participating centers during the observation period (Table 1). During the study period, 3,747 lung transplants were performed across the five reporting centers, yielding an incidence of sTMA of 1.33% among lung transplant recipients (Figure 1, Supplementary Material).

The cohort consisted of 24 females (49%), with a mean age of 54 years at the time of transplantation. The most common underlying diseases leading to lung transplantation were chronic obstructive pulmonary disease (COPD) (55%), interstitial lung disease (ILD) (24%), cystic fibrosis (8%), and alpha-1-antitrypsin deficiency (6%). Pre-transplant renal disease history was unavailable for most of the cohort. The median time from lung transplantation to sTMA diagnosis was 312 days (IQR

93–546). 11 patients (22.4%) were diagnosed within the first month post-transplant, and 15 patients (30.6%) were diagnosed within the first year. In total, 26 patients (53%) were diagnosed within the first year following transplantation. Cytomegalovirus (CMV) disease was present in 6 patients (12.2%) at the time of sTMA diagnosis.

For induction immunosuppressive therapy 15 patients (30.6%) received alemtuzumab, 11 patients (22.4%) received anti-thymocyte globulin, 10 patients (20.4%) received basiliximab and 8 patients (16.3%) did not receive induction therapy, and data were missing for 5 patients (10.2%).

Pre-transplant sensitization was documented in 8 patients (16.3%), and a positive crossmatch was observed in 6 patients (12.2%), with missing data for 4 and 3 patients, respectively. Persistent donor-specific antibodies were detected in 11 patients (22.4%) at 6 months post-transplantation. Immunosuppressive regimens included tacrolimus-based therapy in 73% of patients and cyclosporine-based therapy in 27%. Chronic lung allograft dysfunction (CLAD) was diagnosed in 16 patients (32.7%), with a median time to CLAD onset of 549 days post-transplant.

Four patients (8%) developed antibody-mediated rejection (AMR), with two occurring prior to and two following sTMA episodes, all within the first-year post-transplant. Additionally, six patients experienced acute cellular rejection (ACR).

TMA episode characteristics

At the time of diagnosis, acute kidney injury (AKI) was present in all patients (Table 2). The mean hemoglobin concentration was 8.9 ± 1.6 g/dL, the mean platelet count was 74 ± 56 G/L, and the mean lactate dehydrogenase (LDH) level was 1243 ± 809 IU/mL. The mean serum creatinine level was 2.87 ± 1.34 mg/dL. Acute kidney injury KDIGO stage 1, 2 and 3 were present in 20 (40.8%) patients, 5 (10.2%) patients and 24 (49%) patients, respectively. A

¹ <http://www.strobe-statement.org/>

TABLE 2 Presentation and outcome of sTMA.

Characteristic	All patients
Mean laboratory parameter at presentation	
Hemoglobin (g/dL)	8.91 (± 1.58)
Platelets (G/L)	74 (± 56)
Lactate dehydrogenase (U/L)	1243 (± 809)
ADAMTS13 (% activity)	68.96 (± 24.94)
Serum creatinine (mg/dL)	2.87 (± 1.34)
KDIGO AKI stages	
Stage 1	20 (40.8%)
Stage 2	5 (10.2%)
Stage 3	24 (49%)
RRT during TMA episode	23 (46.9%)
Presumed CMV disease at TMA diagnosis, n	6 (12%)
Kidney biopsy available, n	11 (22.4%)
Therapy after TMA diagnosis	
Switch of IS regimen, n	41 (83.7%)
Plasma therapy at diagnosis, n	23 (46.9%)
Anti C5 treatment, n	12 (24.5%)
First plasma, then anti c5, n	5 (10.2%)
Outcome of TMA episode	
CKD, n 33	33 (67.3%)
ESRD, n	11 (22.4%)
Death, n	5 (10.2%)
ESRD after supportive treatment, n	2 (4.1%)
ESRD after treatment with PEX, n	3 (6%)
ESRD after treatment with PEX then Ecu, n	3 (6%)
ESRD after treatment with Ecu, n	2 (4.1%)
Multiple TMA episodes, n	2 (4.1%)
Genetic investigations	
CFH/CFI/CD46, n	20 (40.8%)
All relevant genes, n	10 (20.4%)
n/a, n	29 (59.2%)
Rare genetic variants, n	5 (10%)

Abbreviations: ADAMTS13, A Disintegrin and Metalloproteinase with Thrombospondin Motif 13; eGFR, estimated glomerular filtration rate; CMV, cytomegalovirus; TMA, thrombotic microangiopathy; IS, immunosuppression; anti C5 treatment, eculizumab or ravulizumab; CKD, chronic kidney disease; ESRD, end stage renal disease; PEX, plasma exchange; ecu, eculizumab; CFH, complement factor H; CFI, complement factor I; n/a, not available).

total of 23 patients (46.9%) received RRT during the episode and of those 10 (43%) remained dependent on chronic RRT and 3 (13%) died during the episode. The other 11 patients had a mean eGFR of 45 (± 17) mL/min/1.73 m² 3 months after the TMA episode. Mean serum creatinine before the beginning of the TMA episode was 1.14 mg/dL (± 0.58). After 3 months 11 (22.4%) patients had CKD

stage 4 or lower, 5 (10.2%) were dependent on chronic RRT and 5 (10.2%) had died.

Neurological complications were noted in 4 patients (8%). ADAMTS13 activity was measured in 86% of patients, with a mean level of 69% $\pm$ 25%. Haptoglobin levels were undetectable in all patients. Renal biopsy was performed in 10 patients (20.4%), and all biopsies demonstrated typical features of acute TMA like fibrin thrombi and endothelial cell activation. Chronic TMA lesions (double contouring of basal membranes and multilayering of arteries and arterioles) were only seen in 1 patient (Figure 2).

Upon diagnosis, 23 patients were treated with plasma exchange (46.9%), another 5 were first started with plasma exchange and then switched to eculizumab (10.2%) and 12 (24.5%) were treated with eculizumab as a first line therapy. Median time from diagnosis to first plasma exchange was 1 day (range 0–246 days) and 2 days (range 0–232 days) from diagnosis to first eculizumab. Of the 24 patients with AKI stage 3, 3 (12.5%) received supportive therapy, 9 received plasma exchange (37.5%), 8 (33.3%) received eculizumab and 4 received eculizumab after plasma exchange (16.7%). In those 4 patients time from first plasma exchange to first eculizumab was 2 days in one patient and 21 days in the three others.

In a multivariable logistic regression model, age was independently associated with the composite outcome of CKD stage 5 or death at 3 months (OR 1.07, $p = 0.012$). Eculizumab treatment was not significantly associated with the composite outcome of CKD stage 5 or death at 3 months (OR 0.73, 95% CI 0.12–4.61, $p = 0.74$ Supplementary Table S2).

Modifications to immunosuppressive regimens were made in 83.6% ($n = 41$) of patients. The most common modification was switching from tacrolimus to cyclosporine ($n = 35$, 66%). Other changes included switching to belatacept ($n = 3$, 5.7%), mTOR inhibitors ($n = 2$, 4.1%), or MMF ($n = 1$, 2%).

Renal and clinical outcomes

At 3 months follow-up chronic kidney disease (CKD) of any grade developed in 33 patients (67.3%), end-stage renal disease (ESRD) was observed in 11 patients (22.4%) and 5 patients (10.2%) died during the acute episode of sTMA, with one patient being dialysis-dependent prior to sTMA diagnosis (Figure 3).

Genetic investigations were only performed in a minority of patients and rare variants were found in 5 (10%) of patients, with one variant in CFH considered clinically significant and the other variants were considered to be of unknown significance.

Discussion

Secondary thrombotic microangiopathy (sTMA) is increasingly recognized as a serious complication following solid organ transplantation, though it remains underreported, particularly after lung transplantation. In this study, we observed an incidence of sTMA of 1.33% of 3,747 lung transplants performed across the participating centers. This is consistent with a study from France, which reported an incidence of 1.8% among 4,565 lung and heart-lung transplant recipients [14]. While our results align with these findings, our incidence is lower than previously reported in smaller studies, such as the 2.9% incidence reported by Rosseels et al.

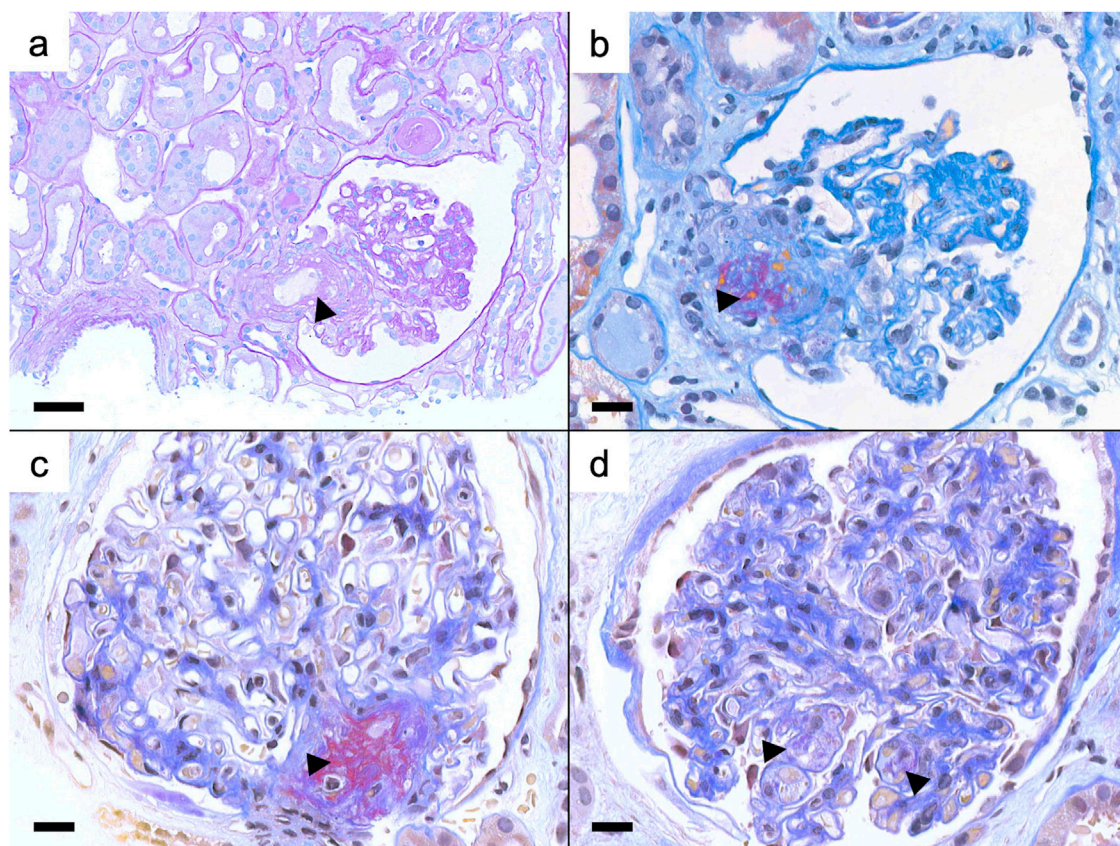


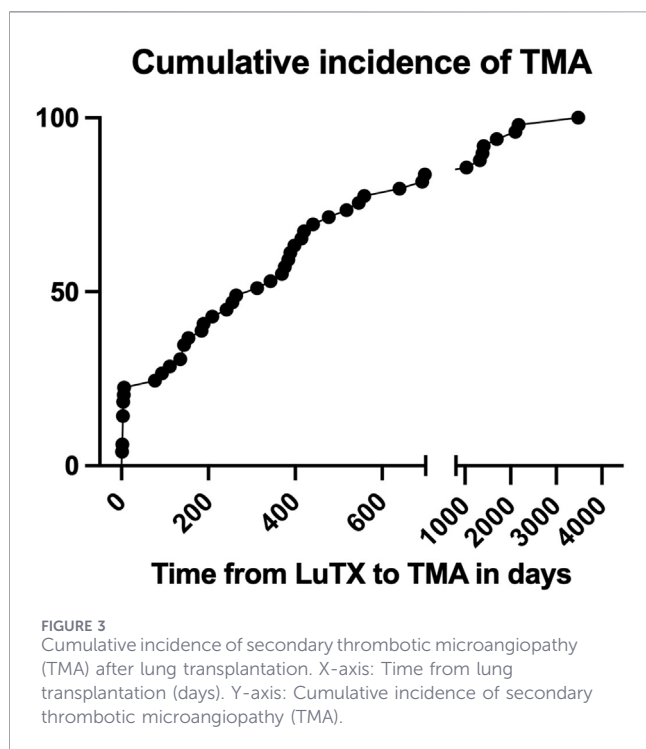
FIGURE 2

Histological TMA after LuTX in kidney biopsies. (A) Glomerulus with collapsed capillary loops, intimal mucoid changes, and vacuolation of smooth muscle cells (black arrowhead) at the vascular pole (Periodic Acid-Schiff stain (PAS) stain; scale bar = 50 µm). (B) Deeper section of the same collapsed glomerulus, showing a thrombus composed of fibrin and erythrocytes (black arrowhead) at the vascular pole (Acid Fuchsin Orange G (AFOG) stain; scale bar = 20 µm). (C) Another glomerulus with polar thrombosis (fibrin, black arrowhead) extending toward nearby glomerular capillaries (AFOG stain; scale bar = 20 µm). (D) Glomerulus with global endothelial cell swelling and segmental thromboses (black arrowheads) containing some fibrin, and subendothelial or intramural debris of erythrocytes or platelet (AFOG stain; scale bar = 20 µm).

and the 3.8 cases per 100 patient-years seen in Hachem et al.'s study [4, 6]. This discrepancy could be due to variations in diagnostic criteria, immunosuppressive protocols, or underreporting of sTMA, underscoring the need for standardized diagnostic approaches across centers.

We observed significant intercenter variability in the recognition and documentation of sTMA, with 11 out of 20 centers reporting no cases. This highlights the importance of uniform diagnostic criteria and suggests that diagnostic thresholds for sTMA may vary considerably. These variations may contribute to discrepancies in the reported incidence and underscore the necessity of improving consistency in TMA reporting across transplant centers. Renal involvement was nearly universal in our cohort, with hemolysis (indicated by undetectable haptoglobin levels) observed in all patients, confirming that renal injury is a core feature of sTMA. Thrombocytopenia and elevated lactate dehydrogenase (LDH) were present in a subset of patients but not consistently, making diagnosis challenging in some cases. In our cohort, renal biopsy was performed in 10 patients (20.4%), and it was diagnostic in all cases, emphasizing the importance of kidney biopsy in confirming the diagnosis of sTMA when clinical suspicion is high but hematologic signs are not fully consistent.

