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Editorial

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AI in transplantation: levelling the playing field and raising the methodological standards

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Introduction

Artificial intelligence has rapidly entered the scientific publishing ecosystem, often faster than the norms designed to govern it. A recent analysis of more than 1.1 million papers across arXiv, bioRxiv, and Nature portfolio journals estimates that text modified by large language models has been rising steadily since early 2023, reaching up to 22% of abstracts in computer science and roughly 9% in the life sciences [1]. This shift is broad, global, and most pronounced among authors from regions where English is not the dominant language. Importantly, the transformation extends well beyond writing. AI is increasingly shaping how we generate hypotheses, build predictive models, analyze imaging and omics data, and interpret what counts as evidence. As editors in transplantation medicine, we believe that both fronts, linguistic and methodological, require the same editorial response: not rejection of the technology, but the construction of standards that allow its responsible use.

Levelling the linguistic field

For decades, science has been built on an implicit assumption that fluent English reflects good scholarship, and that linguistic proficiency signals intellectual merit. The consequences have been well documented. Non-native English speakers spend disproportionate time, financial resources, and effort to produce manuscripts that appears review-ready, while native speakers benefit from an invisible advantage. The manifold costs of conducting science in a second or third language, ranging from delays in publication to reduced citation visibility and limited participation in international debates have been extensively documented [2]. Of note, GPT-detection tools have been shown to systematically misclassify non-native writing as machine-generated with error rates above 60%, while achieving near-perfect accuracy on samples written by native English speakers [3]. When detection tools themselves carry such language bias, any attempt to police AI use rests on an unstable basis.

Against that backdrop, AI can act as a meaningful equalizer. Nature Methods has explicitly acknowledged that generative models can help scientists who struggle with

language or writing to refine their manuscripts and communicate more clearly [4]. Elsevier, Springer Nature, and other major publishers now allow AI-assisted editing, provided that authors remain accountable for content and disclose their use. In practice, disclosure remains limited: only 2 out of 200 randomly sampled computer science papers reported the use of large language models in writing [1]. Taken together, these data suggest that AI is quietly smoothing the edges of scholarly English across disciplines, and the relevant question is no longer whether this is happening, but under which conditions it should be accepted.

This raises an uncomfortable but necessary question: if a manuscript becomes easier to read because an author used AI to improve their English, does that diminish the underlying science, or does it allow reviewers to judge research more directly on its substance? The academic community has long conflated laborious writing with intellectual rigor, although no elegant prose can rescue a weak hypothesis, and no awkward syntax negates a well-designed study. AI may help bring this conflation into focus [5]. The effect is particularly relevant for early-career researchers, for whom the hidden curriculum of stylistic fluency often weighs as heavily as the science itself. Used responsibly, AI can act as a structural scaffold that helps younger researchers organize their ideas and find their professional voice, provided that they remain the authors of what they publish. For decades, young scientists have been socialised to mimic their supervisors' writing style, as though acquiring the "right" academic voice were a prerequisite for belonging to the ivory tower. But elegant phrasing is not the essence of science and if AI can take over some of the stylistic tasks, it may finally allow early-career researchers to invest more of their limited time where it belongs: in designing better studies, interrogating data more critically and nurturing genuine scientific curiosity.

Notwithstanding these potential benefits, the risks should not be underestimated. The Nature Methods guidance highlights accuracy, hallucination, and unverifiable claims as persistent concerns, requiring active human oversight and explicit responsibility [4]. Large-scale corpus analyses have also reported that heavy LLM use correlates with greater stylistic homogeneity across papers, an early signal that overreliance could flatten scholarly voice and reduce diversity of expression [1]. In peer review, uploading manuscripts into external AI platforms compromises confidentiality, a breach now explicitly prohibited by most publishers. The more ambitious vision of a multilingual publishing ecosystem, in which authors write in their own language and reviewers receive AI-translated versions, remains aspirational and raises additional equity concerns related to translation quality for low-resource languages [6]. These risks do not justify rejection of the technology. These argue for clear standards.

Beyond language: AI as methods

If AI is reshaping how we write about science, it is reshaping even more profoundly how we conduct it. Predictive models of graft survival, deep learning classifiers of allograft biopsies, transcriptomic signatures of rejection, foundation models trained on multimodal clinical data, and conversational agents embedded in clinical workflows are no longer prospective developments. They are already present in our literature, in our practice, and increasingly in our editorial submissions. Here too, an inequity is at work, although of a different kind. It is no longer primarily a linguistic gap, but a methodological one.

The technical barrier to building models has fallen sharply. Open-source machine learning libraries, accessible tutorials, and large language models capable of generating analytical pipelines on request have made it possible to produce a predictive model in a weekend. The conceptual barrier to understanding what these models actually do, and which claims they can legitimately support, has not decreased; if anything, it has increased. The same literature that helps levelling the writing field also produces papers in which data leakage is unrecognized, calibration is not reported, external validation is missing, and predictive performance is conflated with causal effect. These shortcomings are not exotic. They are systemic patterns documented across the AI-in-medicine literature, and transplantation is no exception [7, 8].

This second front matters because the consequences differ. A poorly written but methodologically sound paper represents a missed opportunity for the reader. A fluently written but methodologically unsound AI paper may lead to a misallocation of clinical attention, and, if the model is ultimately deployed, of patient care. The editorial response to AI in transplantation cannot stop at the level of the manuscript's surface. It should also engage with the methods themselves and the quality of the evidence they produce.

What this calls for editorially

To address this dual responsibility, Transplant International is launching a new editorial series entitled Decoding AI for Transplantation. The series is designed to fill the gap that the linguistic discussion alone cannot cover. Across recurring issues, it will provide short and structured primers, each centered on a single methodological or implementation concept, illustrated with a clinical scenario, and closing with a set of actionable questions that readers, reviewers, and clinical users can apply when evaluating an AI tool. Topics will span the full path from manuscript to bedside, including calibration and decision curve analysis, data leakage in longitudinal transplant data, external validation and transportability, the distinction between prediction and causal inference, uncertainty quantification, survival analysis with deep learning, digital pathology of allograft biopsies, the critical appraisal of foundation models and large language models, the integration of AI tools into transplant clinical workflows, post-deployment monitoring and performance drift, and the assessment of AI tools as clinical interventions in their own right.

This breadth reflects a deliberate editorial choice. The questions raised by AI in transplantation cannot be answered solely at the level of the published manuscript. Predictive models, image classifiers, and decision support tools are increasingly proposed for use in clinical practice, often before their behaviour in routine workflows is well characterized. Of note, the introduction of an AI tool is itself a form of clinical intervention, with potential effects on biopsy thresholds, treatment decisions, alert handling, and patient outcomes. These effects deserve the same scrutiny applied to any other intervention in transplantation. Issues such as how performance should be

monitored over time and across centers, how model outputs should be communicated to clinicians and patients, how integration into electronic health records can avoid alert fatigue, and how equitable access can be preserved across centers with heterogeneous resources are central to the responsible use of AI in our field, and will be addressed alongside the methodological primers.

The objective is not to celebrate AI, nor to catalogue its applications. It is to equip the transplantation community with the conceptual tools required to read AI papers carefully, to review them rigorously, to assess their suitability for clinical deployment, to monitor their performance once in use, and, when authors themselves, to design and report their work in ways that will withstand scrutiny. Each primer will be written by invited teams combining clinical, methodological, and implementation expertise, with a recognizable structure and a unified visual style across issues. The intent is to maintain a didactic tone, a critical perspective, and an honest discussion of the limitations of the methods and tools presented. At its core, AI is a powerful engine for pattern recognition and imitation and superior in copying, summarising, and amplifying, but it does not originate purpose or curiosity. Innovation in science still begins with a human mind willing to ask a question that has never been asked before, reative leap cannot simply be automated.

Taken together, levelling the linguistic field and raising the methodological standards are not competing aims. They reflect a single editorial commitment. AI will not make weak studies strong, and it will not, on its own, make our literature more equitable or more rigorous. However, it has made the costs of inaction more visible than they were a decade ago. The task of editors in transplantation is to build the norms that allow responsible use of AI in writing, in reviewing, and in the methods on which our claims ultimately rely, so that scientific merit can be assessed on the basis of the science itself.

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Gaza: not to act is to act

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Many will be surprised to hear that prior to the start of the latest war in Gaza, on October 7th, 2023, over 100 living donor renal transplants had been performed in the territory, with the hope that the programme could be expanded to match that of the West Bank, where over 500 transplants have taken place [1]. Although transplantation continues in the West Bank, in Gaza not only has transplantation stopped but patients with renal failure have no reliable treatment options. In December of last year, Nasser Hospital in Khan Younis, which is currently the main hospital within Gaza, had no peritoneal dialysis options, due to a lack of catheters, dialysis fluid and a reliable sterile environment, and had 31 functioning haemodialysis machines, with 238 dialysis patients. A four-storey dialysis centre within the hospital grounds, built just before the war, remains burnt out and unused following an attack on the hospital in June 2024. Al Aqsa hospital, the other significant hospital in the area has 23 dialysis machines, whilst a Belgian Field Hospital has 18. Three of six Government-run dialysis centres were destroyed or inactive by November 2024, with only 629 end-stage renal failure patients alive and receiving dialysis, compared with 1100 at the start of the war [2]. At that time, half the respondents in one study received 2 or fewer dialysis sessions per week, and 42% had an average of 9 days between sessions [2]. The pre-war population of Gaza was 2.4 million, with over 80% of the population displaced, resulting in over 1 million living in the central area served by Nasser Hospital; clearly the provision of care for end stage renal disease is woefully inadequate. Furthermore, access to Nasser Hospital has remained difficult-few vehicles are functioning, and prior to the recent 'ceasefire' movement was particularly risky due to the continued bombing. Additionally, medication for those with renal failure or a previous transplant has been difficult or impossible to obtain due to the restrictions on medical supplies. Finally, with over 1.3 million people [3] (more than half the population) living in tents or makeshift shelters lacking electricity and basic sanitation, storage of medication or fluids and adequate care of permanent lines is essentially impossible. With 71,548 fatalities in Gaza (including 20179 children) [4], directly due to trauma, it is clear that there are many further indirect deaths from the consequences of inadequate access to healthcare [5]. A Lancet publication estimated that by June 2024, when the known fatality total was 37,396, the total number of deaths likely exceeded 186,000, or 8% of the total population [6].