The baseline characteristics of our cohort reflect the typical European lung transplant population, with a mean age of 54 years and a predominance of chronic obstructive pulmonary disease (55%), interstitial lung disease (24%), and cystic fibrosis (8%). The high prevalence of pre-transplant sensitization (16.3%) and positive crossmatch (12.2%) further underscore the immunological burden seen in lung transplant recipients, which may predispose them to the development of complications such as sTMA. Notably, CMV high-risk status was observed in 27% of our cohort, and 12% of patients developed sTMA in the context of presumed CMV reactivation. This suggests that CMV reactivation, combined with intensified immunosuppressive therapy, may act synergistically to trigger sTMA, as seen in other transplant populations. However, the exact pathophysiological mechanisms remain speculative, and further investigation is needed to better understand these interactions. Interestingly there are 2 timepoints when *de novo* TMA after LuTX occurs. Firstly, in the first few days after the transplant with 22% of the cohort diagnosed in the first thirty days. Then after 100 days on, when infectious complications like CMV are more common. Genetic investigations in a cohort of secondary TMA remains a topic of debate. In recent literature rare variants are reported to be found in as many as 30% of patients, while other



larger cohort report variants in only 5% of patients [11, 12]. Since no single, definitive marker to distinguish complement-mediated TMA from secondary TMA is available, one can speculate that the distinction between the disease is not always flawless.

Treatment strategies for sTMA in our cohort were highly variable. Plasma exchange was performed in 55.1% of patients, while eculizumab was used in 26.5% of patients as first-line therapy and in 10.2% after plasma exchange. Despite the variability in treatment strategies, no significant difference in outcomes (progression to end-stage renal disease (ESRD), or mortality) was found between the treatment groups. This lack of difference in outcomes is consistent with previous studies that found immunosuppressive modifications, including switching calcineurin inhibitors or adding mTOR inhibitors, often fail to prevent recurrent episodes of sTMA [14].

Eculizumab has been used in secondary TMAs in various case reports and case series [14, 15]. Earlier administration of eculizumab has been associated with better outcomes [5, 16]. This highlights the importance of early recognition and prompt therapeutic intervention in preventing severe renal complications. In our cohort despite early treatment initiation eculizumab was not associated with a more favorable outcome. However, this might be due to our low event rate and relatively small sample size. Further studies are needed to assess the optimal timing and effectiveness of eculizumab in lung transplant recipients with sTMA.

This study has several limitations. Its retrospective, multicenter design introduces the possibility of underreporting and missing data, particularly regarding pre-transplant renal function and ADAMTS13 testing. Case identification likely varied across centers, with lower-volume sites potentially underrecognizing or underreporting sTMA, which may have led to underestimation of true incidence. Treatment strategies, including plasma exchange, eculizumab, and immunosuppressive modifications, were not

standardized and depended on local protocols, physician judgment, and disease severity, introducing potential indication bias and inter-center variability. Kidney biopsy was performed in only a subset of patients, limiting assessment of acute versus chronic lesions and their impact on outcomes. Finally, patient-level data for all lung transplant recipients were unavailable, precluding analyses of lung graft survival or time-dependent outcomes beyond the defined 3-month post-TMA episode. Despite these limitations, our findings provide the largest multicenter assessment to date of post-lung transplant sTMA and underscore the need for prospective, standardized studies to optimize diagnosis, risk stratification, and management.

Secondary thrombotic microangiopathy following lung transplantation, though rare, is associated with significant renal morbidity and mortality. Early recognition and intervention are crucial, particularly in patients presenting with acute kidney injury and hemolysis. Clinicians need to be aware of this complication and centers should adopt a standard of practice for diagnosis and treatment. Renal biopsy remains a valuable diagnostic tool in uncertain cases. Although treatment strategies varied, early initiation of targeted therapy with eculizumab may offer a more effective approach, though further studies are needed to confirm its efficacy. Standardized diagnostic criteria and treatment protocols, along with earlier intervention, could substantially improve outcomes for lung transplant recipients affected by sTMA.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The study was approved by the Ethics Committee of the Medical University of Vienna (reference number 1361/2014). All procedures were carried out in accordance with the STROBE guidelines for observational research (<http://www.strobe-statement.org/>). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

ZR: Conceptualization, study design, data collection, statistical analysis, manuscript writing, and editing. JH: Data collection, review. BS-G: Data collection and analysis, manuscript review. FC: Manuscript review, data collection and editing. GM: Data collection, manuscript review. PJ: Manuscript review and editing. SS: Data collection, manuscript review. DD: Data collection, manuscript review. MS: Data analysis, manuscript review. MG: Manuscript review, analysis and editing. AS: Analysis manuscript review. GS-P: Statistical analysis, manuscript review. CA: Study supervision, analysis, manuscript writing, review and editing.

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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.

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Supplementary material

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Potential for donation after circulatory death in Germany: a multicenter retrospective study at seven university hospitals

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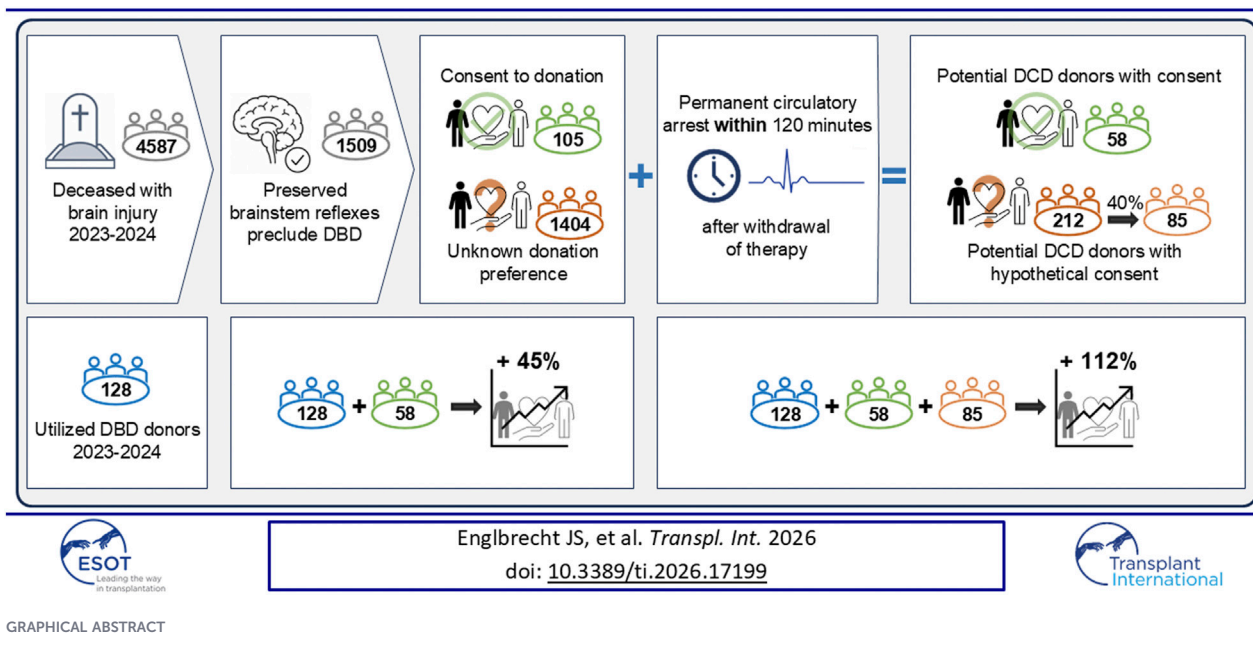
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Many countries have established donation after circulatory death (DCD) in addition to donation after brain death (DBD). In Germany, DCD is not permitted, and its potential to increase organ donation rates has not yet been quantified. We retrospectively identified all deceased with brain injury between 2023–2024 at seven German university hospitals. Eligible DCD donors were defined as patients with preserved brainstem reflexes precluding DBD donation, documented consent or an unknown donation preference, and death occurring within 120 min after withdrawal of life-sustaining measures. For patients with unknown preference, a consent rate of 40% was assumed. Among 4,587 deceased, 1,509 had preserved brainstem reflexes as the main reason against DBD. Of these, 58 patients with documented consent and 212 patients with an unknown donation preference died within 120 min after treatment withdrawal. Compared with 128 utilized DBD donors, this corresponds to an additional theoretical DCD potential of 45% based solely on documented consent. When applying the assumed consent rate to patients with an unknown preference, the hypothetical increase reaches 112%. The introduction of a DCD program could substantially increase organ donation rates at German university hospitals. However, its actual impact would depend on establishing appropriate legal, organizational, and ethical frameworks.

KEYWORDS

brain death, circulatory arrest, consent, organ donation, withdrawal of life-sustaining measures

Potential for Donation After Circulatory Death in Germany A Multicenter Retrospective Study at seven University Hospitals



Introduction

Given the persistent disparity between organ supply and demand, many countries have complemented donation after brain death (DBD), based on the determination of brain death/death by neurologic criteria (BD/DNC), with programs for donation after circulatory death (DCD) [1, 2].

DCD donors are commonly classified according to the Maastricht criteria into four (five in countries formally recognizing the possibility of organ donation after euthanasia) categories [3, 4]. Among these, category III DCD donors account for the largest proportion of DCD procedures (controlled donation after circulatory determination of death (cDCDD)) [1]. These donors are typically patients with a devastating brain injury who do not meet the criteria for BD/DNC, but whose prognosis is considered so poor that withdrawal of life-sustaining measures (WLSM) is deemed appropriate in the patient's best interests [5]. Death subsequently occurs following permanent circulatory arrest after WLSM. The interval between WLSM and circulatory arrest is referred to as the agonal phase [4]. Determination of death after WLSM is based on the occurrence of permanent circulatory arrest. Permanence—and thus death—is confirmed after a predefined observation period to exclude autoresuscitation. This so-called “No-touch” period between circulatory arrest and formal death determination typically ranges from 5 to 20 min, depending on national regulations [1, 6, 7].

Organ quality in DCD donation is significantly influenced by the duration of warm ischemia. Total warm ischemia time (WIT) encompasses both the agonal phase and the interval between circulatory arrest and the start of cold perfusion, or, when used, normothermic regional perfusion [6]. Functional warm ischemic

time (FWIT) represents a shorter period and is generally defined as the interval from the onset of sustained organ hypoperfusion following WLSM—typically marked by a decline in blood pressure and/or oxygen saturation—to the initiation of *in situ* preservation [6]. To minimize ischemic injury and preserve graft viability, many transplant programs apply maximum acceptable FWIT thresholds ranging from 30 to 120 min, depending on the organ to be transplanted [2, 7, 8].

In 2024, Germany had the lowest deceased donor rate within the Eurotransplant region, with 10.9 donors per million population [9]. The lack of a DCD program may contribute to this persistently low donation rate [10, 11]. Evidence from countries with established DCD programs indicates that DCD can substantially increase the donor pool without adversely affecting DBD activity [12–16]. Nevertheless, German regulations currently do not recognize permanent circulatory arrest as equivalent to death determined by BD/DNC. Consequently, DCD donation and the transplantation of organs recovered from DCD donors are not permitted in Germany [17]. In this context, some German-language publications use outdated terms such as “cardiac arrest” or “non-heart-beating donation.” In relation to cDCDD, these terms refer to permanent circulatory arrest following planned WLSM rather than an unexpected cardiac arrest.

To date, estimates of the potential contribution of DCD to organ donation in Germany have relied largely on modelling studies and extrapolations from international experience, while empirical data on potential DCD donors are lacking [16]. Therefore, this study sought to quantify the number of potential cDCDD donors among deceased patients with severe brain injury at seven German university hospitals.

Patients and methods

This study was performed in accordance with the Declaration of Helsinki. The Ethics Committee of the University of Muenster approved the study protocol (file number 2021-801-f-S) on 28 May 2025. The need for informed consent was waived due to the retrospective analysis of routinely collected patient data.

All patients with primary and/or secondary brain injury who died during hospitalization between January 2023 and December 2024 at seven German university hospitals (Aachen, Bonn, Düsseldorf, Essen, Leipzig, Magdeburg, and Münster) were retrospectively included. These patients were identified using *TransplantCheck*, a screening tool provided by the German Organ Procurement Organization (DSO). The software analyzes routinely collected hospital discharge data submitted in accordance with Section 21 of the German Hospital Remuneration Act (*Krankenhausentgeltgesetz*) and identifies all deceased patients with primary and/or secondary brain injury [18].

Cases with absolute contraindications to organ donation, patients not receiving mechanical ventilation, and all utilized DBD donors were excluded. The remaining cases underwent a case-by-case medical record review to identify patients in whom preserved brainstem reflexes (BSR), precluding the determination of BD/DNC, represented the principal reason for not proceeding to DBD donation. Patients with a previously documented objection to organ donation or whose medical condition precluded organ donation (e.g., suspected malignancy or severe organ dysfunction) were excluded from further analysis.

Subsequently, the medical records were reviewed to assess whether the patient's organ donation preferences had been evaluated. Cases with preserved BSR and documented consent to organ donation were classified as potential DCD donors with consent (pDCD-C), whereas cases without documented evaluation were classified as potential DCD donors with unknown donation preference (pDCD-U).

Assessment of the agonal phase followed a stepwise retrospective procedure for all pDCD-C and pDCD-U. First, medical records were reviewed to determine whether complete WLSM had been performed at a clearly identifiable time point and whether death subsequently occurred within 120 min. Complete WLSM was defined as withdrawal of all relevant life-sustaining measures, including discontinuation of hemodynamic support and mechanical ventilation. Because sustained organ hypoperfusion following WLSM is a key predictor of transplant outcomes, a predefined eligibility window of 120 min after complete WLSM was applied based on established cDCDD practice [2, 7, 19]. Once a case did not meet these eligibility criteria (complete WLSM could not be clearly identified or death did not occur within 120 min), no further time-to-death data were abstracted. Consequently, these two reasons could not be quantified separately among cases not meeting the eligibility criteria. The exact duration of the agonal phase was recorded only for patients who died within 120 min after complete WLSM. These cases were subsequently classified as eligible DCD donors with consent (eDCD-C) and eligible DCD donors with unknown donation preferences (eDCD-U), respectively.

For all eDCD-C and eDCD-U, the following data were collected:

- Age and sex

- Type of brain injury
- Length of intensive care unit stay
- Performance of decompressive neurosurgical surgery
- Notification to the DSO
- Documented organ donation preference

To estimate the number of cases within the eDCD-U cohort that might have consented to organ donation if donation preferences had been evaluated, published consent rates for DBD donation were used. Reported consent rates for DBD donation in Germany range from 37% to 53% [9, 10, 20]. Therefore, a conservative hypothetical consent rate of 40% was applied to the eDCD-U cohort [21]. The number of eligible DCD donors with hypothetical consent (eDCD-hC) was estimated as 40% of the eDCD-U cohort ($eDCD-hC = eDCD-U \times 0.4$).

The total number of eligible DCD donors was calculated as the sum of eDCD-C and eDCD-hC. The theoretical increase in organ donation activity was determined relative to the number of DBD donors utilized during the study period.