An unfortunate, and unprecedented, aspect of this war has been the systematic targeting of healthcare facilities. There have been 687 attacks on healthcare facilities, and 211 on ambulances and other healthcare transport, with 985 healthcare workers killed, and 306 healthcare workers detained [4]. Indeed, a quarter of Gaza's most experienced specialists had been killed or detained by October 2024, and according to Healthcare Workers Watch 'In Al-Shifa Hospital alone . . . the heads of the internal medicine department, the obstetrics and gynaecology department, the emergency department, the pathology department, the radiology department and the

orthopaedic department (were killed)'. Adding to this, during the invasion of the hospital, they detained the general director, the acting head of the emergency department, the two acting heads of the orthopaedics department and the head of the anaesthesia and ICU departments.' [7] At least three detained doctors have been tortured to death [7]. Only 18 of the pre-existing 36 hospitals are functioning, but none of these are able to provide even a basic standard of care, with constant shortages of equipment, medication and personnel. Post-operative mortality remains very high due to infection and lack of ICU care. There is currently no provision for any specialist services in the north of Gaza [4]. Hospitals which do remain open often rely on junior doctors and medical students to staff highly specialised services, such as ICU or anaesthesia. There are only two vascular surgeons working in the whole of Gaza. Prior to the war, there were 5 pathologists in Gaza, but two retired and two were killed, leaving only one pathologist to serve over two million people [7].

Despite the ceasefire, the health of most Palestinians in Gaza remains precarious. 171,353 people have been injured [4], and most of these are polytrauma, burns and blast injuries [8], which require specialist care. Famine has been an ongoing issue despite the 'ceasefire,' with 113 children dying from malnutrition in 2025, and a further 63,000 enrolled in treatment for malnutrition [4]. Safe elective surgery is essentially impossible due to a lack of experienced staff, basic anti-sepsis measures, lack of medication and diagnostic facilities and the poor nutritional state of the patients.

The psychological trauma of living under constant bombardment, repeated displacement, and the loss of so many friends and family members cannot be overestimated [9], and currently there are almost no services to deal with this. The use of drones adds to the trauma-prior to 2023, surveillance drones were in constant use. During the war, drones have been used to deliver explosives and other munitions, and thus represent a risk of death. Their continued presence during the "ceasefire" will not help psychological recovery.

In summary, the civilian population of Gaza have been subjected to an unprecedented, severe and collective attack for 2 years. Palestinians have not been allowed to enter or leave Gaza (only 3,140 medical evacuations have taken place [4]), and huge numbers have been killed and injured. Despite a "ceasefire," during which 463 Palestinians have been killed [10], medical supplies and food are woefully inadequate. The healthcare system is in unable to function to a reasonable standard of secondary care, and malnutrition remains a significant problem. Some have argued that there is a distinction between medical neutrality and silence, and called on medical societies to speak out [11]. What is certainly clear is that as healthcare professionals we have a duty to consider how to help those who are in desperate need of medical care, but to whom it is denied.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: No datasets used.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

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The European Board of transplant medicine: evolution, present role and future directions toward harmonised transplant medicine training in Europe

Nuria Montero [1,2]*, Miha Arnol [3,4], Susanne Beckebaum [5], Isabelle Binet [6], Vito Cicinnati[5], David Cucchiari [7,8], Caroline Den Hoed [9], Antoine Durrbach[10], Speranta Iacob [11,12], Smaragdi Marinaki[13], Anna Paola Mitterhofer [14], Anna Mrzljak [15], Adam Remport [16], Pablo Ruiz [17], Susana Sampaio[18,19], Francesca Tinti [20] and Marios Prikis [21]*

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education and training, harmonization, hepatology, nephrology, transplant care

Over the past four decades, organ replacement has evolved into a cornerstone of modern medicine. Nowadays kidney and liver transplantation offer durable and life-saving therapy for patients with end-stage organ failure. The field is no longer defined solely by surgical innovation, it also encompasses organ preservation technologies (including machine perfusion), xenotransplantation, precision immunology, artificial organs and regenerative medicine. Transplant physicians, particularly transplant nephrologists and hepatologists given the higher transplant volumes in these specialties, are now deeply involved in the evaluation of transplant candidates, perioperative decision-making, and lifelong post-transplant care. These responsibilities require specific expertise that extends beyond general hepatology or nephrology training. Despite this clinical maturity, transplant hepatology and transplant nephrology remain

inconsistently structured across Europe and are not formally recognised as subspecialties in most Union Européenne des Médecins Spécialistes (UEMS) member states. Training pathways, certification mechanisms, and competency standards are heterogeneous and not uniformly defined.

The aim of this article is to provide an update on the EBTM's current activities, increase awareness of its role in transfusion medicine, and promote broader engagement across European countries.

UEMS is a professional organisation that represents medical specialists across Europe. Since its foundation in 1958, UEMS has worked to promote high standards in specialist medical training, education, and clinical practice. The Division of Transplantation of UEMS was established in 2007 to address these challenges in the field of transplantation medicine, following preparatory work by the Transplant Working Group of the UEMS Section of Surgery and the European Board of Surgery. In 2010, the European Board of Transplantation Medicine (EBTM) was formally constituted as a joint initiative of UEMS and the European Society for Organ Transplantation (ESOT) reflecting both regulatory and scientific perspectives. Its objective is not to replace national systems but to promote a harmonized European framework capable of ensuring high standards of professional training and patient care. From its inception, the EBTM was designed as a non-profit body with a clear mandate, to safeguard the highest standards of care in transplantation medicine by harmonising postgraduate specialist training across Europe. The Board is composed of transplantation medicine physicians that are national representatives from UEMS member states, together with a representative appointed by ESOT.

The EBTM does not license physicians and does not interfere with national certification processes. Rather, it provides a structured, comprehensive and harmonized European-level assessment of Transplant Medicine that complements national training. The EBTM's collaboration with ESOT has the potential to further support the standardisation of specialist qualifications, facilitate cross-border recognition of medical specialists, and contribute to shared quality benchmarks in European healthcare. The overarching objective of these joint initiatives is to ensure the highest standards of transplantation care for patients across Europe. ESOT is a strategic academic partner of the EBTM, and this collaboration is already operational in several concrete ways, including its basis in existing agreements such as the Memorandum of Understanding (MoU), where applicable. ESOT has an appointed representative on the EBTM Board who participates in all Board meetings and also serves as an examiner during the certification examinations. In addition, the EBTM examinations are held in conjunction with the ESOT Congress, with ESOT providing logistical support, including the venue. Furthermore, both organisations are currently strengthening their educational collaboration through ESOT's existing learning platform, Transplant Live, which already hosts relevant courses and modules aligned with EBTM content.

A central activity of the EBTM has been the development of a structured modular examination system [1, 2]. The examination currently consists of three modules: (a) Common pathway module, (b) Kidney transplantation module, and (c) Liver transplantation module. Future goal is the expansion to include examinations in other organs such as pancreas, heart and lung. The Common Trunk evaluates foundational knowledge applicable across organ systems, including transplant immunology, mechanisms of rejection, immunosuppressive pharmacology, infectious complications, organ allocation systems, and ethical and moral considerations. The organ-specific modules assess advanced clinical expertise in kidney or liver such as waiting list management, organ donation and allocation principles, perioperative management of organ recipients and management of both short and long-term medical complications such as infections, malignancies and allograft rejection and dysfunction as well as immunosuppressive protocols. The certification by UEMS is a 2-step process based on the evaluation of training and clinical practice of the applicant, and an oral examination conducted in English, enabling assessment of integrative clinical reasoning and ethical judgment through case-based discussion. All the information required to apply is available on the website of the UEMS (https://uemssurg.org/surgicalspecialties/transplant-medicine/ebsq-examinations). Successful candidates are awarded the Fellowship of the European Board of Transplant Medicine, a credential that is increasingly recognised within the European transplant community and, in this sense, has institutional, pan-European recognition through the UEMS structure. The practical advantages associated with the credential vary significantly depending on the national and institutional context. In some countries or institutions, it may be valued as a marker of additional expertise and may support career progression, academic recognition, or professional credibility, while in others its impact may be more limited or informal.

Transplant Medicine practice has significantly evolved in most European countries. Yet, training national standards and fellowship pathways differ substantially across european borders (Table 1). Comparative analyses of individual state systems demonstrate significant diversity in transplant medical training. In some, transplant exposure is structured, while in others it is not. Both transplant nephrology and transplant hepatology, although clinically established, are not formally recognised as a subspecialties in any surveyed systems [3]. An isolated exception seems to be Germany, with an officially recognised national certification pathway in Transplant Medicine.

The EBTM framework defines minimum requirements regarding duration of structured transplant training, documented clinical exposure, participation in multidisciplinary teams, core knowledge domains, and ethical and professional competencies (Table 2). These standards promote consistency while respecting national autonomy. Applicants are evaluated through a robust review process to determine eligibility for the examination. We have a review committee in place: the President appoints three blinded reviewers, ensuring they are not aware of each other's involvement. In the event of discrepancies in their evaluations, the review committee convenes to discuss and reach a consensus, and the matter is then escalated to the full Board when necessary. Additionally, we contact referees via telephone or email to gather further information. Eligibility for EBTM certification requires both clinical practice and scientific development aspects, such as documented participation in congresses, courses, and educational activities. Following a thorough evaluation of the relevant competencies, the eligible examinees can participate in the examination for the obligatory common pathway module and then subsequently, depending on their training either the transplant hepatology or nephrology modules.