The study-specific donor categories used in this analysis were derived from the Critical Pathway for Deceased Donation terminology [22] and adapted for a retrospective assessment of DCD potential in the absence of a DCD program. Consequently, the categories “potential DCD donor” and “eligible DCD donor” were defined according to predefined study criteria and do not correspond directly to the respective donor categories used within the terminology.

Statistical methods

Statistical analyses were performed using SPSS Statistics (IBM Corp., Version 31). Categorical variables are presented as absolute and relative frequencies and were compared using the Pearson chi-square test. Fisher's exact test was applied when expected cell counts were less than five. For dichotomous variables, odds ratios (OR) with 95% confidence intervals (CI) were calculated as measures of effect size. Continuous variables were assessed for normality using the Shapiro–Wilk test. As most variables were not normally distributed, they are presented as median and interquartile range (IQR; 25th–75th percentile). Group comparisons were performed using the Mann–Whitney U test. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

Results

Eligible DCD donors

A total of 4,587 deceased patients with documented brain injury were identified. After exclusion of utilized DBD donors, patients with absolute contraindications to donation and patients without mechanical ventilation, 2,794 patients underwent a case-by-case analysis. Among these, preserved BSR represented the primary reason for ineligibility for DBD donation in 1,509 cases (54%). The remaining 1,285 cases (46%) had other primary reasons for ineligibility for DBD donation. These included medical condition precluding donation (27%), circulatory

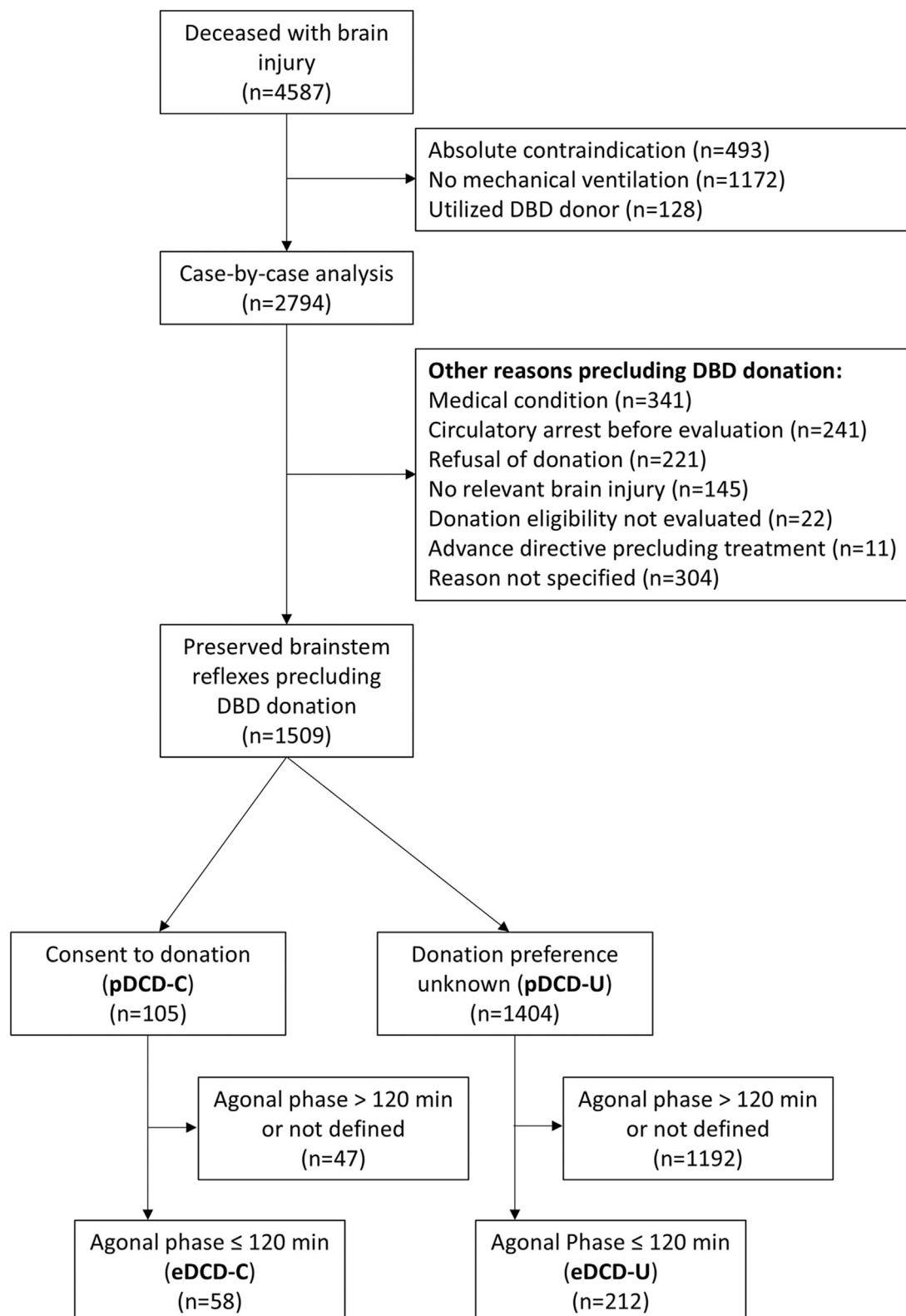


FIGURE 1

Flow chart of the study cohort. DBD: donation after brain death, pDCD-C, potential donation after circulatory death donor with consent; pDCD-U, potential donation after circulatory death donor with unknown donation preference; eDCD-C, eligible donation after circulatory death donor with consent; eDCD-U, eligible donation after circulatory death donor with unknown donation preference.

TABLE 1 Eligible donation after circulatory death donors with agonal phase ≤ 120 min.

Variable	eDCD-C (n = 58)	eDCD-U (n = 212)	p-value
Agonal phase (minutes)	19 [13–35]	32 [17–53]	0.002
Age (years)	59 [49–74]	72 [63–81]	<0.001
Sex			
• Male	37 (63.8%)	124 (58.5%)	0.466
• Female	21 (36.2%)	88 (41.5%)	
Type of brain injury			
• Intracranial hemorrhage	30 (51.7%)	66 (31.1%)	0.029
• Hypoxic brain injury	15 (25.9%)	58 (27.4%)	
• Ischemic stroke	7 (12.1%)	60 (28.3%)	
• Traumatic brain injury	4 (6.9%)	18 (8.5%)	
• Other	2 (3.4%)	10 (4.7%)	
Intensive care unit length of stay (hours)	126 [76–214]	137 [66–263]	0.560
Neurosurgical decompressive surgery			
• Yes	14 (24.1%)	37 (17.5%)	0.249
• No	44 (75.9%)	175 (82.5%)	
Notification to the DSO			
• Yes	33 (56.9%)	6 (2.8%)	<0.001
• No	25 (43.1%)	206 (97.2%)	
Type of consent			
• Written declaration	14 (24.1%)	-	
• Verbal declaration	14 (24.1%)	-	
• Presumed will (as stated by SDM)	27 (46.6%)	-	
• SDM own values	3 (5.2%)	-	
• Not assessed	0	212	

Categorical variables are presented as absolute and relative frequencies, and continuous variables as median [IQR]. eDCD-C, eligible donation after circulatory death donor with consent, eDCD-U, eligible donation after circulatory death donor with unknown donation preference, DSO, German organ procurement organization, SDM, substitute decision maker.

arrest before evaluation (19%), refusal of organ donation (17%), absence of relevant brain injury (11%), lack of evaluation of donation eligibility (2%), and an advance directive precluding further treatment (1%). In 24% of cases, the reason was not further specified in the medical records. Among the 1,509 patients with preserved BSR, documented consent to organ donation was available in 105 cases (7%; pDCD-C), whereas organ donation preferences had not been evaluated in 1,404 cases (93%; pDCD-U) (Figure 1).

Overall, 270 of the 1,509 patients with preserved BSR (18%) had a clearly identifiable time point of complete WLSM and died within 120 min thereafter. The remaining 1,239 patients were not assessed further once either complete WLSM could not be clearly identified or death did not occur within 120 min. The proportion of patients with an agonal phase within 120 min was significantly higher among pDCD-C than among pDCD-U, resulting in 58 eDCD-C and 212 eDCD-U, respectively (55.2% vs. 15.1%; OR 6.94, 95% CI 4.60–10.47; $p < 0.001$). Overall, the median agonal phase among the 270 eligible DCD donors was 29 min [IQR 15–50; range 0–117]. In the eDCD-C cohort, the median agonal phase was 19 min [IQR 13–35; range 0–117]. Thirty-nine patients (67%) died within 30 min, 13 (22%) between 31 and 60 min, and 6 (10%) between

61 and 120 min. In the eDCD-U cohort, the median agonal phase was 32 min [IQR 17–53; range 0–117], with 101 patients (48%) dying within 30 min, 66 (31%) between 31 and 60 min, and 45 (21%) between 61 and 120 min.

Compared with eDCD-U, eDCD-C had a significantly shorter agonal phase, were younger, and were more frequently reported to the DSO. Intracerebral hemorrhage was more common and ischemic stroke less common among eDCD-C. No significant difference was observed regarding the performance of decompressive neurosurgical surgery. Among eDCD-C cases, consent was most frequently based on presumed will communicated by a substitute decision maker (Table 1).

Theoretical increase in organ donation activity through DCD

Based on 128 utilized DBD donors during the study period, inclusion of all eDCD-C would theoretically increase the donor pool by 45%. Applying a conservative hypothetical consent rate of 40% to the eDCD-U cohort yielded an additional 85 eDCD-hC. The combined inclusion of eDCD-C and eDCD-hC would result in a theoretical overall increase in donor numbers of 112% compared with utilized DBD donations alone (Table 2).

TABLE 2 Number of organ donors by cohort.

Cohort	n (%)
Case-by-case analysis	2,794 (100%)
• eDCD with consent (eDCD-C)	58 (2.1%)
• eDCD with unknown donation preference (eDCD-U)	212 (7.6%)
◦ With hypothetical consent (eDCD-hC = eDCD-U x 0.4)	85 (3.0%)
• With consent (eDCD-C) or hypothetical consent (eDCD-hC)	143 (5.1%)
Potential increase	
• Utilized DBD donors (reference)	128
• DBD + eDCD-C	186 (+45%)
• DBD + eDCD-C + eDCD-hC	271 (+112%)

Categorical variables are presented as absolute and relative frequencies. eDCD-C, eligible donation after circulatory death donor with consent, eDCD-U, eligible donation after circulatory death donor with unknown donation preference, eDCD-hC, eligible donation after circulatory death donor with hypothetical consent.

Discussion

Our data indicate a considerable untapped potential for DCD donation in German university hospitals. Based solely on eligible DCD donors with documented consent, donor numbers at the participating centers could theoretically have increased by up to 45%. Applying a conservative hypothetical consent rate of 40% to eligible DCD donors with unknown donation preferences yielded a projected overall 112% increase compared with utilized DBD donations alone.

Potential of eligible DCD donors

At first glance, the proportion of eDCD-C among all cases undergoing case-by-case chart review (2.1%) appears relatively small. However, this cohort represents only cases in which consent to organ donation had been evaluated. This does not imply that organ donation would have been declined in all remaining cases. Rather, it reflects the current regulatory framework governing organ donation in Germany. In patients with preserved BSR, organ donation preferences may often remain unevaluated because a diagnosis of BD/DNC cannot be established and DBD donation is therefore not feasible [18]. Similarly, although refusal of organ donation was documented as the primary reason against DBD donation in only 8% of patients undergoing case-by-case analysis, this should not be interpreted as a representative refusal rate, because donation preferences were often not evaluated when other medical or procedural reasons had already precluded DBD donation.

The limited availability of documented consent also raises broader questions regarding the current German opt-in system. A transition to an opt-out system would change how the absence of a documented donation preference is handled and might increase the number of patients in whom donation can be considered. However, longitudinal evidence indicates that changing the consent default alone does not necessarily increase donation rates. Effective donor identification and referral, public awareness, communication with relatives, and sustained public acceptance remain essential [11, 23–25]. Accordingly, the introduction of a DCD program may expand the donor pool

but is unlikely to resolve organ scarcity as a standalone measure and should form part of a broader strategy to strengthen organ donation.

Nevertheless, because donation preferences had been evaluated in only a small proportion of potentially eligible cases, the eDCD-C cohort likely underestimated the true DCD potential. To address this limitation, a hypothetical consent rate was applied as previously used in comparable studies [21]. Using this approach, eligible DCD donors with documented or hypothetical consent accounted for 5.1% of all cases undergoing individual chart review. Despite differences in methodology and donor definitions, this proportion is broadly consistent with findings from international studies, which have identified potential DCD donors in 2.8%–8.6% of patients dying in intensive care units [21, 26–28].

However, the application of a hypothetical consent rate has further limitations. Available data on consent rates for DBD donation in Germany are heterogeneous. While representative surveys indicate a generally favorable attitude towards organ donation, with approximately 73% of individuals who have made a decision expressing support for donation [29], consent rates in the actual donation process appear substantially lower. A major contributing factor is the frequent absence of documented donation preferences, leaving the substitute decision maker to decide on behalf of the patient, often resulting in refusal of donation [10, 30].

An additional limitation is that the hypothetical consent rate applied in the present analysis was derived from data on DBD donation and may not be directly transferable to the DCD setting. Existing evidence regarding consent rates for DCD donation is inconsistent. One study reported lower consent rates for DCD than for DBD donation (55% vs. 64%), whereas another found higher overall donation consent rates in countries where both DBD and DCD programs were available [31, 32]. Consequently, it remains uncertain whether, and to what extent, the introduction of a DCD program would influence consent rates in Germany. The estimates presented in this study should therefore be interpreted as hypothetical projections rather than precise predictions of future donation activity.

Another important limitation is that the available data does not allow determination of how many of the identified eligible DCD donors would ultimately have met the medical criteria for organ donation. Such an assessment would only be possible during a real donor evaluation process. Although cases with absolute contraindications to organ donation were excluded *a priori* and the age of eDCD-C was comparable to that of utilized DBD donors in Germany [9], additional factors may have precluded donation. Analyses of established cDCDD programs demonstrate that donor pathways are progressively reduced by medical contraindications, DCD-specific eligibility criteria, lack of authorization, death occurring outside the predefined time window following WLSM, and final organ-specific suitability [5, 27]. In a large US cohort, approximately two-thirds of authorized and medically suitable potential DCD donors ultimately proceeded to donation, although this proportion depends on program characteristics and the definitions applied [33]. Data from the UK national DCD program indicate that adult DCD donors yield, on average, 2.9 transplantable organs per donor [34]. Therefore, although

each cDCDD donor may provide multiple transplantable organs and implementation of cDCDD would likely result in a substantial increase in transplant activity, estimating the exact number of additional transplantations arising from our retrospective cohort would require assumptions beyond the scope of this study. Accordingly, the estimated increases of 45% and 112% were not adjusted for subsequent non-utilization within a real cDCDD pathway and should therefore be interpreted as theoretical donor potential rather than expected increases in realized donation activity.