The EBTM examination is currently held every 2 years within the framework of the ESOT Congress. The next examination will be held in September 2027. It is an in-person, oral, case-based, and competency-driven assessment that evaluates integrative reasoning rather than simple factual recall. Its governance is transparent, with clearly defined eligibility criteria and independent panels of examiners.

The EBTM provides structured curriculum standards, defined eligibility criteria, and established examination processes that could support subspecialty recognition in Transplant Medicine [4], should national and European regulators decide to pursue this pathway. Looking ahead, EBTM's strong efforts to build partnerships with ESOT and the sections of EKITA (The European Kidney Transplant Association) and ELITA (The European Liver and Intestine Transplant Association) as well as other UEMS specialty sections, will strengthen its role and mission, assisting in progressively building a broader, harmonized European transplant medicine training and certification framework. Joint efforts could focus on aligning curricula with evolving clinical needs, integrating EBTM-related educational activities within ESOT's portfolio, and promoting shared competency frameworks for all organ transplantation disciplines. By leveraging ESOT's educational platforms and the EBTM's examination standards, such initiatives could contribute to more harmonized competencies and facilitate cross-border recognition of expertise. Consequently, EBTM's is committed to expanding its certification beyond nephrology and hepatology, enhancing the recognition, visibility, and adoption across Europe, and pursuing formal recognition of subspecialties such as transplant nephrology and hepatology. Despite ongoing efforts to promote engagement, participation in the EBTM framework remains incomplete across European countries, underscoring the need for continued outreach and expansion to achieve broader European integration of transplant medicine training standards. Extending the certification to additional Transplant Medicine disciplines such as heart, lung, and pancreas transplantation would further harmonise competencies across the full spectrum of transplant care and better reflect its multidisciplinary nature. To strengthen awareness and adoption, key strategies include closer integration with ESOT educational activities, increased engagement with national societies and training programmes, focused outreach initiatives, and greater promotion of the certification as a tool for facilitating professional mobility and standardised expertise across Europe. Eligibility for certification by the European Transplant Medicine Board is open to European clinicians, as well as to non-European clinicians who have completed and validated a period of clinical practice in one of the member UEMS countries.

In conclusion, the EBTM represents meaningful and maturing step towards the harmonization of Transplant medicine training and certification across Europe. By establishing structured curricula, defined competency framework, and rigorous examination standards, it offers a valuable complement to existing national systems and contributes to the broader recognition of transplant nephrology and hepatology as distinct clinical disciplines. Continued efforts to expand geographic participation, extend certification to additional transplant disciplines, and strengthen collaboration with ESOT, UEMS sections and national societies will be vital in further consolidating its role. Together, these initiatives reflect a shared commitment to promoting high standards of transplant medicine training and, ultimately, to improving the quality of care for transplant patients across Europe.

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 authors.

Author contributions

NM and MP conceived the study and drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Long-term HLA-incompatible kidney transplant outcomes

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Many centers avoid human leukocyte antigen (HLA) -incompatible kidney transplantations due to increased risk of graft loss, although it may be the only option for highly sensitized patients. We assessed the association of pre-transplant donor-specific HLA-antibodies (DSAs) with biopsy-proven acute rejection (BPAR), antibody mediated rejection (AMR), and death-censored graft survival (DCGS). All deceased donor kidney transplantations in Finland between 2006 and 2021 were included (n = 3209), with 226 DSA-positive recipients. DSA characteristics, including specificity and mean fluorescence intensity (MFI), were collected. DSAs were associated with worse DCGS, higher risk of BPAR (HR 3.22, 95% CI 2.57–4.04), and especially AMR (HR 35.1, CI 22.4–55.1). Higher cumulative MFI was associated with lower 10-year DCGS (no-DSA 83%, ≥10,000 66%). A similar trend was seen in multivariable models (HR 1.81, CI 0.995–3.27 for MFI ≥10,000). Class II DSAs indicated higher risk for BPAR (HR 4.2 vs. HR 3.1), and AMR (HR 32.3 vs. HR 21.9), than class I DSAs. Collectively, pretransplant DSAs and higher cumulative MFI were associated with poorer graft survival, and especially class II DSAs were associated with higher risk of AMR. However, DCGS with even very high-level pretransplant DSA could be considered acceptable, supporting consideration of HLA-incompatible transplantations for highly sensitized patients.

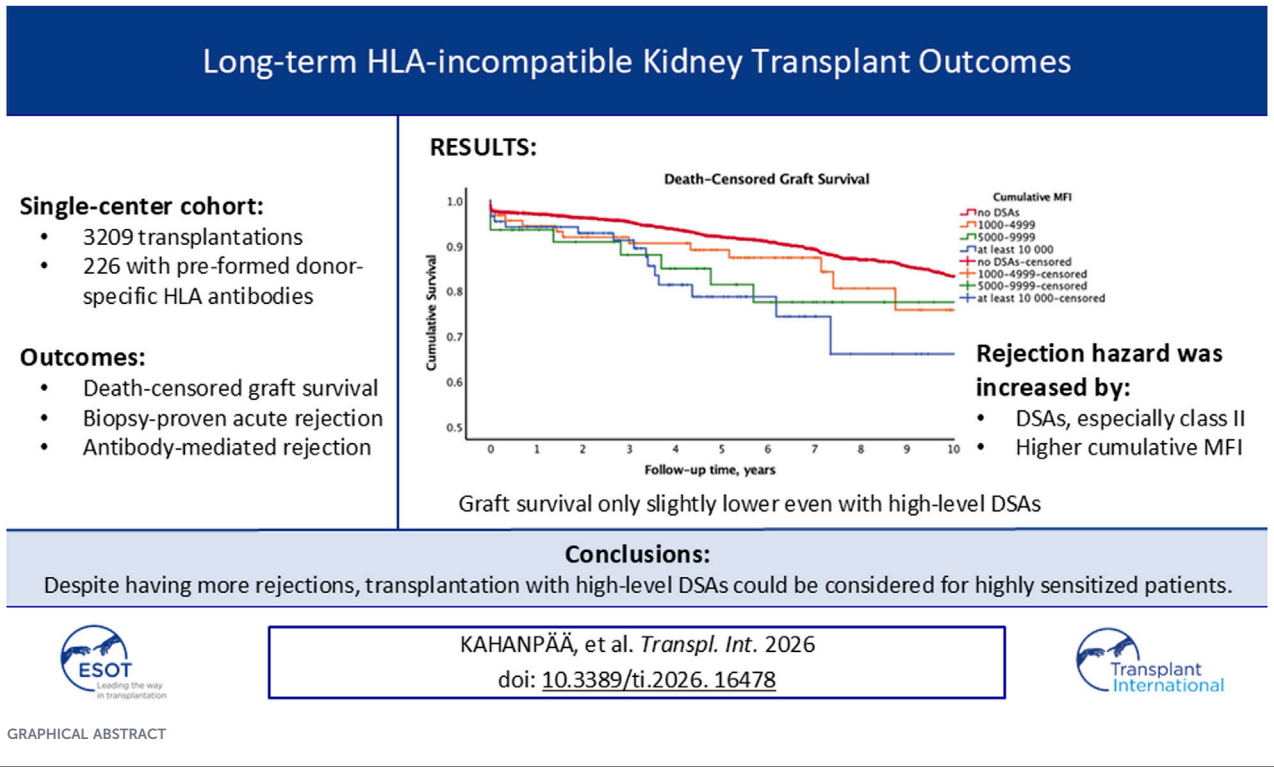
KEYWORDS
acute rejection, antibody-mediated rejection, donor-specific antibodies, HLA incompatible, kidney transplantation

Introduction

Although access to HLA-compatible transplantation has been increased in the recent years due to increased utilization of acceptable mismatch programs and living donor kidney paired exchange programs, [1, 2], HLA- incompatible (HLAi) transplantation remains the best alternative to get timely access to kidney transplantation for many very highly sensitized patients.

HLA- incompatible kidney transplantation can refer to the presence of pre-existing DSAs or to a positive flow cytometry or cytotoxic crossmatch, with an incremental increase in the risk of graft loss or early AMR [3]. In optimal circumstances with a living kidney donor, desensitization can be planned and performed pretransplantation. However, with deceased donor transplantation the options are scarce for rapid antibody removal. Recently, imlifidase has become available in some parts of the world (European Union, Australia), but only limited real-world experience exists until recently and high costs of the treatment limit the use of imlifidase to special circumstances [4].

The outcome of HLAi kidney transplantation is inferior compared to HLA compatible transplantation, and pre-existing DSAs (positive virtual crossmatch) are often avoided in organ allocation. On the other hand, the survival benefit of HLAi transplantation still



GRAPHICAL ABSTRACT

exceeds survival while staying in dialysis [5]. Although many studies have shown the inferior graft survival and high risk of AMR associated with pre-existing donor-specific antibodies [6–8], many details of this association, e.g., with regard to what is the maximum level of DSAs still acceptable and what is the association for long-term survival beyond the first 10 years, have not been characterized adequately.

The aim of this nationwide cohort study is to characterize the association of pre-existing DSAs with long-term graft survival and the risk of AMR in detail, with special focus on those patients who have very high levels of DSAs pretransplantation, to be able to define a maximum threshold for pre-existing antibodies with still acceptable graft survival.