Moreover, our analysis cannot determine whether this additional donor potential would translate into a proportional increase in transplant activity or measurable improvements in waiting-list outcomes. International data indicate that utilization is lower for DCD than for DBD donors and varies considerably by organ type [35]. Kidneys represent the most established DCD grafts, whereas utilization of pancreata remains more restricted [36, 37]. There is also evidence that post-transplant outcomes may differ between DCD and DBD grafts depending on the organ and clinical context [36, 38]. These aspects could not be assessed in the present study and can only be evaluated prospectively following implementation of a German DCD program, including organ-specific utilization, transplantation activity, waiting-list outcomes, and graft- and patient-centered outcomes.

Another limitation is that only deceased with a diagnosed brain injury were included in the analysis. This approach may underestimate the overall potential of DCD donation, as DCD is also feasible in patients with other underlying conditions. However, experience from countries with established DCD programs indicates that donors without brain injury account for only a small proportion of utilized DCD donations [13, 39].

The study cohort comprised 128 utilized DBD donors across the participating centers during the two-year study period, representing less than 10% of all utilized DBD donations in Germany. Nevertheless, the donor conversion rate (utilized DBD donors divided by all deceased patients with brain injury) was 2.8%, exceeding the national average across all donor hospitals in Germany (1.5%) and closely matching that reported for German university hospitals overall (2.7%) [18, 40]. These findings suggest that the observed relative increase in donor numbers is unlikely to be substantially inflated by unusually low DBD donation rates at the participating centers.

Because only university hospitals were included, the findings cannot be directly extrapolated to all donor hospitals. In Germany, the 38 university hospitals account for approximately 35% of all utilized DBD donors, while hospitals with neurosurgical services (133 centers) contribute a further 42%, and hospitals without neurosurgical services (948 centers) account for the remaining donors [9]. University hospitals therefore achieve the highest number of utilized DBD donors per institution. However, patient populations, case mix, and disease severity differ considerably between hospital types and levels of care and are likely to influence the number of potential DCD donors. Consequently, the DCD potential identified in this study cannot be assumed to apply to hospitals of other levels of care. Moreover, the participating centers represented only three of Germany's 16 federal states and therefore constituted a regional rather than a nationally representative sample. Regional

differences in case mix, referral patterns and end-of-life practices may also influence DCD potential.

Agonal phase

The type and extent of treatment limitations applied to patients with a poor prognosis are not standardized and likely vary considerably between hospitals [41]. Overall, both withholding and withdrawal of life-sustaining therapies in German intensive care units have become increasingly common [42, 43]. For a DCD program to function effectively, clear criteria for prognostic assessment, particularly regarding the anticipated timing of death after WLSM, as well as standardized end-of-life care protocols are required [5, 44].

Two prospective multicenter studies reported that circulatory arrest occurred within 1 hour after WLSM in 55%–76% of potential DCD donors and within 2 hours in 63%–83% [45, 46]. However, no patient-related factors have yet been consistently identified that reliably predict the duration of the agonal phase [2, 45]. Consequently, accurate prediction of death following WLSM remains one of the major challenges in the implementation of cDCDD programs.

As Germany has no established DCD program, no standardized DCD-specific WLSM protocol was in place in our cohort. The observed agonal phase therefore reflects routine end-of-life care rather than a structured DCD pathway and should be interpreted with caution regarding its transferability to a future cDCDD program. In addition, the exact agonal phase was recorded only for patients who died within the predefined 120-min eligibility window, precluding assessment of the complete time-to-death distribution. The overall proportion of patients with preserved BSR dying within 120 min was 18%, substantially lower than reported in prospective DCD cohorts. However, these populations are not directly comparable, as previous studies included preselected potential DCD donors undergoing planned WLSM, whereas our denominator comprised all retrospectively identified patients with preserved BSR. Notably, 55.2% of the pDCD-C cohort died within 120 min, compared with 15.1% of pDCD-U. The lower overall proportion was therefore largely driven by the large pDCD-U cohort. Nevertheless, retrospective case identification and the absence of a standardized DCD-specific WLSM process may have introduced selection or misclassification bias.

Despite these limitations, a clear difference between the cohorts remained evident. The odds of an agonal phase within 120 min were nearly sevenfold higher in the pDCD-C cohort than in the pDCD-U cohort. Furthermore, the eDCD-C cohort exhibited a significantly shorter agonal phase and was more frequently reported to the DSO than the eDCD-U cohort. These findings suggest that organ donation preferences were more likely to be evaluated in patients with more severe brain injury and a higher likelihood of progressing to BD/DNC. The greater severity of neurological injury may also explain the shorter time to death following WLSM observed in this group. Conversely, less severe brain injury may have been associated with a lower expectation of progression to BD/DNC and, consequently, a lower likelihood of organ donation evaluation. This interpretation is supported by the higher

prevalence of intracerebral hemorrhage among eDCD-C and by recent German data demonstrating that assessment of organ donation preferences is performed substantially less frequently when progression to BD/DNC is not anticipated than when it is expected [47].

Some authors have argued that DCD should be considered in all potential DCD donors [45]. While prognostic tools such as the Wisconsin criteria and the DCD-N score have been developed to estimate the likelihood of circulatory arrest following WLSM, reliable and generalizable patient-related predictors of death within a predefined time frame after WLSM remain lacking [44, 48, 49]. As proposed by others, our findings indicate that clinical judgement by intensive care physicians may play an important role in identifying patients likely to experience a short agonal phase [48]. This observation is particularly relevant if organ donation discussions within a DCD program are to be limited to situations in which DCD donation represents a realistic possibility, thereby avoiding unnecessary burden on patients' families and caregivers.

Ethical implications

Our findings highlight that a substantial proportion of patients in Germany with a devastating brain injury and documented consent to organ donation are currently unable to donate because they do not fulfil the legal and medical requirements for organ donation. Consequently, opportunities for organ transplantation may be lost despite the patient's clearly documented wish to donate. Our findings therefore reveal more than an untapped donor potential. They demonstrate a discrepancy between patients' documented preferences and the options currently provided within the German legal framework. This discrepancy has recently been addressed in a German interdisciplinary analysis of medical, ethical, and legal perspectives on DCD [50]. The analysis highlights the situation of patients who may be medically suitable donors but remain excluded from donation because they do not fulfil the criteria for BD/DNC. It further emphasizes that a documented willingness to donate represents an important expression of personal autonomy, while such consent does not establish an individual entitlement to organ donation and must be balanced against the requirements of appropriate end-of-life care and reliable determination of death. Any future introduction of a DCD program would therefore require strict independence of WLSM decisions, proportionate organ-preserving measures, and safeguards maintaining public trust. These ethical considerations should form an integral part of any future societal, political, and legislative debate on the introduction of cDCDD in Germany.

Limitations

Several limitations should be considered when interpreting the findings of this study. First, the classification of patients into eDCD-C and eDCD-U was not based on predefined inclusion criteria but rather reflected the existing clinical documentation. Consequently, comparisons between these groups should be interpreted with caution, as systematic differences between them cannot be excluded.

Second, the agonal phase rather than the clinically more relevant FWIT was used for donor eligibility assessment. This approach was necessary because the available data did not allow determination of FWIT. Furthermore, because no standardized DCD-specific WLSM protocol was in place and exact time to death was recorded only within the predefined 120-min window, the observed agonal phase distribution may not be fully representative of a future cDCDD program.

As discussed above, the most important limitations of the potential analysis are the low proportion of deceased patients in whom organ donation preferences had been evaluated, the exclusion of patients without underlying brain injury, and the restriction of the study population to university hospitals. Together, these factors may have influenced the estimated number of potential and eligible DCD donors and limit the generalizability of the findings.

Conclusion

This multicenter retrospective study suggests that the introduction of cDCDD could substantially increase organ donation activity at German university hospitals. Even when considering only eligible DCD donors with documented consent, donor numbers could theoretically increase by up to 45%. The ultimate impact of a DCD program, however, would depend not only on donor availability but also on the establishment of appropriate legal, organizational, and ethical frameworks.

Implementation of a DCD program would require standardized approaches to WLSM, reliable identification of potential DCD donors, and broad ethical and societal consensus. Given Germany's low donation rate within the Eurotransplant region, the establishment of a successful DCD program has been advocated as a matter of particular importance not only for Germany but also for the wider Eurotransplant community [51]. The findings of the present study support this view by demonstrating a substantial untapped DCD donor potential in German university hospitals.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The datasets generated and analysed during the current study are not publicly available due to the inclusion of sensitive patient data. Anonymized raw data supporting the conclusions of this article will be made available on reasonable request. Requests to access these datasets should be directed to jan.englbrecht@ukmuenster.de.

Ethics statement

This study was performed in accordance with the Declaration of Helsinki. The Ethics Committee of the University of Muenster approved the study protocol (file number 2021-801-f-S) on 28 May 2025. The need for informed consent was waived due to the retrospective analysis of routinely collected patient data.

Author contributions

JE, DaS, and MaS were involved in planning and supervised the work, JE, DaS, HK, BS, DiS, JL, MW, and SZ processed the data, and performed the analysis. JE drafted the manuscript and designed figures. RK, MeS, FL, JW, RW, SZ, and MaS aided in interpreting the results and worked on the manuscript. All authors contributed to the article and approved the submitted version.

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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.

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Late kidney transplant dysfunction related to proximal aorto-iliac occlusive disease

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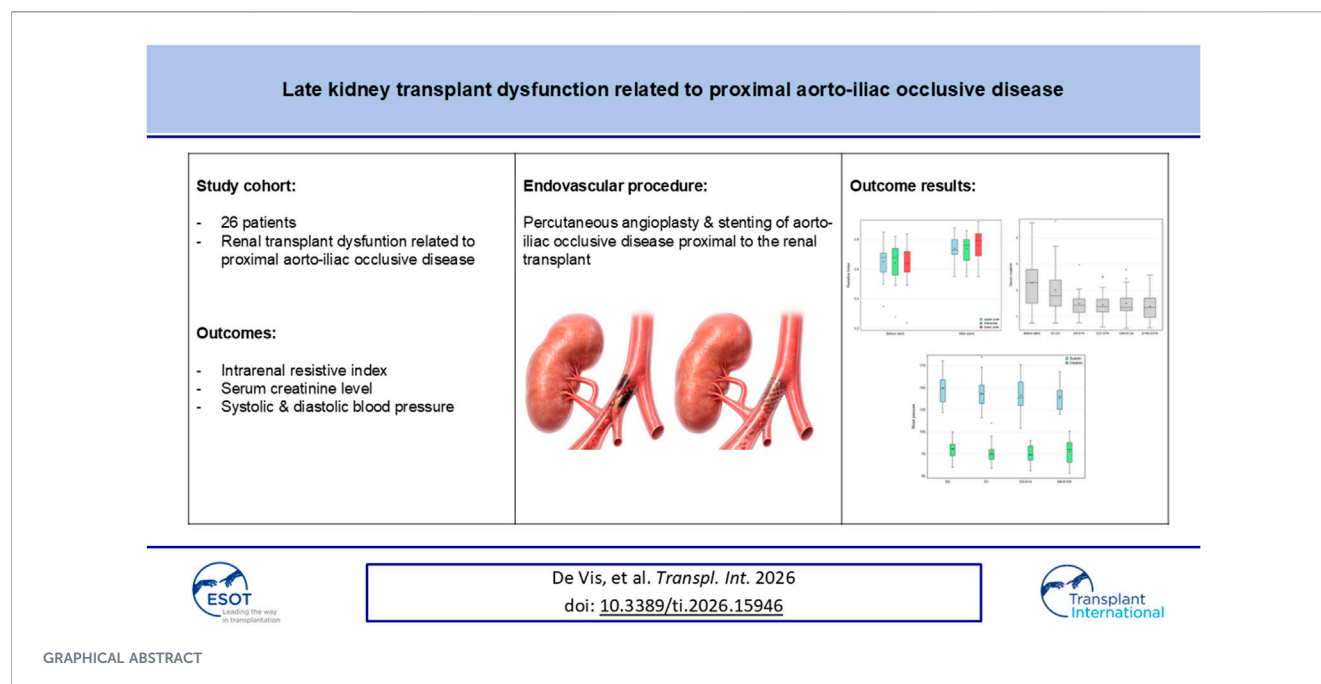
This study is a retrospective analysis of a cohort of patients presenting with transplant renal dysfunction related to proximal aorto-iliac occlusive disease and treated with angioplasty and stenting. Primary outcomes included changes in intrarenal resistive index (RI) and laboratory and clinical data including serum creatinine level, systolic and diastolic blood pressure, and number of anti-hypertensive drugs before and after endovascular intervention. Secondary outcomes included overall patient and transplant kidney survival. Endovascular intervention was successful in all 26 included patients and associated with a significant increase in intrarenal RI in the upper pole (0.65 before vs. 0.74 after stent; $P = 0.0009$), in the interpolar region (0.64 before vs. 0.74 after stent; $P = 0.0028$), and in the lower pole (0.63 before vs. 0.76 after stent; $P = 0.0002$). In addition, there was a significant improvement in serum creatinine (2.29 mg/dL before vs. 1.49 mg/dL 6 weeks after stent; $P < 0.0001$) and systolic blood pressure (149.6 mmHg before vs. 139.8 mmHg 1 week after stent; $P = 0.0233$). Overall estimated transplant kidney survival was 95% at 5 and 10 years of follow-up. Endovascular intervention is a very effective and durable treatment option for the management of transplant renal dysfunction related to proximal aorto-iliac occlusive disease.

KEYWORDS

angioplasty, dysfunction, outcome results, proximal aortoiliac occlusive disease, stent

Introduction

Renal transplantation is a cornerstone treatment for patients with end-stage renal disease, significantly enhancing their longevity and quality of life [1]. Nevertheless, there is a low but notable risk of early and late post-kidney transplant vascular complications, with an incidence of 3%–15% [2, 3]. Vascular arterial complications include the formation of intrarenal pseudoaneurysms or arteriovenous fistulas, often related to posttransplant renal biopsy and transplant renal artery stenosis (TRAS) or aorto-iliac stenosis proximal to the kidney transplant artery (pTRAS) [2, 3]. Potential consequences of (p)TRAS include a decline in kidney transplant function, renovascular hypertension, and ultimately graft loss. Open surgical repair to treat (p)TRAS has been associated with high morbidity and risk of graft loss [4]. Endovascular interventions are minimally



invasive and well-tolerated by renal transplantation patients and are becoming increasingly used.

Several studies investigated the clinical outcome of patients with a TRAS treated with endovascular intervention, demonstrating the safety of this endovascular procedure and the associated clinical benefit in the majority of patients [2, 5].