Materials and methods

Data

This study was a retrospective analysis of all adult kidney-only transplantations in Finland between January 2006 and December 2021. The data were obtained from the national Finnish Transplant Registry, and/or electronic patient records from Helsinki University Hospital (HUS), which is the only transplant center in Finland. HLA antibody analyses were made at the Finnish Red Cross Blood Service, which process this data on behalf of HUS. This study was approved by the Institutional Review Board of HUS, Abdominal Center (HUS/136/2024)

The inclusion and exclusion criteria of the patient material are presented in Figure 1. Living donor transplants and multi-organ transplantations were excluded. All transplantations were from donors after brain death, as donors after circulatory death were not used in our center during the study period. All transplantations were complement dependent cytotoxicity crossmatch negative, examined with donor splenocytes between 2006 and 2015 and peripheral T- and B-cells thereafter. No desensitization was used. According to the local immunosuppression protocol, the baseline immunosuppression was a combination of a calcineurin inhibitor (cyclosporine or tacrolimus, of which cyclosporine was used in earlier years, and tacrolimus increasingly in the later years), mycophenolate (1,000 mg twice daily with cyclosporine or 500 mg twice daily with tacrolimus) and steroids. Induction was with basiliximab for recipients with retransplantations or HLA mismatch grade over 3 in the A, B, and 1 DR loci. Anti-T-lymphocyte globulin was used for induction after 2015 in patients with known or presumed (panel reactive antibody (PRA) percentage over 80%) DSAs at the time of transplantation. Target trough levels for tacrolimus are 7–10 μg/L for the first 3 months and later 4–6 μg/L. As for cyclosporine, target levels are 160–200 μg/L for the first 3 months and 80–110 μg/L until 1 year after transplantation. Steroids were withdrawn after the first posttransplant year for most stable patients with no history rejections or immunological baseline kidney disease.

Data of the recipients included number of previous kidney transplants, time on the waitlist, age at transplantation, sex, height, weight, body-mass index, ABO blood type, smoking

Abbreviations: AMR, antibody-mediated rejection; BPAR, biopsy-proven acute rejection; DSA, donor-specific antibody; DCGS, Death-censored graft survival; HLA, human-leukocyte antigen; MFI, mean fluorescence intensity; TCMR, T-cell mediated rejection.

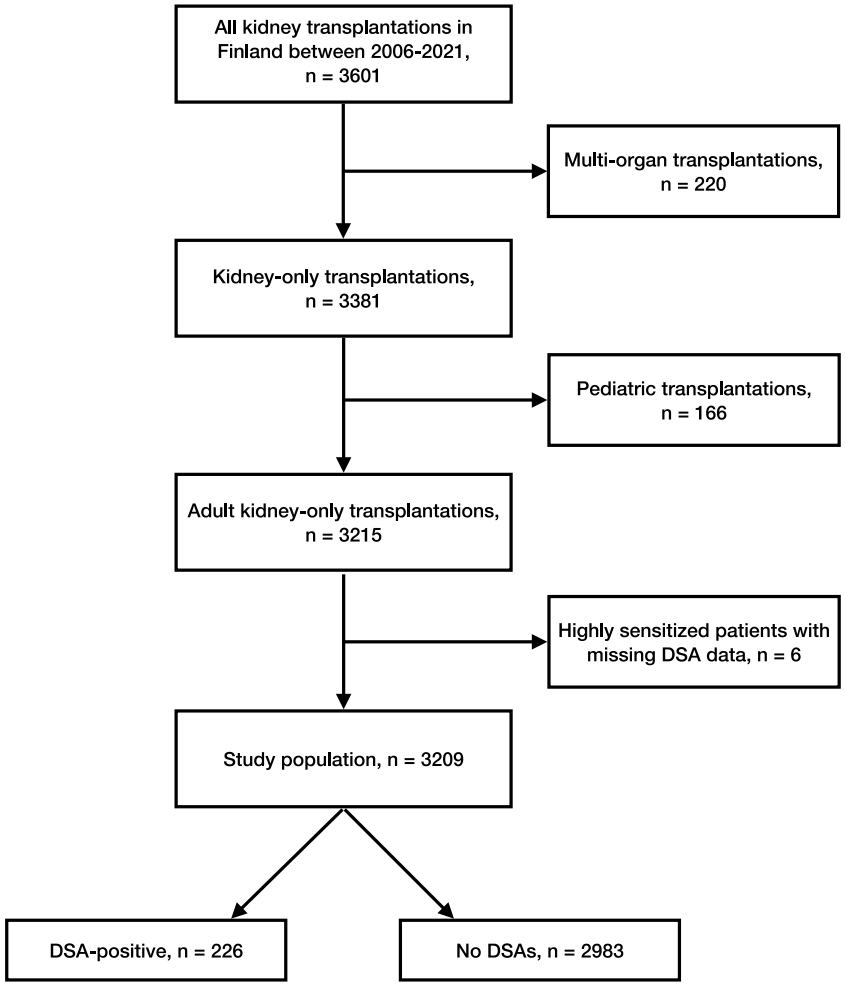


FIGURE 1
Flow chart presenting the inclusion and exclusion criteria of the patient material.

status, ICD-10 code of kidney disease, cytomegalovirus (CMV) status, highest and last calculated PRA percentage for class I and II HLAs pre-transplantation, dialysis time and last dialysis type (hemodialysis or peritoneal dialysis). Donor data included gender, age, height, weight and CMV status. Transplantation data included HLA AB and DR mismatch grades, cold ischemia time, follow-up time and status of graft survival, biopsy-proven acute rejection (yes or no), and rejection time and type (T-cell or antibody mediated), as categorized by the respective Banff classification at the time of biopsy [9]. Borderline findings were registered as rejections if they were treated accordingly. Mixed phenotypes were classified as AMR.

The DSA status of sensitized patients, including specificity and MFI, were collected from posttransplant tissue compatibility reports. One Lambda Labscreen® mixed and single antigen beads with Luminex® were used for HLA antibody screening and identification with the use of HLA Fusion software (One Lambda Inc., Canoga Park, CA). MFI level >1,000 was considered positive. Highly sensitized recipients with no available DSA data (n = 7) were excluded from the study. Donor HLA typing was performed at intermediate resolution, complemented with haplotype analyses.

Analyses

Recipients were compared in different groups based on their DSA status (DSAs vs. no DSAs). Recipients with DSAs were also divided into different subgroups based on their cumulative overall DSA MFI: 1,000–4,999, 5,000–9,999, or at least 10,000. To find out the significance of class I vs. class II DSAs, the DSA group was also categorized based on the separate class I and class II cumulative MFIs, using the same above-mentioned limits. DSA MFI was also tested for the models as a continuous variable, but as the linearity assumption was not met, categorized MFI was used instead.

The outcomes examined included DCGS, defined as return to dialysis or retransplantation, and censoring for deaths; biopsy-proven acute rejections (BPAR) and AMR. For multivariable Cox regression analyzing factors associated with DCGS, confounder analysis for the model was constructed as a directed acyclic graph

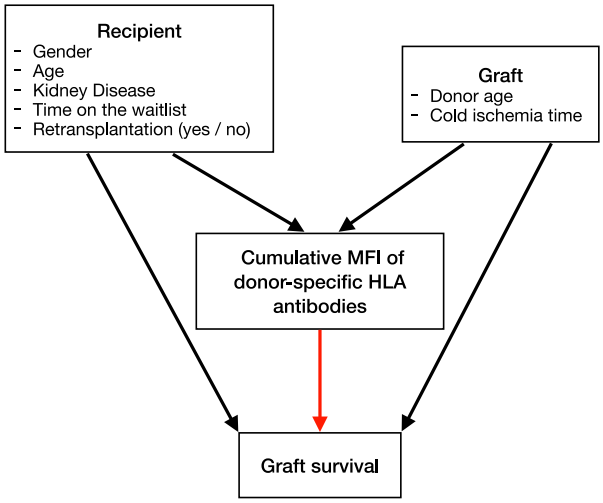


FIGURE 2
Factors possibly affecting the presence of DSAs at the time of transplantation and associating with graft survival.

(DAG) [10]. The DAG (Figure 2) presents factors possibly affecting the presence of DSAs at the time of transplantation and confounding the associations with graft survival. For Cox regression models, we included cumulative MFI (categorized into four groups (no DSAs, 1,000–4,999, 5,000–9,999, at least 10,000)), donor age, recipient sex, age and kidney disease (diabetic kidney disease, glomerulonephritis, polycystic kidney disease or other), retransplantation (yes or no), time on the waitlist, cold ischemia time, use of induction immunosuppression (other than iv steroids), and use of cyclosporine (vs. tacrolimus), as covariates. Relevant first-degree interactions between DSAs and other variables were tested, and the assumption for proportional hazard was supported for DSAs. In addition, interaction between retransplantation and cumulative MFI, was examined (and found nonsignificant). Graft survival was estimated with the Kaplan-Meier method where graft loss (return to dialysis or retransplantation) was used as the event while death and end of follow-up time were censored. Factor comparisons for DCGS were calculated with the Log Rank test.

For multivariable analysis of BPAR and AMR, a Cox regression analysis was run with the same covariates as the analysis regarding DCGS, presented in the DAG, taking rejection time into account. Interaction between retransplantation and cumulative MFI was examined and found insignificant for BPARs and significant for AMRs. To compare the risk of rejections within different groups, univariable analyses were calculated using Cox regression, for DSA status (any DSAs, and class I and class II DSAs separately), and categorized cumulative MFI for total MFI, and class I and class II separately. The assumption for proportional hazard was again supported for DSAs.

As a sensitivity analysis, all statistical tests were repeated for immunodominant MFIs for class I, class II and all DSAs.

All statistical analyses were done using IBM SPSS Statistics, version 28.0. P-value of under 0.05 was considered statistically significant. Missing data were assumed to be missing at random, and as the number of missing data were low for the variables of interest for the multivariable analyses, cases with missing values were excluded from the respective analyses.

Results

Study population

A total of 3209 transplantations were included in this study, of which 226 (7%) recipients were DSA positive at the time of transplantation. The patient characteristics are described in Table 1. The only missing data were for recipient BMI (n = 361), time on the waitlist (n = 4), recipient CMV status (n = 29), donor CMV status (n = 53), donor age (n = 1), cold ischemia time (n = 2), last higher and total PRA% before transplantation (n = 294), average maximum PRA% before transplantation (n = 238), HLA AB mismatch (n = 1) and DR mismatch (n = 1). Statistically significant differences were found for recipient sex, retransplantation, baseline kidney disease, recipient time on waitlist, recipient CMV positivity, donor age, being on tacrolimus (vs. cyclosporine), induction immunosuppression, delayed graft function and HLA AB mismatch. The maximum follow-up time was 16.0 years, with a median of 5.4 years.