In contrast, data on the outcome of patients with symptomatic, late aorto-iliac stenosis proximal to the transplant renal artery and treated with endovascular intervention are scarce and mostly limited to case reports [6–9] and small-size observational studies [10, 11] with a limited number of patients, observed over a limited follow-up period. Therefore, we conducted a retrospective cohort study including patients with transplant kidney dysfunction caused by aorto-iliac occlusive disease proximal to the transplant renal artery who underwent endovascular intervention.

Materials and methods

Study design

This is a retrospective, observational study, including consecutive patients collected from the institutional interventional radiology database who underwent endovascular aorto-iliac intervention for the management of late transplant kidney dysfunction in the authors' institution from January 2005 till August 2022. Patients' demographic data and pre-and post-interventional laboratory and clinical data were collected from the patients' electronic medical records. Patients' cardiovascular risk factors were summarized based on Rutherford's standards for lower extremity ischemia [12].

The institutional Ethics Committee approved this retrospective study (MP 022096).

Baseline clinical and laboratory evaluation

An upstream aorto-iliac stenosis was considered as symptomatic if the patient presented with a concomitant serum creatinine decrease of >30% over a time period of less than 6 months and/or if the patient presented with a progressive and resistant increase in arterial blood pressure up to 150/90 mmHg or more over a time period of less than 6 months, despite administration of additional antihypertensive drugs if supported by the patient.

Duplex ultrasound with resistive index (RI) measurement

The arterial RI was measured in the upper pole, mid-portion, and lower pole of the transplant kidney; RI calculation was performed according to Naesens et al., as $[1 - (V_{\min} \div V_{\max})]$ with $V_{\min}$ representing the end-diastolic velocity and $V_{\max}$ the peak systolic velocity [13]. An RI in renal transplants is within normal limits between 0.6 and 0.8; <0.6 and >0.8 were defined as significantly low and significantly high RIs, respectively [11, 13]. Further, the intrarenal Doppler waveform was also analyzed: a 'tardus (slow) et parvus' (little) waveform reveals a dampened flow and can be used as an indirect sign of a proximal vascular stenosis.

Computed tomography angiography (CTA)

CTA was performed in patients with an acceptable, residual renal function (serum creatinine <1.2 mg/dL). The arterial phase was performed after intravenous injection of 80 mL of iohexol iodized contrast medium (Omnipaque 350, GE Healthcare, Oslo, Norway) at a flow rate of 4 mL/s and when the automated triggering in the proximal abdominal aorta reached 100 Hounsfield units.

TABLE 1 Patients' cardiovascular risk factors and kidney transplant data.

Cardiovascular risk factor	N (%)
Diabetes	
Adult onset, controlled by diet or oral agents	7/26 (27%)
Adult onset, insulin-controlled	5/26 (19%)
Juvenile onset	2/27 (8%)
Tobacco use	
Not current but smoked in last 10 years	6/26 (23%)
Current smoker	4/26 (15%)
Hypertension	
Requires more than two drugs or is uncontrolled	2/26 (85%)
Hyperlipidemia	
Mild elevation, readily controllable by diet	5/26 (19%)
Requiring dietary and drug control	14/26 (54%)
Cardiac status	
Myocardial infarction by history (>6 months)	8/26 (31%)
Stable angina or no angina but significant reversible perfusion defect	
Carotid disease	
Transient or temporary stroke	1/26 (4%)
Complete stroke with permanent neurologic deficit	1/26 (4%)
Renal status	
Kidney transplant	26/26 (100%)
Previous transplants	0/26 (0%)
Maintenance immunosuppression	26/26 (100%)
Pulmonary status	
Vital capacity less than 1.85 L	1/26 (4%)
Kidney transplant data mean median Std range	
Age (years) of donor at transplantation 53 56 13 (22; 70)	
Warm ischemia time (minutes) 31 30 9 (20; 44)	
Cold ischemia time (minutes) 680 751 319 (297; 1165)	
Total number of renal arteries	
1	15/20 (75%)
2	4/20 (20%)
3	1/20 (5%)
Type of arterial anastomosis	
Arterial patch – EIA	19/22 (86%)
Arterial patch – CIA	1/22 (5%)
Donor renal artery – EIA	2/22 (9%)
Donor renal artery – CIA	1/22 (5%)

EIA, external iliac artery; CIA, common iliac artery.
Maintenance immunosuppression: Mycophenolate mofetil (CellCept, Roche) 1000 mg/day + methylprednisolone (Medrol, Pfizer) 4 mg/day + tacrolimus (Prograf, Astelas Pharma) 6–8 mg/day.

Magnetic resonance angiography (MRA)

Contrast-enhanced MRA was performed after intravenous injection of gadobutrol 0.1 mL/kg (Gadovist, Bayer AG, Berlin, Germany) at a dose of 0.5 mmol/mL and a volume based on the formula patient weight (kg) x 0.2. A care bolus injection was also performed to determine the optimal arterial phases.

TABLE 2 Patients' symptoms and pre-interventional imaging.

Patients' symptoms	N (%)
Impaired renal function	5/26 (19%)
Impaired renal function and arterial hypertension	14/26 (54%)
Impaired renal function, arterial hypertension, & claudication	3/26 (11%)
Arterial hypertension	2/26 (8%)
Arterial hypertension and claudication	1/26 (4%)
Incidental duplex sonographic findings during protocol biopsy	1/26 (4%)
Pre-interventional imaging	
Duplex ultrasound	7/26 (7%)
Duplex ultrasound & MR angiography	14/26 (54%)
Duplex ultrasound & CT angiography	1/26 (4%)
Duplex ultrasound, CT, & MR angiography	1/26 (4%)
CT angiography	1/26 (4%)
MR angiography	1/26 (4%)
X-ray angiography	1/26 (4%)

Technique of the interventional procedure

After obtaining the patient's informed consent, the contralateral common femoral artery was punctured under local anesthesia and a 55 or 65 cm long, 6 or 7 French (F) sheath (Flexor, Cook Medical, Bloomington, IN, USA or Arrow sheath, Teleflex, Morrisville, NC, USA) was placed. Angiographic mapping of the aorto-iliac vessels was performed with iohexol iodized contrast medium (Omnipaque 270, GE Healthcare, Oslo, Norway) and/or carbon dioxide (CO2) (Angiodroid, CO2-injector, San Lazzaro di Savena, Italy or CO2-Angioset, Optimed, Ettlingen, Germany). The iliac stenosis was defined as occlusion, high-grade stenosis (>90% stenosis), intermediate grade stenosis (70%–90% stenosis), or low-grade stenosis (<70% stenosis). After an intra-arterial administration of 5000 international units of heparin, the stenosis was retrogradely cannulated and predilated with a 6 mm standard angioplasty balloon (Admiral Xtreme, Medtronic, Minneapolis, MN, USA and Mustang, Boston Scientific Inc, Cork, Ireland); in case of vessel wall recoil, a balloon-expandable stent was placed in the common iliac artery. Depending on the time period, various types of stents were used including Cordis Palmaz-Genesis (Cardinal Healthcare, Miami Lakes, FL, USA), Dynamic, [Biotronik, Berlin, Germany), Express Vascular (Boston Scientific Inc, Natick, MA, USA), Scuba Invatec (Medtronic, Minneapolis, MN, USA); in case of an aortic stenosis, a covered balloon-expandable stent (CP-stent, Numed, Hopkinton, NY, USA) was inserted and, in case of a stenosis at the distal end of the common iliac artery or proximal external iliac artery, a self-expanding nitinol stent (Zilver, Cook Medical, Bloomington, IN, USA) was inserted. Finally, if an additional stent in the transplant renal artery was needed, a balloon-expandable renal stent (Tsunami, Terumo Europe, Leuven, Belgium) was used. After completion of the angiography, the puncture site was closed with a closure device (Angioseal, Terumo Europe, Leuven, Belgium) and the patient was prescribed 80 mg daily aspirin lifelong.

Follow-up and study endpoints

Patients were followed up by the attending nephrologist; the study follow-up period ended in January 2024. Primary outcome data

TABLE 3 Procedural data.

Characteristics of the aorto-iliac stenosis	N (%)
Severity of the stenosis	
Occlusion	1/33 (3%)
High-grade stenosis	30/33 (91%)
Intermediate-grade stenosis	1/33 (3%)
Low-grade stenosis	1/33 (3%)
Length of the stenosis	mm (millimeter)
Mean	12
Median	11
Range	(4; 20)
Location of the stenosis	
Infrarenal abdominal aorta	1/33 (3%)
Right CIA	12/33 (36%)
Right iliac bifurcation	1/33 (3%)
Right EIA	2/33 (6%)
Left CIA	10/33 (30%)
Left EIA	4/33 (12%)
Transplant renal artery	2/33 (6%)

included changes in RI, in serum creatinine levels, in systolic and diastolic blood pressure, in number of administered antihypertensive drugs, and in daily dose intensity (DDI) for antihypertensive drugs, measured according to Min et al. [14]. Secondary endpoints included transplant kidney and overall patient survival.

Duplex-ultrasound with measurements of the RI were performed 1 week, 1 month, 6 months, and yearly after the index endovascular procedure. Laboratory analysis and clinical evaluation were performed at each follow-up visit; for comparative analysis, serum creatinine levels were collected before and 1 and 3 days after intervention as well as 1 week and 2, 3, and 9 months after the index endovascular procedure. Blood pressure measurement and number of prescribed

antihypertensive drugs were collected at 1 week, 1 and 6 months, and 1 year after the index endovascular procedure.

Statistical data analysis

Descriptive statistics were used to characterize the demographic data of the study population.

Linear mixed models for longitudinal measurements were used to analyze the effect of endovascular intervention on blood pressure, serum creatinine level, the number of used antihypertensive drugs, and the intrarenal RI of the transplant kidney. A random intercept was modelled to account for data clustering. Results are reported as mean with 95% confidence intervals and mean differences to compare follow-up measurements (after endovascular intervention) with measurements before the endovascular intervention.

Kaplan Meier estimates were used to estimate the kidney failure rate over time, accounting for death as a competing event. Analyses have been performed using SAS software (version 9.4 of the SAS System for Windows, Cary, NY, USA).

Results

Patient characteristics

In this study, 26 consecutive patients (14 male and 12 female patients) with a mean age of 53.4 ± 12.7 years were included. One patient treated 3 months after kidney transplantation and presenting with two focal external iliac artery stenoses, proximal and distal to the origin of the transplant renal artery and related to a vascular clamp injury during transplantation, was excluded for further analysis. In the same study period, no institutional patient with identical radiological and clinical characteristics and symptoms was managed with conservative or open surgical techniques; in addition, an extensive search of transplant patients' medical records, followed up in the

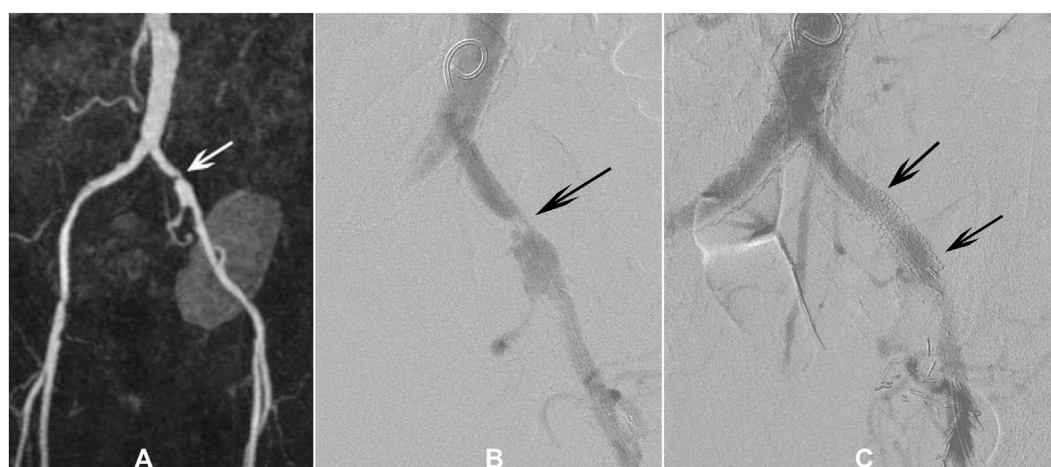


FIGURE 1
Hypertensive patient with serum creatinine decline (3.15 mg/dL) and focal, common iliac artery stenosis, proximal to the transplant kidney. **(A)** Magnetic resonance (MR) aortoiliac angiography shows a focal stenosis (arrow) of the left common iliac artery proximal to the transplant kidney. **(B)** Aorto-iliac angiography with use of carbon dioxide (CO₂) reveals a focal stenosis of the left, distal common iliac artery (arrow), proximal to the transplant kidney. **(C)** Aorto-iliac angiography after stent insertion (arrows) shows restored patency of the left iliac axis.

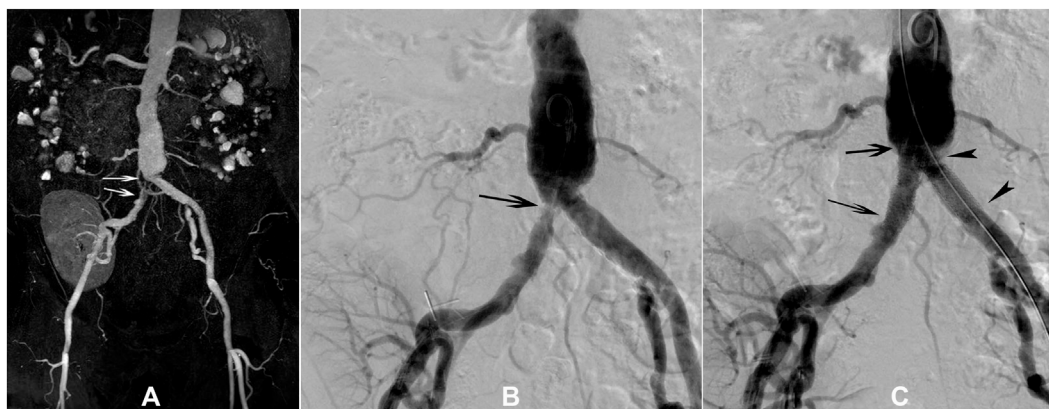


FIGURE 2

Hypertensive patient with an ostial common iliac artery stenosis proximal to the transplant kidney. (A) Magnetic resonance (MR) aortoiliac angiography shows a critical, ostial stenosis of the right common iliac artery (arrows) protruding into the aortic bifurcation. (B) Contrast aorto-iliac angiography shows the focal, ostial stenosis (arrow) protruding into the aortic bifurcation. (C) Post-stenting contrast-aortoiliac angiography shows fully patent kissing stents in the right common iliac (arrows) and left common iliac (arrowheads) arteries.



FIGURE 3

Hypertensive patient with serum creatinine decline (2.95 mg/dL) and focal stenosis in the distal aorta. (A) Magnetic resonance (MR) angiography demonstrates a focal, severe stenosis (arrow) in the infrarenal aorta; loss of signal in the right common iliac artery (arrowheads) due to stent artefact. (B) Unenhanced computed tomography confirms a circumferential and heavily calcified aortic stenosis (arrow). (C) Carbon dioxide (CO₂) aortography reveals a focal, infrarenal aortic stenosis (arrow); note also the stent (arrowheads) in the common right iliac artery. (D) Carbon dioxide (CO₂) aortography after endovascular intervention shows a fully expanded aortic stent (arrows); note also a stent in the proximal right common iliac artery (arrowheads).

authors' institution before 2005, could be identified, making a comparative outcome analysis impossible. Fourteen out of the 26 included patients (54%) were transplanted between January 2000 and September 2022; in the same time period, 2286 kidney transplantations were performed in the authors' institution. Patients' baseline demographics and clinical data are summarized in Table 1.

The kidney transplantation of the included study patients was performed between June 1982 and April 2021. The mean and median time interval between kidney transplantation and endovascular aorto-iliac intervention was 109 ± 89 and 103 months, respectively (range 3–301 months). Details on the initial kidney transplantation and on patients' clinical and radiological work-up are summarized in Tables 1, 2 respectively.

Procedural data

Angiographic findings are summarized in Table 3 (Figures 1–3). All aorto-iliac stenoses were of atherosclerotic origin.

Overall, technical success of the endovascular procedure was 100% and no procedure-related adverse events were reported.

Ultrasonographic, laboratory, and clinical follow-up data

In the transplant renal upper pole, interpolar region, and lower pole, a significant rise in intrarenal RI of 0.097, 0.095, and 0.130 was found, as summarized in Table 4 and Figure 4.

TABLE 4 Intrarenal resistive index before versus after the endovascular procedure.

Region of interest	Before stent	After stent	P-value
Upper pole			
Mean	0.65	0.74	0.0009
Median	0.68	0.73	
Std	0.112	0.079	
Range	(0.35; 0.85)	(0.55; 0.88)	
Interpolar region			
Mean	0.64	0.74	0.0028
Median	0.68	0.76	
Std	0.131	0.093	
Range	(0.28; 0.82)	(0.55; 0.86)	
Lower pole			
Mean	0.63	0.76	0.0002
Median	0.65	0.79	
Std	0.131	0.097	
Range	(0.24; 0.84)	(0.55; 0.92)	

Serum creatinine levels before versus up to 1 year after the endovascular procedure are summarized in Figure 5, showing a significant and sustained decrease in values over time.

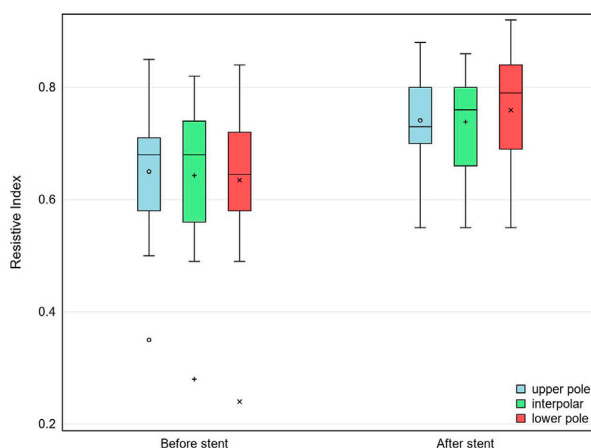
Analysis of the blood pressure before versus after the procedure revealed a significant drop in systolic pressure 1 week and 3 months after versus before the procedure; no

significant drop in diastolic blood pressure over time was found, as demonstrated in Figure 6.

Last, no difference in number of prescribed antihypertensive drugs before versus after the procedure was demonstrated, as summarized in Figure 7A; adversely, the mean antihypertensive daily drug dose before the stent procedure was 2.82 (2.13; 3.52, 95% confidence interval) versus 2.18 (1.49; 2.87, 95% confidence interval) 6 months after the stent procedure, resulting in a mean change of daily drug dose of -0.64 (-1.05 ; -0.24 , 95% confidence interval; $P = 0.0030$) (Figure 7B). In the follow-up period after the endovascular procedure, one patient presented with a progressive transplant kidney failure and dialysis was started up 3 years after a successful CIA stenting, resulting in a transplant kidney survival of 95.0% (78.6; 99.7) and 95.0% (78.6; 99.7) at 5 and 10 years of follow-up respectively (Figure 8). In addition, 17 patients (65%) died during follow-up, resulting in a mean survival of 4.1 (2.0; 10.7) years with an estimated overall survival of 36.0% (15.6; 57.0) and 28.8% (10.3; 50.7) at 5 and 10 years of follow-up respectively (Figure 9).

Discussion

This study reveals a very low incidence of 0.6% of pTRAS compared to reported early data ranging between 1.5% and 12.5% [2–4], most probably related to better screening and management of patients' vascular status before and after

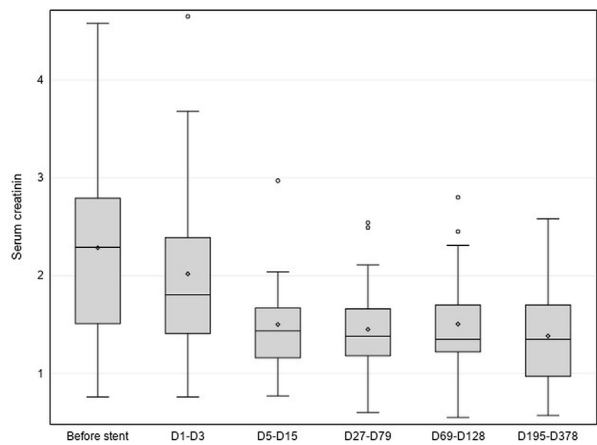


Before / after index EVI	mean RI (95% CI)	mean change in RI (95% CI)	P-value
Before stent – upper pole	0.651 (0.608; 0.693)		
After stent – upper pole	0.748 (0.701; 0.794)	0.097 (0.046; 0.147)	0.0009
Before stent – interpolar region	0.645 (0.594; 0.696)		
After stent – interpolar region	0.740 (0.687; 0.793)	0.095 (0.038; 0.153)	0.0028
Before stent – lower pole	0.635 (0.585; 0.686)		
After stent – lower pole	0.765 (0.711; 0.819)	0.130 (0.072; 0.188)	0.0002

EVI: endovascular intervention
CI: confidence interval

FIGURE 4

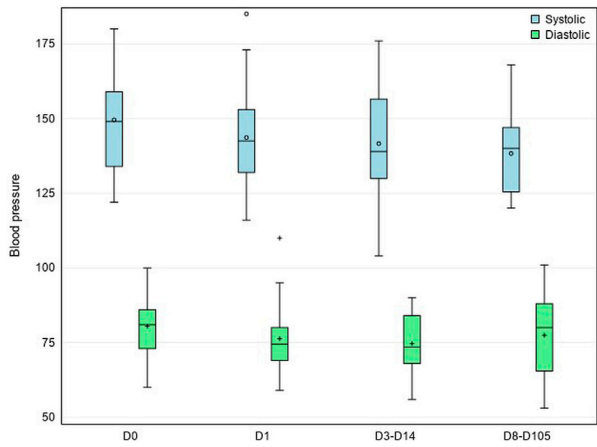
Box plot analysis of the difference in resistive index (RI) before and 1 week after aorto-iliac stent insertion measured in the upper pole, interpolar region, and lower pole of the transplant kidney.



Time point	mean serum creatinine (95% CI)	mean change vs D0 (95% CI)	P-value
Before stent	2.286 (2.023; 2.550)		
D1 - D3	2.006 (1.740; 2.272)	-0.280 (-0.520; -0.041)	0.0219
D5 - D15	1.552 (1.247; 1.857)	-0.734 (-1.015; -0.453)	<.0001
D27 - D79	1.488 (1.219; 1.757)	-0.799 (-1.041; -0.556)	<.0001
D69 - D128	1.516 (1.234; 1.798)	-0.771 (-1.027; -0.514)	<.0001
D195 - D378	1.483 (1.205; 1.762)	-0.803 (-1.055; -0.550)	<.0001

D: day

FIGURE 5
Box plot representation of the serum creatinine level (mg/dL), measured at different time points before and after endovascular intervention.



BP	D0	D1	D3 - D14	D8 - D105
Systolic BP				
Mean	149.6	143.2	139.8	135.3
Median	149	142.5	139	140
StD	15.3	18.5	20.3	14.3
IQR	(134; 159)	(132; 153)	(130; 156)	(125; 147)
Range	(122; 180)	(116; 185)	(104; 176)	(120; 168)
Diastolic BP				
Mean	80.5	77.0	75.0	77.2
Median	81.0	74.5	73.5	80.0
StD	12.1	12.1	9.6	13.8
IQR	(73; 86)	(72;82)	(69;80)	(72;83)
Range	(60; 100)	(59; 110)	(56; 90)	(53; 101)

BP: blood pressure
D: day
StD: standard deviation
IQR: interquartile range

FIGURE 6
Box plot representation of the systolic and diastolic blood pressure (in mmHg) at different time points before and after endovascular intervention.

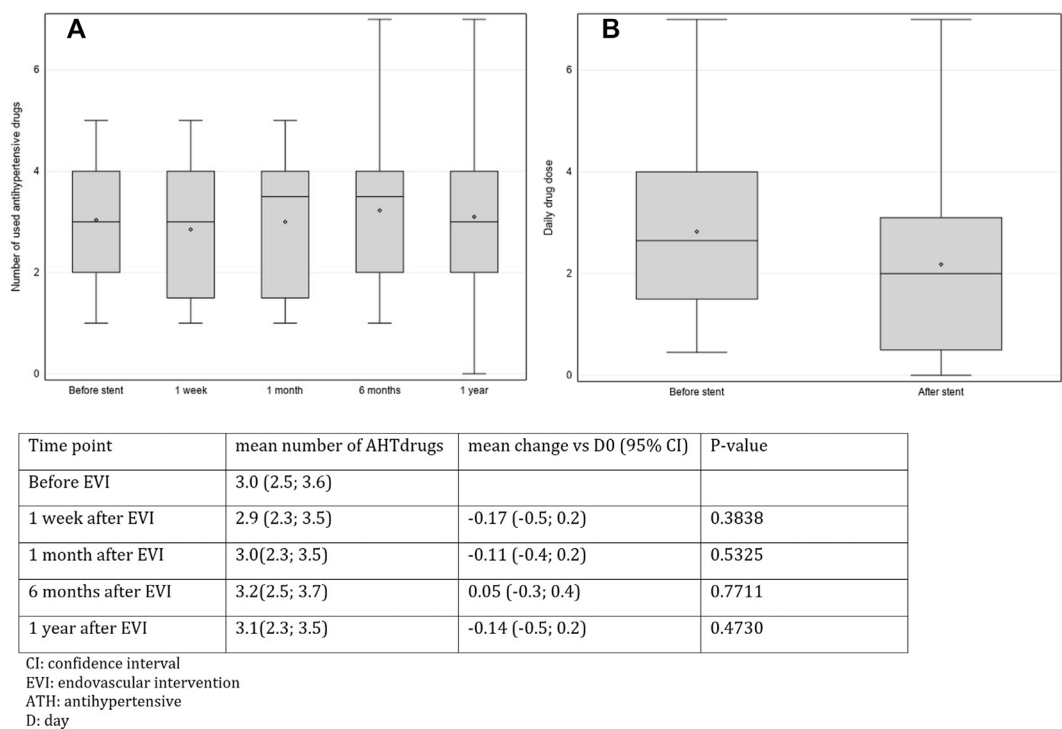


FIGURE 7
(A) Box plot representation of the number of used antihypertensive drugs at different time points before and after endovascular intervention. (B) Box plot representation of the daily drug dose (DDD) before the stent placement: 2.82 (2.13; 3.52, 95% confidence interval) versus: 2.18 (1.49; 2.87, 95% confidence interval) 6 months after stent placement, resulting in a mean change in DDD of -0.64 (-1.05 ; -0.24 , 95% confidence interval) ($P = 0.0030$).

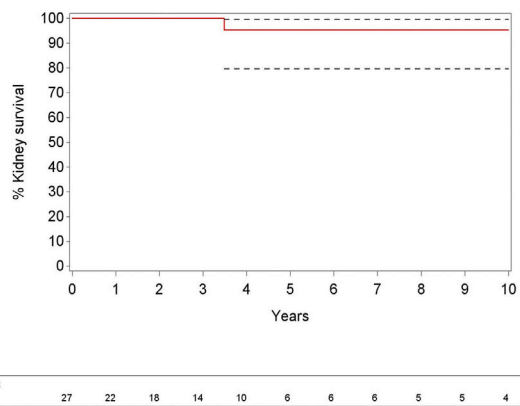


FIGURE 8
Kaplan-Meier analysis for transplant kidney survival. Kidney survival rates (95% confidence interval) show a 95.27% transplant kidney survival at 5 and 10 years of follow-up after aorto-iliac intervention respectively.

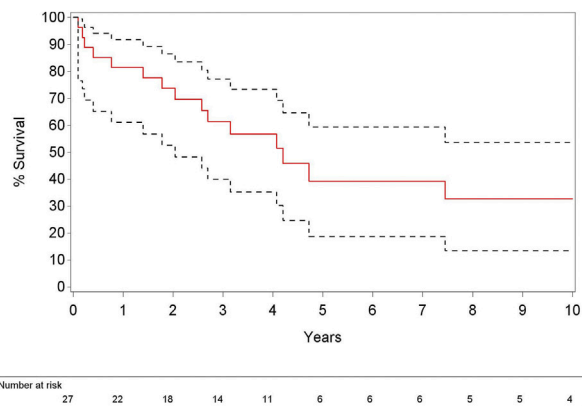


FIGURE 9
Kaplan-Meier analysis for overall survival after aortoiliac intervention proximal to the dysfunctional transplant kidney. Overall survival rates (95% confidence interval) show a median survival of 4.1 (2.0; 10.7) years after index aorto-iliac intervention. The overall survival estimates are 36 (15.6; 57) and 28.8 (10.3; 50.7) years at 5 and 10 years of follow-up after index aorto-iliac intervention, respectively.

transplantation. Potentially, the number of patients with pTRAS and associated transplant renal dysfunction might be underdiagnosed related to a more diffuse atherosclerotic involvement of one of both iliac arteries; in these patients, a chronic decline in renal function rather than a sudden rise in serum creatinine might be observed. Last, some patients might also be treated in other institutions despite

index kidney transplantation and clinical follow-up in the authors' institution.

From a clinical perspective, the majority of patients in this study were diabetic and hypertensive transplant patients with an onset of impaired kidney function after transplantation, which is in line with

earlier data from Voiculescu et al., reporting a significant deterioration of hypertension (144 ± 15 mmHg systolic and 84 ± 9 mmHg diastolic at baseline versus 157 ± 22 mmHg systolic and 90 ± 10 mmHg diastolic immediately before intervention; $P < 0.001$) and increase of serum creatinine (1.7 ± 0.9 mg/dL at baseline and 2.5 ± 1.3 mg/dL) immediately before intervention [4, 11].