Among recipients with DSAs, the mean cumulative MFI was 11,563 (SD 13 886). Altogether 90 recipients had a cumulative MFI of 1,000–4,999, 46 had 5,000–9,999, and 86 had at least 10,000. Four DSA positive recipients did not have the complete MFI data available, of which three recipients had only class I DSAs with missing MFI, and one recipient had both class I and II DSAs with MFI available for class I but unavailable for class II, and these recipients were excluded from the analyses concerning missing data.

Altogether 162 recipients had class I DSAs and 119 had class II DSAs, while 55 recipients had both. Categorized into groups based on class I DSAs, 77 recipients had a cumulative MFI of 1,000–4,999, 43 had 5,000–9,999 and 40 had at least 10,000. As for class II DSAs, 48 patients had a cumulative MFI of 1,000–4,999, 25 had 5,000–9,999, and 45 had at least 10,000.

TABLE 1 Patient characteristics in recipients with and without DSAs.

Patient characteristic	DSA (n = 226)	No DSA (n = 2,983)
Recipient age, median (IQR), years	53 (21)	54 (19)
Recipient sex, male	100 (44%)	1968 (66%)
Recipient BMI, median (IQR), kg/m2	24.48 (5.8)	25.31 (6.2)
Retransplantation	120 (53%)	265 (8.9%)
Baseline kidney disease Diabetic kidney disease Glomerulonephritis Polycystic kidney disease Other	 28 (12%) 75 (33%) 36 (16%) 87 (39%)	 838 (28%) 746 (25%) 530 (18%) 869 (29%)
Recipient time on waitlist, median, years	2.2 (2.5)	0.38 (0.70)
Recipient CMV positive	181 (80%)	2,176 (74%)
Donor CMV positive	175 (79%)	2,304 (79%)
Donor age, median (IQR), years	59 (18)	56 (19)
Cold ischemia time, median (IQR), hours	19 (8.4)	19 (8.1)
On tacrolimus (vs. cyclosporine)	162 (72%)	1,254 (42%)
Induction immunosuppression (other than iv steroids) Basiliximab Anti-thymocyte globulin	67 (61%) 77 (34%) 60 (27%)	633 (21%) 397 (13%) 236 (8%)
Delayed graft function	83 (37%)	831 (28%)
Last higher PRA% (class I or II) before transplantation, median (IQR)	91 (25)	0 (8)
Last PRA% (class I and II) in total before transplantation, median (iQR)	116 (95)	0 (8)
Average maximum PRA% before transplantation, median (IQR)	71 (47)	0 (11)
HLA AB mismatch, median (IQR)	2 (1)	2 (2)
HLA DR mismatch, median (IQR)	1 (0)	1 (1)

Graft survival

DSAs were associated with worse death-censored graft survival ($p < 0.001$) in comparison to no DSAs (Figure 3). Recipients with DSAs had a 5-year DCGS of 84% and 10-year survival of 74% while recipients without DSAs had a 92% 5-year DCGS and an 83% 10-year DCGS.

Higher cumulative MFI indicated worse 5-year DCGS (no-DSA: 92%, MFI 1,000–4,999: 89%, 5,000–9,999: 81%, at least 10,000: 79%, $p < 0.001$) and 10-year graft survival (no-DSA 83%, 1,000–4,999: 76%, 5,000–9,999: 78%, at least 10,000: 66%) (Figure 4). However, there were no statistically significant differences between the groups with different cumulative MFI levels ($p = 0.441$).

The results of multivariable Cox regression analysis regarding DCGS are presented in Table 2. Recipient age, baseline kidney disease, cold ischemia time, donor age and retransplantation were independently associated with DCGS. A trend was seen in the association of categorized cumulative MFI with worse DCGS, but this association did not reach statistical significance.

Regarding class I DSAs, there was no statistically significant ($p = 0.841$) association of higher cumulative MFI indicating worse 5-year DCGS or 10-year DCGS (Figure 5). Similarly, regarding class II DSAs, there was no statistically significant ($p = 0.069$) association of higher cumulative MFI indicating worse 5-year DCGS or 10-year DCGS (Figure 6).

Acute rejections

Rejection frequencies for BPAR, AMR and TCMR are described in Table 3. Hazard ratios for BPAR and AMR are presented in supplementary material, Supplementary Table S1.

DSAs were associated with more BPAR (HR 2.0, 95% CI 1.6–2.5, $p < 0.001$), with even higher HR for acute AMR (HR 22.7, 95% CI 14.3–36.2, $p < 0.001$), as 40% of DSA positive recipients had BPARs and 26% had AMR. Comparing only the class I or class II DSA status to those without the above-mentioned DSAs, both acute overall rejections (class I 39.5% vs. class II 47.9%) and acute AMR (class I 25.9% vs. class II 34.5%) were more prevalent in recipients with class II DSAs, but the HRs were higher for class I. Comparing recipients with class I DSAs to those without them, HR for BPAR was 2.2 (95% CI 1.7–2.9, $p < 0.001$) and HR for acute AMR was 16.4 (95% CI 10.5–25.6, $p < 0.001$), while comparing recipients with class II DSAs to those without them, the HR for BPAR was 1.8 (95% CI 1.4–2.4, $p < 0.001$) and the HR for acute AMR was 13.9 (95% CI 9.0–21.4, $p < 0.001$).

Examining the cumulative effect of DSAs, both the hazard ratio of BPAR ($p < 0.001$) and acute AMR ($p < 0.001$) was increased with the increasing cumulative MFI, categorized into 1,000–4,999, 5,000–9,999 and at least 10,000. Regarding cumulative class I MFIs, the frequency of acute AMR ($p = 0.0499$) was increased with the increasing categorized cumulative MFI. There was no statistically significant difference for the frequency of BPAR, but the HR increased for every MFI limit for both BPAR and AMR. As for different categories of cumulative class II MFIs, the frequency of BPAR ($p = 0.057$) and AMR ($p < 0.001$) was decreased at the limit of 10,000, which was also seen in hazard ratios at the same limit.

The multivariable Cox regression analyses for the risk of acute rejections using the categorized cumulative total MFI are presented in Table 4. For acute rejection, statistically significant risk factors were categorized cumulative MFI, donor age, induction immunosuppression, and being on cyclosporine vs. tacrolimus recipient age, while categorized kidney disease, cold ischemia time, recipient sex, retransplantation and time on the waitlist were statistically unsignificant. Regarding acute AMR, the only statistically significant risk factors were categorized cumulative MFI and recipient age.

Sensitivity analyses

As a sensitivity analysis, all analyses were repeated for immunodominant MFIs for class I, class II and all DSAs. The results were considered similar to the primary analyses, as higher MFI for the immunodominant DSA was similarly associated with

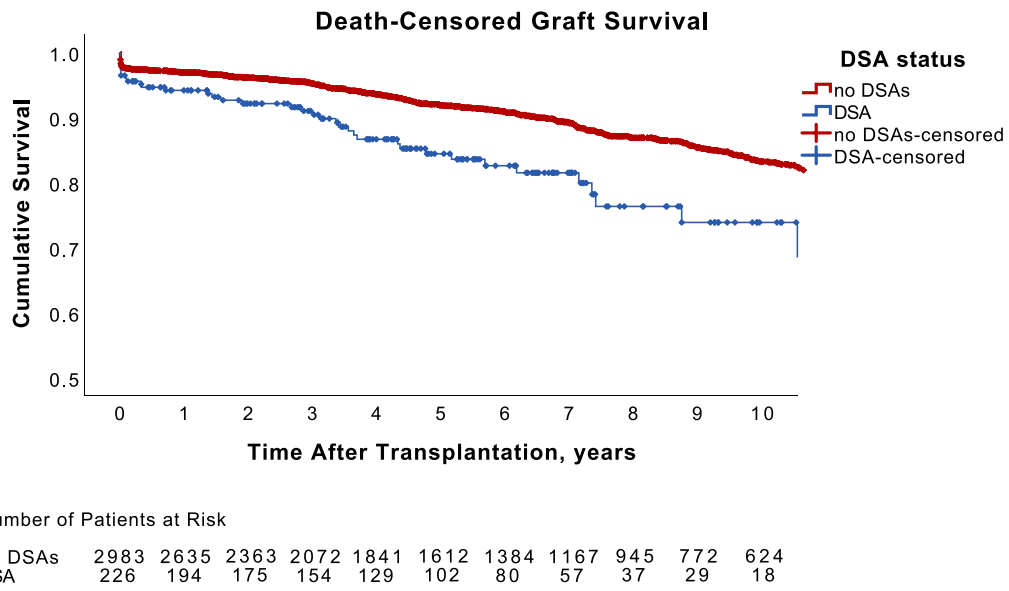


FIGURE 3
Death-censored graft survival in recipients with and without DSAs.

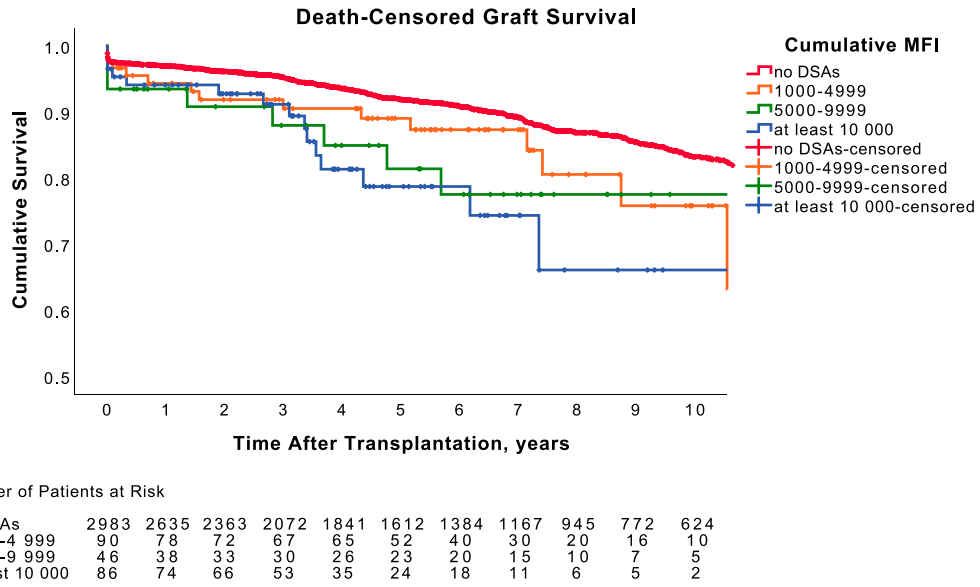


FIGURE 4
Death-censored graft survival in recipients without DSAs and with different cumulative MFI levels of DSAs.

increased risk of rejection and inferior graft survival in all analyses. The results of these sensitivity analyses are presented in supplementary material, Supplementary Tables S2, S3 and Supplementary Figures S1–S3.

Discussion

Our aim was to evaluate our national transplant center's long-term experience with HLA incompatible deceased donor transplantations. As has been described previously, DSAs were associated with worse graft survival, and especially cumulative MFI of DSAs was associated with worse prognosis. However, we were able to show that this association did not reach statistical significance in multivariable models in long-term follow-up of up to 10 years. Although our findings may be confounded by multiple known or unknown factors, this finding suggests that the independent association of donor-specific antibodies with long-term graft survival may be less prominent than has been previously described. Importantly, we were able to show that

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TABLE 2 Multivariable Cox regression analysis for DCGS.

Variable	Hazard ratio (95% CI)	p-value
Baseline kidney disease (vs. diabetic kidney disease)		0.019
Glomerulonephritis	1.050 (0.796–1.384)	0.732
Polycystic kidney disease	0.613 (0.429–0.876)	0.007
Other	0.917 (0.693–1.213)	0.543
Categorized cumulative MFI (vs. no DSAs)		0.087
1,000–4,999	1.441 (0.820–2.530)	0.204
5,000–9,999	1.722 (0.839–3.535)	0.138
At least 10,000	2.024 (1.096–3.737)	0.024
Cold ischemia time (for each 1 min increased)	1.001 (1.000–1.001)	<0.001
Donor age (for each 1 year increased)	1.025 (1.016–1.034)	<0.001
Induction immunosuppression, other than iv steroids (vs. no)	0.787 (0.569–1.087)	0.146
On cyclosporine (vs. tacrolimus)	1.235 (0.952–1.601)	0.112
Recipient age (for each 1 year increased)	0.985 (0.977–0.993)	<0.001
Recipient sex (vs. female)	0.952 (0.767–1.181)	0.655
Retransplantation (vs. no)	1.418 (1.002–2.008)	0.049
Time on the waitlist (for each 1 day increase)	1.000 (1.000–1.000)	0.334

long-term graft survival was acceptable even with the highest DSAs. For many of these highly sensitized patients, HLA compatible transplantation is not a realistic option without extensive waiting time, and the outcome of these HLAi transplantation should be compared with patients on dialysis. Furthermore, longer time on dialysis before transplantation is associated with worse survival [11], suggesting that some patients may benefit from HLA incompatible transplantation instead of waiting long periods on dialysis for an HLA compatible transplant.

Although graft survival was comparable after HLAi transplantation, the risk of acute rejection, especially antibody-mediated rejection was high, as expected. However, most of the rejections were reversible with standard treatment (iv steroids for TCMR and plasma exchange and IvIG for AMR), and only 4 grafts were lost due to irreversible antibody-mediated rejection.

There are several previous studies, which show that pre-existing DSAs are associated with worse graft survival and higher risk of AMR [12–14]. Especially higher MFI antibodies and class II antibodies have been associated with the risk of AMR [15]. In addition, persistent presence of DSA has been associated with worse outcomes [16], and especially class II DSAs seem to persist more frequently compared to class I DSAs [17]. Our findings are in line with previous studies, as also in our cohort class II DSAs seemed to be associated with even higher risk of AMR after transplantation. Regarding the intensity of DSAs, there is little previous data on recipients with as high DSA MFI levels as in our study, and the threshold limits for the analyses have been set significantly lower [13, 18]. Some studies have reported on more rejections and worse graft survival at the MFI level of 10,000 [19] or 11,000 [15], but the study samples have remained very small for crossmatch negative transplantations. In addition, in the current study follow-up times are long, even up to >10 years. Data regarding persistence of DSAs were, unfortunately, not available in our cohort.

Our novel findings of the relatively good long-term results in HLA-incompatible transplantation have several clinical implications. First, although acceptable mismatch programs (such as Scandiatransplant Acceptable Mismatch Program [1]) or paired exchange programs [2] provide the best alternative to find HLA

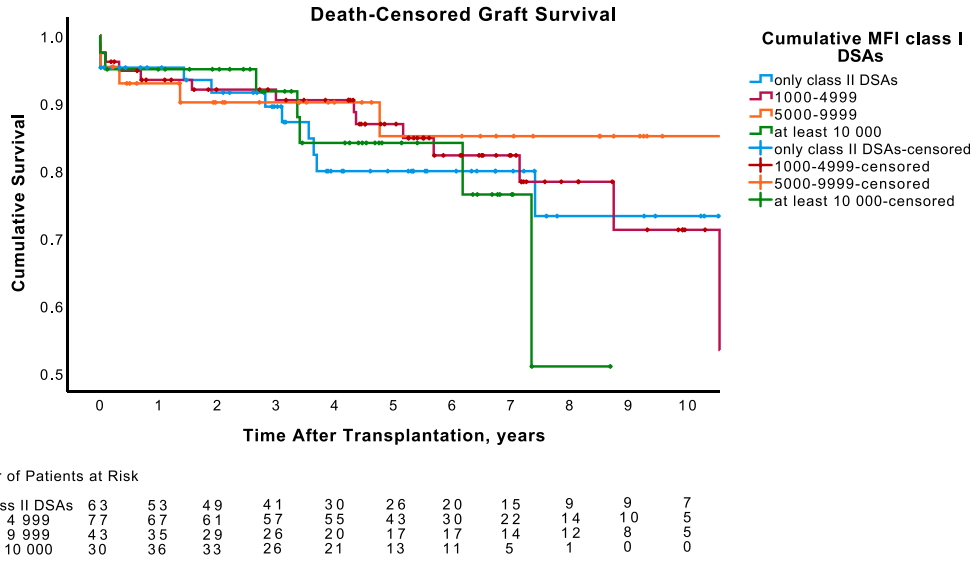

FIGURE 5
Death-censored graft survival with different cumulative MFI levels of class I DSAs.

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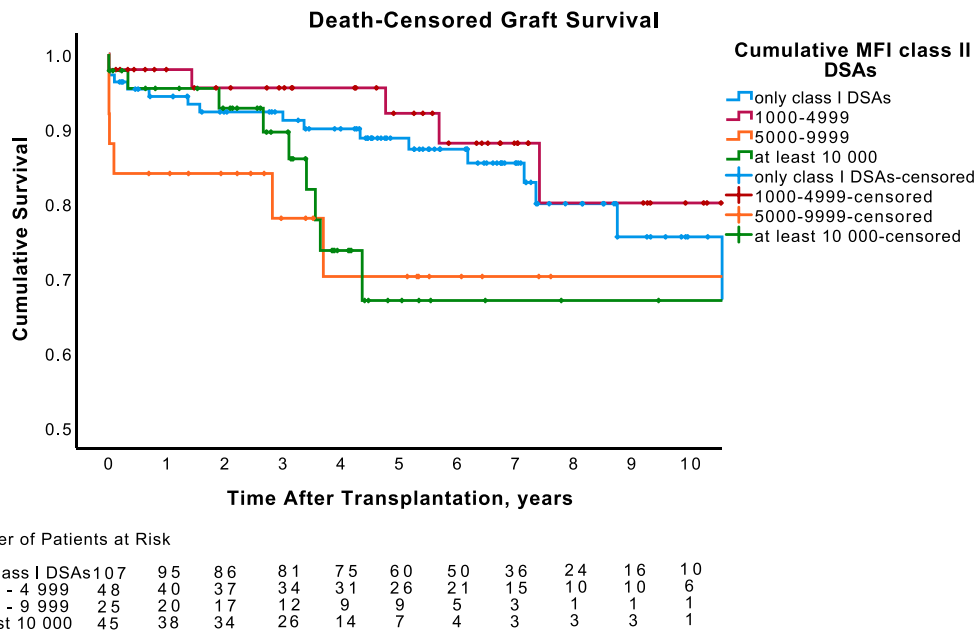

FIGURE 6
Death-censored graft survival with different cumulative MFI levels of class II DSAs.

TABLE 3 Biopsy-proven acute rejection, antibody-mediated rejection and T-cell mediated rejection frequencies within different comparison groups.