Duplex-ultrasound with RI measurements was diagnostic in the majority of cases, however, in 13% of patients, the proximal aorto-iliac stenosis was demonstrated by CTA/MRA only. Adversely, a tardus-parvus waveform was found in less than half of the patients.

Duplex-ultrasound with RI measurements seems to be a valuable tool for pTRAS screening: in 87% of patients, a low RI was found. Additional duplex-ultrasound evaluation of the common iliac artery, demonstrating a monophasic flow pattern, might be another sonographic, indirect sign for pTRAS [15].

Catheter-directed angioplasty and stenting of aorto-iliac occlusive disease has become the treatment of choice given the minimally invasive nature of the treatment, avoiding procedure-related morbidity and mortality and the current, high, and durable primary and primary-assisted patency rates [16], which is in contraindication to early reports demonstrating >50% restenosis after standard balloon angioplasty for pTRAS [11].

The clinical outcome of aorto-iliac stenting for pTRAS is favorable, with clear beneficial impact on renal function, which is in line with other reports on pTRAS [11] and TRAS [5]. In our study, a significant decrease in systolic pressure but not in diastolic pressure or in number of prescribed antihypertensive drugs was found, which contrasts with the findings of Voiculescu et al., who reported a drop in systolic and diastolic pressure and in antihypertensive medication [4].

Finally, this study has limitations. First, the retrospective study design might be associated with biased study results; second, the long interval of patient inclusion might influence clinical outcome results, in particular overall survival of patients treated early in the study might be different to patients treated more recently. In addition, the type of different stents used during the study period also changed; however, the technique of angioplasty and stenting did not change over time. Third, associated medical treatment, especially use and type of antihypertensive drugs, might be different throughout the study patients and potentially could have an effect on clinical outcome and patients' overall survival.

In conclusion, endovascular management of pTRAS is safe, effective, and associated with a significant and durable increase in renal function and systolic pressure.

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 the UZ Leuven Ethics Committee approved this retrospective study (MP 022096). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because retrospective study analysis (MP 022096).

Author contributions

Study conception: GM. Methodology: GM and EV. Material preparation: EV and AL. Data collection: EV and AL. Data analysis: EV and AL. Writing original draft: all authors. Writing review and editing: all authors. Read and approved final manuscript: all authors. Supervision: GM. All authors contributed to the article and approved the submitted version.

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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.

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Beyond the acceptance decision: integrating genetic findings into lifelong living donor care

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donor follow-up, donor safety, genetic testing, kidney transplantation, living kidney donation, postdonation care, registry

Dear Editors,

The process of living kidney donation transforms a one-time acceptance or refusal decision into a lifelong relationship with an otherwise healthy volunteer. Genetic testing is often treated as similarly definitive, yet many results are variants of uncertain significance (VUS): findings for which evidence is insufficient to classify a variant as benign or pathogenic. Their meaning may change as population, segregation, functional, and genotype-phenotype data accumulate. In healthy donors facing a once-in-a-lifetime decision, variants initially considered insignificant may later become clinically relevant whereas likely pathogenic variants may remain clinically silent. Yet current care structures do not define who should monitor, reinterpret, and communicate updated genetic findings after nephrectomy. Targeted donor genetics must therefore be linked to registry-supported lifelong donor care.

In current practice, genetic testing in living donor evaluation is targeted: it is considered when family history, young donor age, genetically unexplained kidney disease in the intended recipient or family, or features such as persistent hematuria, albuminuria, cystic disease, recurrent nephrolithiasis, congenital urogenital anomalies, or extrarenal phenotypes suggest inherited risk, preferably after index-case testing. Universal testing would mean broad sequencing of all donor candidates irrespective of such suspicion. Schott et al. tested 46 approved donors prospectively and 122 donors who developed adverse renal outcomes retrospectively; pathogenic or likely pathogenic variants were identified in 4% and 19% of these cohorts, respectively, and VUS in 59% of all 168 donors [1]. These findings support targeted testing in high-risk constellations. However, the baseline prevalence of pathogenic variants in donors without adverse outcomes remains unknown, causality between identified variants and subsequent morbidity is uncertain, and many genetic results retain interpretive uncertainty. These data raise important questions about donor selection, counseling, and post-donation responsibilities.

In a dedicated renal genetics cohort, variant reclassification occurred in 5% of cases; when it did, it led to a new or revised diagnosis in 60% and significant management changes in 67%, with a median time to reclassification of 8.4 months [2]. Genetic results issued before donation cannot therefore be considered definitive. Baseline variant uncertainty combined with clinically meaningful post-issuance reclassification creates a longitudinal care obligation that current evaluation frameworks do not address.

Current practice resources guide testing indications, recommend index-case testing and counseling, and caution against inappropriate donor exclusion for VUS [3, 4]. KDIGO frames living donor evaluation and care as risk estimation, informed consent, and postdonation follow-up [5]. These documents define the predonation pathway,

including use of genetics to inform donor selection, but do not assign responsibility for genetic findings afterward. Even in hereditary oncology, where variant reclassification is well recognized, it remains contested whether there is a duty to actively seek reclassification and, if a clinically relevant reclassification becomes known, who should recontact the patient [6]. Transplant medicine has no equivalent debate, let alone resolution, despite the additional ethical complexity of healthy-volunteer donors.

We propose integrating genetic findings obtained during donor evaluation into lifelong donor care across three dimensions. Clinical stewardship requires systematic documentation of genetic results and index-case diagnoses, a mechanism to receive clinically relevant updates from genetics or laboratory services, and cascade testing when index-case findings change. Longitudinal communication requires defined recontact pathways when relevant reclassifications are flagged or when a new genetic diagnosis is established in the family. Psychosocial support addresses anxiety or decisional burden from uncertain findings or late reclassifications. This approach does not treat every genetic uncertainty as a contraindication; it accepts that uncertainty must be managed after donation. Currently, no guideline designates whether anyone should actively seek reclassification, who should flag updates, who—the transplant centre, referring nephrologist, renal genetics service, or laboratory—should recontact donors, or whether donors themselves are expected to initiate follow-up after nephrectomy.

A positive or reclassified genetic finding rarely creates a genotype-specific therapy, but it should lower the monitoring threshold and narrow the time window for clinical detection. A donor carrying a heterozygous COL4A3 or COL4A4 variant or a COL4A5 variant may warrant earlier assessment for hematuria, albuminuria, and hypertension than one without known genetic risk—not because treatment differs, but because earlier detection enables earlier intervention. Health behavior and timely renoprotection may modify risk. As the DESCARTES working group emphasized, donor information, health-promoting behavior, and individualized long-term risk assessment are central after living donation [7]. Genetically informed postdonation surveillance should therefore address blood pressure, albuminuria, kidney function, lifestyle modification, and avoidance of nephrotoxins; renin-angiotensin-aldosterone system blockade and sodium-glucose cotransporter 2 inhibitor therapy should be initiated when guideline-supported indications arise [8].

The implementation question is where this longitudinal responsibility should reside. Routine clinical care is episodic and visit-dependent, not designed to track variant reinterpretation, family diagnoses, or psychosocial outcomes. The Safety of the Living Kidney Donor—German National Registry (SOLKID-GNR) offers a structural model, with sustained donor contact [9] and donor-reported outcomes that capture clinically relevant complications not reflected in centre records—an infrastructure also applicable to documenting genetic stewardship events such as relevant reclassifications, new family diagnoses, and psychosocial burden [10]. Embedding genetic findings into SOLKID-GNR

would mean linking genetic results and index-case diagnoses to donor records, flagging relevant reclassification events and new family diagnoses, and collecting donor-reported psychosocial burden and clinical changes—without central genomic data storage. The registry would not itself reclassify variants; rather, it would provide a structure through which updates generated by genetics or laboratory services can be linked to donor follow-up. A national registry thus offers data infrastructure and a governance model: a defined institutional locus for genetic stewardship beyond donation.

Living kidney donation will always require balancing donor and recipient benefits through informed consent and shared decision-making. Targeted genetic testing in selected donors can improve this balance when it informs donor selection and the intensity of long-term postdonation care. Sequencing identifies what the genome contains; only structured, registry-supported lifelong follow-up determines what that information means for this donor—and who remains responsible for acting on it.

Author contributions

SR conceived and drafted the manuscript. DB, KB, and BS critically revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Pre-transplant HbA1c and BMI are associated with long-term survival after lung transplantation

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BMI changes, lung transplant, pre-transplant hba1c, risk assessment, survival benefit

Dear Editors,

Metabolic complications after lung transplantation are well recognized and are typically framed as downstream consequences of immunosuppressive therapy [1–3]. However, whether metabolic risk is already established before transplantation—and whether it is associated with post-transplant survival—remains insufficiently defined [3–6]. We therefore examined the association between pre-transplant metabolic parameters, specifically hemoglobin A1c (HbA1c) and body mass index (BMI), and long-term survival following lung transplantation, with a particular focus on the temporal stability of this association.

We conducted a retrospective cohort study including 257 consecutive adult lung transplant recipients transplanted at a single academic tertiary center between 2015 and 2024. The study was approved by the institutional review board (Req-2026-00435). Patients undergoing retransplantation were included at the time of their first transplantation and censored thereafter. Standard immunosuppressive therapy consisted of a calcineurin inhibitor, mycophenolate mofetil, and corticosteroids, with a center-wide transition from cyclosporine to tacrolimus during the study period [7]. Pre-transplant HbA1c and BMI were analyzed as continuous variables in relation to overall survival using Cox proportional hazards models adjusted for age, sex, transplant era, diabetes status and underlying lung disease. To explore temporal changes in predictive performance, time-dependent receiver operating characteristic analyses were performed at predefined intervals following transplantation.

During a follow-up period of up to 10 years, 81 deaths occurred, corresponding to a median survival of 8.5 years. Survival estimates were 89.7% at 1 year, 65.0% at 5 years, and 44.6% at 10 years. Among the 81 observed deaths, rejection-related causes were the most frequent (38/81, 46.9%), followed by infectious causes (23/81, 28.4%), cardiovascular (14/81, 17.3%), and malignancy-related deaths (5/81, 6.2%). Cause of death was missing in one patient. Mean HbA1c increased from 5.73% pre-transplant to 5.99% at 1 year, while BMI increased from 22.9 to 25.7 kg/m², reflecting the expected post-transplant metabolic trajectory.

In multivariable Cox regression, pre-transplant HbA1c and BMI remained independently associated with mortality. Each 1% increase in HbA1c was associated with increased mortality risk (HR 1.41, 95% CI 1.08–1.80; $p = 0.011$), as was each 1 kg/m² increase in BMI (HR 1.07, 95% CI 1.01–1.14; $p = 0.033$). Importantly, these associations persisted after adjustment for underlying lung disease, suggesting that differences between transplant indications alone are unlikely to fully explain the observed relationship.

The temporal behavior of this association provides additional insight. Time-dependent ROC analyses demonstrated modest discrimination of pre-transplant HbA1c for early post-transplant mortality, with an area under the curve (AUC) of 0.61 at 12 months after transplantation. However, predictive performance declined progressively over time, with AUC values of 0.53 at 36 months, 0.52 at 60 months, and 0.46 at 120 months, indicating limited long-term discriminatory ability. These findings suggest that pre-transplant glycemic status may provide prognostic information primarily during the early post-transplant period, while its predictive value diminishes during longer-term follow-up. Importantly, these findings should be interpreted as changes in predictive performance rather than evidence of true biological changes in metabolic risk over time, as formal longitudinal or time-varying effect modeling was not performed. Potential explanations, including cumulative immunosuppressive exposure, infection-related inflammation, rejection episodes, and progressive metabolic alterations such as weight gain and insulin resistance, remain hypotheses requiring further investigation. Accordingly, pre-transplant metabolic status may represent an early risk marker with diminishing discriminatory value over time rather than a fixed long-term predictor.

The observed divergence between metabolic burden and outcomes across immunosuppressive regimens provides an additional clinically relevant observation. Recipients receiving tacrolimus-based immunosuppression demonstrated higher observed survival compared with those receiving cyclosporine (HR 1.69, 95% CI 1.06–2.70, $p = 0.029$), despite less favorable metabolic profiles, including higher HbA1c levels ($p = 0.0024$) and greater weight gain ($p = 0.0436$). These findings illustrate the complex interplay between immunological efficacy and metabolic toxicity; however, they should be considered hypothesis-generating rather than evidence of a causal survival benefit. Residual confounding related to transplant era, evolving clinical practice, center experience, and factors influencing immunosuppressive selection cannot be excluded. [8]. Notably, HbA1c retained its prognostic significance after adjustment for diabetes status, suggesting that glycemic burden may provide additional risk information beyond a binary classification of diabetes. This observation is consistent with data from non-transplant populations demonstrating a continuous relationship between HbA1c and mortality, even below diagnostic thresholds for diabetes [9, 10]. Similarly, BMI contributed independently to risk, supporting the concept that metabolic risk is multifactorial and cannot be adequately captured by a single parameter.

From a clinical perspective, these findings support increased awareness of metabolic risk assessment before and after transplantation. Importantly, our study does not provide evidence regarding the effectiveness of specific interventions. Nevertheless, prospective studies evaluating optimization of glycemic control, nutritional assessment, physical rehabilitation, and weight management may help determine whether modification of metabolic risk can improve outcomes after transplantation. Future investigations should also evaluate emerging metabolic therapies, including incretin-based approaches, and structured lifestyle interventions in transplant populations before routine recommendations can be established.

Several limitations should be acknowledged. First, HbA1c and BMI represent only selected markers of metabolic status and do not

capture the broader complexity of metabolic health, including lipid profile, insulin resistance, body composition, sarcopenia, nutritional status, and frailty. Therefore, the interpretation of metabolic risk in this study should remain restricted to the variables assessed. Second, the retrospective single-center design introduces the possibility of residual confounding. Although adjustment for clinically relevant covariates was performed, important factors influencing outcomes after lung transplantation, including perioperative severity, donor characteristics, primary graft dysfunction, rejection burden, infection burden, renal dysfunction, and functional status, were not fully captured.

Third, although post-transplant metabolic changes were described, formal longitudinal modeling was not performed, limiting causal inference regarding the interaction between baseline and evolving metabolic risk. Finally, the observational nature of this study prevents conclusions regarding whether targeted metabolic interventions can improve survival.

In conclusion, pre-transplant metabolic risk markers, specifically HbA1c and BMI, are associated with survival after lung transplantation. Their prognostic relevance appears strongest during the early post-transplant period. These findings should be interpreted as risk associations rather than evidence of causality, and further longitudinal studies incorporating comprehensive metabolic characterization are required to clarify mechanisms and determine whether targeted interventions can modify outcomes.

Sincerely,

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.