Group (n)	BPARs (%)	AMRs (%)	TCMRs (%)
No DSAs vs. DSAs			
No DSAs (2,983)	474 (16)	28 (0.94)	447 (15)
DSAs (226)	90 (40)	59 (26)	32 (14)
	p = 0.000	p = 0.000	p = 0.737
Cumulative MFI			
1,000–4,999 (90)	27 (30)	11 (12)	16 (18)
5,000–9,999 (46)	16 (35)	11 (24)	6 (13)
At least 10,000 (86)	45 (52)	35 (41)	10 (12)
	p = 0.008	p < 0.001	p = 0.488
Class I DSAs: Cumulative MFI			
no class I DSAs (63)	26 (41)	17 (27)	10 (16)
1,000–4,999 (77)	23 (30)	12 (16)	11 (14)
5,000–9,999 (43)	18 (42)	15 (35)	3 (7.0)
At least 10,000 (40)	22 (55)	14 (35)	8 (20)
	p = 0.067	p = 0.0499	p = 0.382
Class II DSAs: Cumulative MFI			
no class II DSAs (107)	33 (31)	18 (17)	15 (14)
1,000–4,999 (48)	21 (44)	10 (21)	11 (23)
5,000–9,999 (25)	14 (56)	12 (48)	3 (12)
At least 10,000 (45)	21 (47)	18 (40)	3 (6.7)
	p = 0.057	p < 0.001	p = 0.159

compatible transplantations for many patients, some very highly sensitized patients have extremely low likelihood of finding an HLA compatible transplantation. Our findings suggest that for patients unable to get timely access to HLA compatible transplantation, HLA incompatible transplantation may be an acceptable alternative compared to dialysis, depending on the individual patient status. This may be true even in patients with high-level DSAs with negative cytotoxic crossmatch. One purpose of the current study was to identify thresholds or characteristics for unacceptable DSAs, e.g., to identify the most suitable patients for desensitization treatments (such as imlifidase). However, no MFI cut-offs or specific characteristics (such as class I or class II) could be identified, as even patients with the highest DSA MFI levels had acceptable outcomes.

Our current study has some limitations. The findings are from a single center, and they cannot be directly generalized to other cohorts, as the patient characteristics, and allocation, immunosuppression and rejection treatment protocols may vary from other regions. In addition, even though the long study period of 16 years could be considered a strength of this study, it includes some changes in our own immunosuppression protocols, most importantly the increasing use of tacrolimus in comparison to cyclosporine. However, no other major changes have occurred during this time span. The graft biopsy scoring and rejection criteria have also changed in accordance with the evolution of the Banff Classification [9], which could affect the generalizability of the results.

Another limitation is that DSAs were not always known at the time of transplantation, as for some patients the pretransplant DSA status was determined only after transplantation, not prospectively. Therefore, immunosuppression has not always been modified accordingly, and as a result only 61% of the patients with DSA received induction, and only 27% received lymphocyte-depleting induction. However, our findings suggest that graft survival with

TABLE 4 Results of multivariable Cox analysis regarding BPARs and AMRs.

Variable	BPARs, hazard ratio (95% CI)	BPARs, p-value	AMRs, hazard ratio (95% CI)	AMRs, p-value
Categorized cumulative MFI (vs. no DSAs)		<0.001		<0.001
1,000–4,999	1.943 (1.288–2.929)	0.002	9.342 (4.325–20.178)	<0.001
5,000–9,999	2.311 (1.352–3.951)	0.002	15.769 (6.865–36.218)	<0.001
At least 10,000	4.505 (3.041–6.674)	<0.001	35.884 (16.723–77.001)	<0.001
Categorized kidney disease (vs. diabetic kidney disease)	0.892 (0.704–1.129)	0.217 0.341	1.512 (0.693–3.299)	0.430 0.299
Glomerulonephritis	0.748 (0.565–0.989)	0.042	1.422 (0.574–3.521)	0.447
Polycystic kidney disease	0.944 (0.756–1.177)	0.607	1.848 (0.869–3.932)	0.111
Other				
Cold ischemia time (for each 1 min increased)	1.000 (1.000–1.000)	0.953	1.000 (1.000–1.001)	0.349
Donor age (for each 1 year increased)	1.022 (1.014–1.029)	<0.001	1.017 (1.000–1.035)	0.056
Induction immunosuppression, other than iv steroids (vs. no)	0.771 (0.618–0.962)	0.021	1.443 (0.852–2.441)	0.172
On cyclosporine (vs. tacrolimus)	0.603 (0.499–0.729)	<0.001	0.618 (0.360–1.061)	0.081
Recipient age (for each 1 year increased)	0.981 (0.974–0.988)	<0.001	0.972 (0.956–0.989)	0.001
Recipient sex (v. female)	1.186 (0.991–1.419)	0.063	0.994 (0.633–1.562)	0.980
Retransplantation (v. no)	0.953 (0.723–1.255)	0.730	0.922 (0.501–1.695)	0.793
Time on the waitlist (for each 1 day increased)	1.000 (1.000–1.000)	0.168	1.000 (1.000–1.001)	0.065

DSAs is acceptable even without heavy lymphocyte-depleting induction therapy, which increases the risk for leukopenia, infections, and malignancies after transplantation. Flow cytometry crossmatch is not in routine use in our country, so no data regarding the flow cytometry crossmatch results for the study cohort were available. Another limitation is the retrospective nature of this study, and causality cannot be concluded. On the other hand, a strength of our study is the large uniform cohort with long-term follow-up, including patients with very high levels of DSA at the time of transplantation, showing the natural course and good outcomes up to 10 years after transplantation.

In multivariable models, statistical significance was not always achieved, which could be related to limited statistical power or residual confounding. It is also debatable how strongly pre-transplant DSAs and acute rejections relate to long-term graft survival, although our results illustrate a consistent trend of the association. The ultimate decision-making of HLA incompatible transplantations with high-level DSAs should, however, be based on individual risk and benefit assessment.

Conclusion

In conclusion, although pretransplant DSA and higher cumulative MFI of DSA were associated with worse kidney graft survival, the association did not remain significant in all models after adjustment with confounding factors. Long-term graft survival among patients even with high-level pretransplant DSAs could be considered acceptable in comparison to prolonged dialysis treatment, and these transplantations could be considered for highly sensitized patients as the last option, especially when desensitization is unavailable or contraindicated. DSAs, however, especially class II DSAs are associated with a high risk of antibody-mediated rejection, which should be taken into consideration when balancing risks and benefits of HLA incompatible transplantation.

Data availability statement

The datasets presented in this article are not readily available because According to Finnish law, sharing individual-level data outside the research personnel is prohibited (Act on Secondary Use of Health and Social Data, 2019). Requests to access the datasets should be directed to ilkka.helantera@helsinki.fi.

Ethics statement

The requirement of ethical approval was waived by Helsinki University Hospital Abdominal Center Review Board for the studies involving humans because According to Finnish law, ethical committee approval is not needed for studies using only registry and electronic medical records data (Act on Secondary Use of Health and Social Data, 2019). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board also waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because According to Finnish law, written informed consent is not needed for studies using only

registry and electronic medical records data (Act on Secondary Use of Health and Social Data, 2019).

Author contributions

Concept and design: JL, IH, and VS; Data collection and analyses: MK, JL, and IH; manuscript preparation: MK and IH; registry data: ML, KA, and IH; funding: IH and VS. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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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.2026.16478/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Death-censored graft survival in recipients without DSAs and with different immunodominant MFI levels of DSAs, $p < 0.001$.

SUPPLEMENTARY FIGURE S2
Death-censored graft survival with different immunodominant MFI levels of class I DSAs.

SUPPLEMENTARY FIGURE S3
Death-censored graft survival with different immunodominant MFI levels of class II DSAs.

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Landscape of current practices and future perspectives in living donor kidney donation in Europe: proceedings of a pan-European symposium by the European kidney transplant association section of the European Society for Organ Transplantation

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Living donor kidney transplantation (LDKT) offers superior outcomes for most patients with end-stage kidney disease (ESKD), yet its uptake across Europe remains highly variable. This proceedings article summarizes key themes from a pan-European symposium held in November 2025 in Prague, organized by the European Kidney Transplant Association (EKITA) in collaboration with the DESCaRTES Working Group. Discussions highlighted substantial heterogeneity in LDKT activity across Europe, driven by differences in healthcare capacity, legal frameworks, donor evaluation practices, and access to kidney exchange programmes. Marked inequities persist between regions, particularly in the Balkans and Western Balkans, for women those who are socioeconomically disadvantaged, ethnic minority populations, paediatric and elderly patients and individuals with obesity. The symposium identified wide variation in donor selection criteria, risk assessment, informed consent practices, and long-term donor follow-up, despite existing international guidelines. Emerging strategies to address these challenges include harmonisation of donor evaluation and consent, expansion of paired and cross-border kidney exchange programmes, increased use of unspecified kidney donation, and adoption of innovative surgical and immunological approaches to safely broaden donor eligibility. Advances in outcome measurement, including validated surrogate endpoints, machine learning methods, and integrated, harmonised transplant registries, were discussed as critical tools to improve quality, transparency, and research efficiency. Collectively, the proceedings underscore the need for coordinated

clinical, policy, and data-driven solutions to reduce inequities and unlock the full potential of LDKT across Europe, with implications for international transplant practice.

KEYWORDS

cross-border organ exchange, donor evaluation and safety, equity in transplantation, living donor kidney transplantation, transplant registry harmonisation

Introduction

Living donor kidney transplantation (LDKT) provides the best outcomes for most patients with end-stage kidney disease (ESKD), particularly when performed pre-emptively before dialysis initiation [1, 2], yet its uptake across Europe remains highly variable. Differences in clinical practice, legal frameworks, donor evaluation, and access to kidney exchange continue to drive inequities in LDKT across Europe. Reflecting the need for coordinated European action, EKITA has identified promotion of LDKT as a strategic priority for 2026–2027. This proceedings article summarizes key themes from a pan-European symposium held in Prague in November 2025, organized by EKITA and the DESCaRTES Working Group, highlighting current practice, unmet needs, and future strategies to improve equitable access to LDKT in Europe.

Variation in living donation across Europe

Across the continent, LDKT activity remains unevenly distributed. The overall living donor transplant rate is approximately 13 per million population (pmp), compared with ~27 pmp for deceased donor transplantation, with extremes ranging from negligible to non-existent activity in some countries such as Moldova, Slovenia and Serbia with ~0 pmp rates, to ~39 pmp in Turkey. Countries such as the Netherlands and parts of Scandinavia demonstrate high LDKT activity, supported by mature national and kidney exchange programs, whereas many Western, Central, and Southern European countries, including Poland, France, Italy, and much of Central Europe, exhibit comparatively lower rates. In Central Europe, 2024 LDKT rates ranged from 0.95 pmp in Slovenia and 2.18 pmp in Poland to 7.59 pmp in Germany, despite well-developed transplant infrastructures (Figure 1) [3].