Ethics statement

The studies involving humans were approved by Kantonale Ethikkommission, Kanton Zürich. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

All authors participated in the design, interpretation of the study, and analysis of the data. ZR, LS, AM, TG, CS, FP, NA, GL, ÖS, IO, ID, SU, JM, RH, and MS contributed to the data collection, statistical analysis, and manuscript review. ZR, LS, AM, and TG conducted the primary data analysis, while CS, FP, and NA contributed to the clinical data curation. GL, ÖS, IO, ID, SU, JM, RH, and MS supervised the study, ensuring its integrity and providing critical insights. ZR wrote the manuscript, and all authors reviewed and approved the final draft. All authors contributed to the article and approved the submitted version.

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Supplementary material

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Posttransplant lymphoproliferative disorder after uterus transplantation

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infection, infertility, PTLT, recipient, uterus transplant

Dear Editors,

Posttransplant lymphoproliferative disorder (PTLD) comprises a spectrum of abnormal lymphoid proliferations that occur in the setting of posttransplant immunosuppression [1]. Epstein–Barr virus (EBV) plays a central role in most cases [2], as impaired T-cell immune surveillance permits proliferation of EBV-infected B cells, ranging from polyclonal expansion to malignant lymphoma.

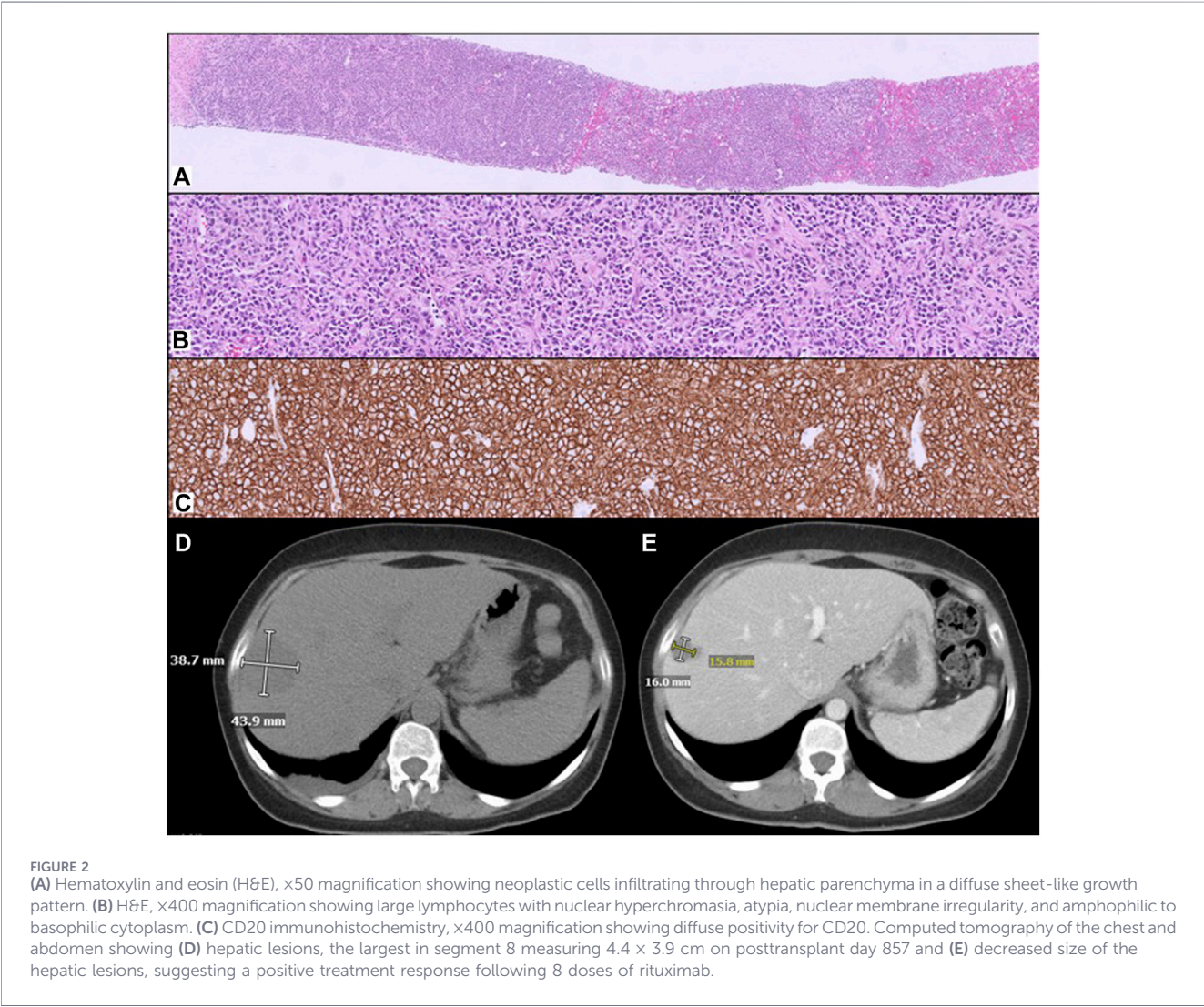
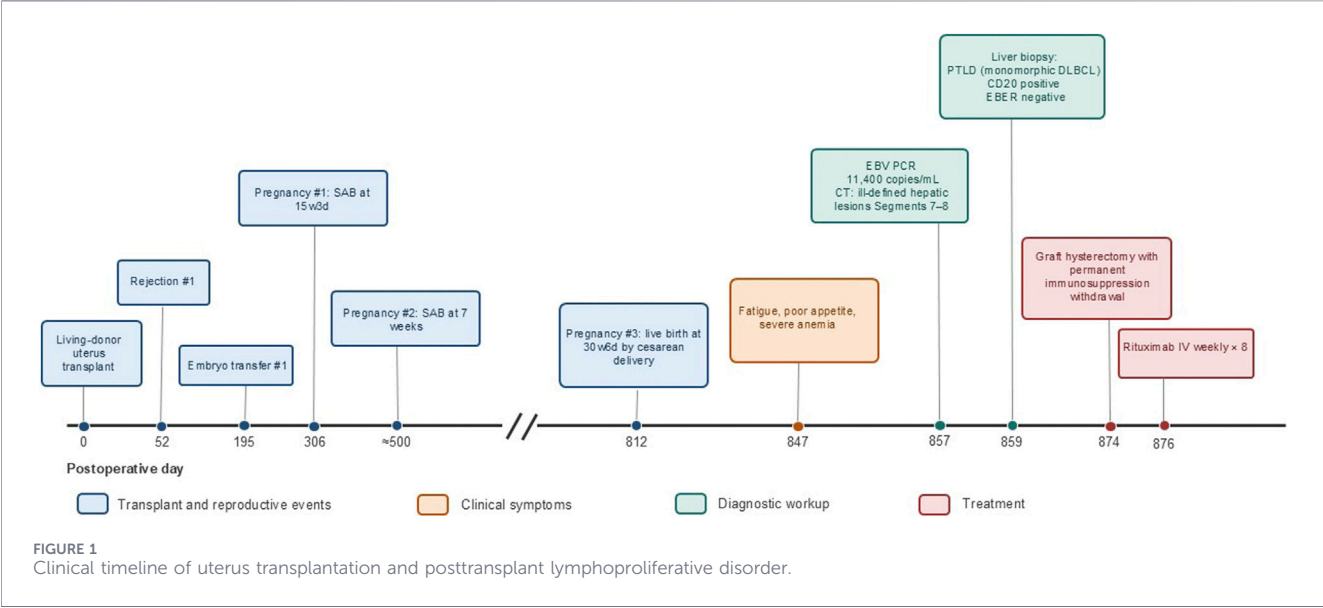
Although PTLT is well described following solid-organ and hematopoietic transplantation, its occurrence after vascularized composite allografts (VCAs), particularly uterus transplantation (UTx), remains poorly characterized [3]. As UTx becomes an established treatment for absolute uterine-factor infertility, reporting rare but serious complications is essential for informing patient counseling, risk assessment, and immunosuppressive management.

We experienced a case of PTLT that developed during the postpartum period following UTx. A 38-year-old woman with absolute uterine-factor infertility due to Mayer–Rokitansky–Küster–Hauser syndrome underwent living-donor UTx in April 2023 (Figure 1). Her medical history included chronic hypertension and a body mass index of 26 kg/m². Pretransplant testing showed negative EBV viral capsid antigen IgG and IgM, indicating no detectable EBV antibodies, while cytomegalovirus (CMV) IgG was positive. *In vitro* fertilization with cryopreservation of euploid embryos was completed before transplantation.

The donor was a 40-year-old parous woman who was EBV IgG-positive and CMV IgG-negative. Cold and warm ischemia times were 151 and 87 min, respectively, and the surgery was uncomplicated.

Induction immunosuppression consisted of antithymocyte globulin (total 4.5 mg/kg), followed by maintenance therapy with tacrolimus, azathioprine, and prednisone. Tacrolimus targets were later reduced. CMV and Pneumocystis prophylaxis were administered for 3 months, and fluconazole was given for 1 month.

Menses resumed on posttransplant day (PTD) 32. One episode of moderate T-cell-mediated rejection on PTD 52 resolved with intravenous steroids. No infections were documented after transplantation. Embryo transfer began on PTD 249. Four transfers resulted in three clinical pregnancies and one implantation failure. Two pregnancies ended in spontaneous abortion, including one at 15.3 weeks associated with placenta previa and bleeding requiring dilation and curettage.



The third pregnancy resulted in a preterm live birth. Cervical insufficiency required cerclage at 21 weeks. At 30 weeks and 6 days, premature rupture of membranes and preterm labor occurred, leading to cesarean delivery of a healthy male infant weighing 1.46 kg. The infant's neonatal intensive care unit course was uncomplicated.

On postpartum day (PPD) 35 (PTD 847), the patient reported progressive fatigue and poor appetite. Physical examination demonstrated pallor and an inflamed cervix. Laboratory studies revealed anemia with a hemoglobin level of 7.9 g/dL. Cervical biopsy demonstrated severe T-cell-mediated rejection, and high-dose intravenous steroids were administered.

Despite treatment, she developed worsening constitutional and gastrointestinal symptoms accompanied by a 4 kg weight loss. Persistent anemia and leukopenia were present, and EBV polymerase chain reaction testing demonstrated a viral load of 11,400 copies/mL.

Computed tomography of the chest and abdomen identified new hypodense lesions in hepatic segments 7 and 8, the largest measuring 4.4×4.0 cm, without thoracic involvement. Lactate dehydrogenase was elevated. Given the combination of EBV viremia and hepatic lesions, immunosuppression was discontinued. Histopathology of a liver biopsy demonstrated PTLD classified as diffuse large B-cell lymphoma, positive for CD20 and negative for EBV-encoded RNA (EBER) (Figure 2). Withdrawal of immunosuppression led to declining EBV viral loads.

Thirty days after symptom onset, the patient was admitted, and on PPD 62 (PTD 874), graft hysterectomy was performed to permit permanent discontinuation of immunosuppression.

Postoperatively, intermittent fevers secondary to urinary tract infection caused by *Klebsiella* and *Escherichia coli* were successfully treated with antibiotics. Rituximab (375 mg/m² weekly) was initiated for four planned cycles. Follow-up imaging 51 days later demonstrated partial response with reduction in hepatic lesion size, prompting four additional weekly cycles. At 3-month follow-up after hysterectomy, the patient reported substantial clinical improvement. Imaging demonstrated continued regression of hepatic lesions without new disease, positron emission tomography showed no metabolic activity, and EBV viral load was undetectable. At 12-month follow-up after hysterectomy PET scan showed no evidence of fluorodeoxyglucose (FDG) avid lymphoma.

PTLD is a recognized complication of immunosuppression, most commonly resulting from impaired T-cell surveillance and uncontrolled B-cell proliferation [2, 4]. Although extensively reported after kidney and other solid-organ transplantation, PTLD is exceedingly rare in VCAs [2, 5–7]. Only four previous cases have been reported among nonuterus VCA recipients. These cases included recipients of hand, lower-extremity, facial, and upper-extremity transplants. Presentations ranged from EBV-associated diffuse large B-cell lymphoma to late-onset EBV-negative PTLD. Management strategies included reduction or withdrawal of immunosuppression, rituximab-based therapy, and, in some cases, graft explantation, with variable outcomes [2, 5–7].

EBV mismatch between donor and recipient is a well-established risk factor for EBV-positive PTLD in solid-organ

transplantation, and routine EBV monitoring is standard practice [2, 4]. However, the relationship between EBV mismatch and EBV-negative PTLD remains less clear. Because UTx is intended to restore fertility rather than preserve life, the balance between benefit and long-term risks differs fundamentally from that of traditional organ transplantation.

In this patient, EBV viremia prompted further evaluation, yet histopathology demonstrated EBER-negative diffuse large B-cell lymphoma. This finding highlights that PTLD may develop independently of direct EBV-driven oncogenesis, particularly after prolonged or intensive immunosuppression [2, 4]. EBV-negative PTLD is thought to arise through alternative mechanisms, including accumulation of genetic alterations and impaired immune surveillance related to chronic immunosuppression. Importantly, EBV DNAemia does not necessarily indicate that the lymphoma is EBV-driven. The patient's cumulative exposure to thymoglobulin induction, triple-agent maintenance therapy, and repeated high-dose steroids for rejection likely contributed to PTLD development.

Donor-recipient EBV mismatch deserves particular consideration in UTx. Although donor selection is often constrained by anatomical and logistical factors, the elective nature of UTx raises questions regarding acceptable infectious and oncologic risks. Whether EBV mismatch should influence candidate selection, surveillance protocols, or immunosuppressive strategies remains uncertain and warrants further study.

Management of PTLD in UTx differs from that in life-sustaining organ transplantation. Because the uterus is a temporary graft, hysterectomy permits permanent discontinuation of immunosuppression. In this case, graft removal combined with rituximab therapy resulted in favorable clinical and radiographic outcomes.

To our knowledge, PTLD following UTx has previously been mentioned only in aggregate reporting without detailed clinical characterization [1]. This case provides a comprehensive description of presentation, diagnostic findings, management, and short-term outcomes. This case highlights the importance of EBV risk assessment, careful immunosuppression management, and vigilant surveillance in UTx. Continued reporting of rare complications will be critical to refining patient selection, counseling, and long-term management strategies in this evolving field.

Data availability statement

The datasets presented in this article are not readily available because Single patient data; data will not be available due to patient confidentiality. Requests to access the datasets should be directed to liza.johannesson@bswhealth.org.

Ethics statement

The studies involving humans were approved by Baylor University Medical Center, Dallas IRB 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. 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

Conception or design of work – LJ, KS, and GT; Acquisition, analysis, or interpretation of data – LJ and KS; Drafting/revising of manuscript – LJ, KS, and GT; final approval of manuscript – all. All authors contributed to the article and approved the submitted version.

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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.

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