Disparities are even more pronounced in the Balkans and Western Balkans, where living donation often compensates for underdeveloped deceased donor programs. Living donation rates range from 0.3 to 0.5 pmp in Bulgaria to 2.8–2.9 pmp in Romania, with Greece representing a regional outlier at approximately 10 pmp. In the Western Balkans, Albania (~9.3 pmp), Bosnia and Herzegovina (~9.7 pmp), and North Macedonia (~9 pmp) rely predominantly on living donation, whereas Serbia demonstrates critically low activity and Kosovo lacks a domestic transplant program. Overall, fewer than 25% of patients with ESKD in the Western Balkans receive a kidney transplant, compared with ~40% across the European Union, highlighting persistent inequities driven by healthcare capacity, cultural factors, and limited regional integration.

Analysis of European practices in living kidney donor evaluation

Thorough assessment of living kidney donors is essential to ensure donor safety. Despite the availability of multiple national and international guidelines for living donor evaluation [4–6], substantial variation in clinical practice persists across Europe. In the first Europe-wide survey conducted by the DESCaRTES and EKITA working groups (124 centers in 16 countries, representing ~45% of European centers and ~3,700 living kidney donations annually), marked heterogeneity was observed in donor evaluation and follow-up practices (Table 1) [7]. Low-consensus areas included kidney function assessment, nephrolithiasis, albuminuria, microscopic haematuria, and BMI thresholds, highlighting the need for harmonised donor assessment criteria across Europe (Table 1). Practice variation reflects not only differences between countries but also centre-level policies and organisation. For example, a recent UK survey demonstrated marked variation in donor acceptance criteria, evaluation timelines, and follow-up practices despite a shared healthcare system and excellent outcomes [8].

Equally important is protecting potential donors from prolonged evaluation processes and avoiding unnecessary investigations, especially those which are invasive. Unnecessarily prolonged processes can lead to frustration, psychological burden and increase withdrawal rates from donation [9–12]. From the recipient perspective, delays reduce the opportunity to perform transplantation pre-emptively, thereby exposing recipients to dialysis-related morbidity and potentially diminishing the clinical benefits associated with timely LKDT [1, 2]. Incidental findings during the evaluation process, particularly on imaging, are common (reported prevalence range from 6%–75%) [13–15] but most are benign and clinically insignificant, with transmitted donor-derived malignancies being exceedingly rare [16]. Common incidental findings include renal cysts, angiomyolipomas, nephrolithiasis, and microscopic haematuria, for which guideline recommendations are often ungraded due to limited evidence.

Finally, the role of genetic testing in CKD and consequently in living donor evaluation is rapidly evolving. Genetic testing identifies a monogenic cause in ~10% of adults with CKD and up to 40%–60% in selected groups, often changing diagnosis and management [17, 18]. Targeted genetic testing is most informative in biologically related donors and those with early-onset or unexplained CKD, extrarenal features, or high-risk ancestry (e.g., APOL1). When combined with counseling, it improves risk stratification and donor safety, although challenges remain due to limited guidance, variable expertise, uncertain variant interpretation, access to counseling, and cost.

Over the last decade, living donor selection in several European countries has gradually shifted from fixed exclusion criteria toward more individualised, risk-based assessment. This is now reflected in contemporary guidelines [5] but the impact of these changes is difficult to assess at a European level because donor selection policies, data collection, and follow-up practices remain heterogeneous. Nonetheless, the total number of living donor kidney transplants performed in Europe has increased, exceeding

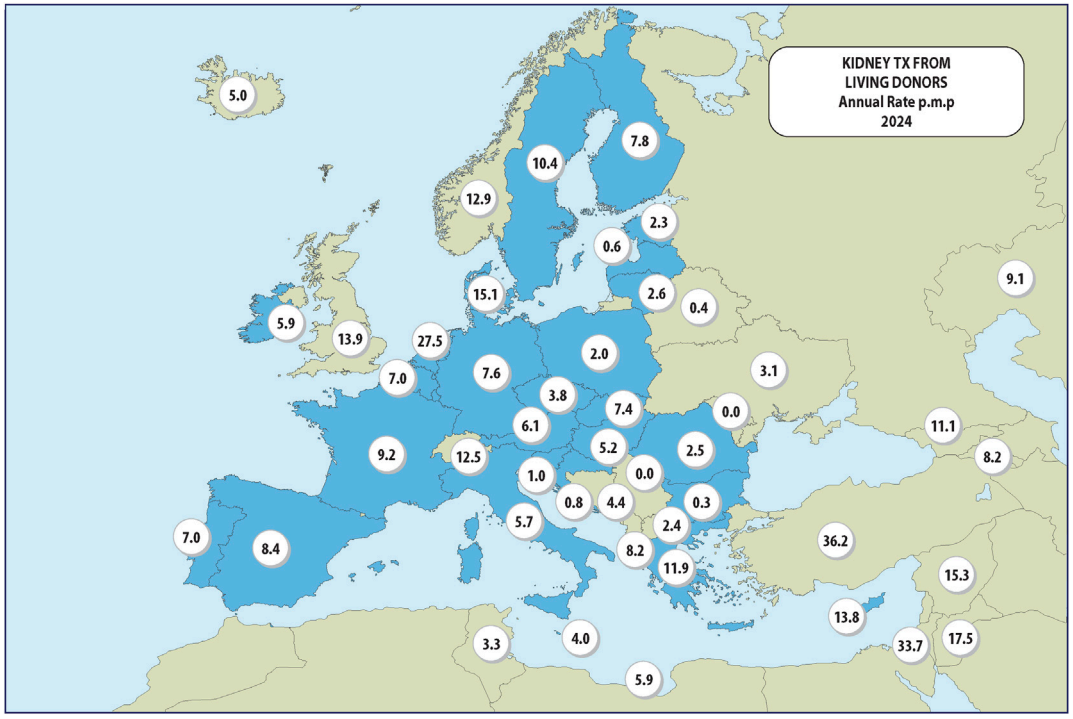

FIGURE 1
Living donor kidney transplantation rates (per million population) across Europe in 2024. Source: European Directorate for the Quality of Medicines & HealthCare (EDQM). Newsletter Transplant 2025 (from reference 1).

7,000 procedures across Council of Europe countries in 2024, compared with the mid-2010s when annual numbers were generally reported at around 5000–6000 LDKT [3].

Donor safety, ethics and outcomes

Ethical dilemmas between potential donors and transplant teams remain common. KDIGO guidelines recommend frameworks to protect donors while recognising that being declined, particularly when labelled "marginal," may undermine autonomy and cause distress [4, 19–21]. In keeping with contemporary terminology, such candidates are better described as potential donors with expanded criteria. However, respect for donor autonomy does not override the responsibility of transplant teams to prioritise donor safety and clinical judgement.

Autonomous informed consent requires ensuring donor understanding and freedom from coercion. Transplant programmes should clearly define and communicate how decisions are made and offer second opinions to minimise paternalism [21–25]. A systematic review of informed consent in living kidney donation demonstrated substantial variation across transplant centres and highlighted the need for a standardized yet flexible approach to ensure equitable donor education and decision-making [26]. To address this gap, the DESCaRTES Working Group proposed a 3-Step Model for informed consent in living kidney donation [27], adapted from the Three-Talk Model of shared decision-making [28]. This framework defines consent as a longitudinal process-team, option, and decision talk-standardizing timing and risk communication while allowing individualization based on donor values and understanding (Figure 2).

Living donor evaluation also poses challenges in the interpretation and communication of long-term risk, particularly for the risk of ESKD [29]. Landmark cohort studies by Mjøen et al. and Muzaale et al. demonstrated that, while living kidney donors have a higher relative risk of ESKD compared with healthy controls, the absolute risk remains low (~0.5% and 0.31% at ~15 years) [30, 31]. These findings were reinforced by a recent meta-analysis estimating an absolute risk of ESKD of approximately 0.5 cases per 1,000 donor-years. Therefore the attributable risk, which is the excess risk that may be associated with donation itself, remains very small in absolute terms [32]. Interpreting these data requires careful consideration of study design, comparator selection, duration of follow-up, and the extent to which study populations reflect the characteristics of contemporary donor candidates in individual transplant programmes. Healthcare professionals should therefore understand the distinction between relative, absolute, and attributable risk and communicate these concepts clearly to potential donors and recipients, so that risk is interpreted in an accurate and clinically meaningful context.

The high cardiovascular mortality associated with dialysis is well recognised and closely related to the duration of ESKD, with kidney transplantation representing the most effective strategy to reduce this risk [33]. Concerns remain regarding the long-term cardiovascular effects of living kidney donation; however, unlike other unilaterally nephrectomised, often comorbid individuals, living kidney donors generally retain adequate renal functional

TABLE 1 Summary table of key findings Living Kidney Donation Practices in Europe: A Survey of DESCaRTES and EKITA Transplantation Working Groups (ref).

Domain	Key finding	Interpretation/Consensus
Survey scope	125 respondents from 124 transplant centers in 16 European countries, representing ~45% of European transplant centers and ~3,700 living donor transplants annually	
Kidney function assessment	56% use eGFR (CKD-EPI); 34% use 24-h creatinine clearance; 41% use combined cystatin c and creatinine; 70% use measured GFR (mGFR)	Low consensus/Substantial heterogeneity
GFR thresholds	64% use age-dependent GFR thresholds; 26% of fixed-threshold centers use 80 mL/min/1.73 m^2	Most centers individualize thresholds according to donor age
Age criteria	63% have no upper age limit; 53% use 18 years as the lower age limit	Age alone is not considered an absolute contraindication
BMI cut-offs	BMI ≥30 kg/m^2 used by 39%; BMI ≥35 kg/m^2 by 42%	Obesity management varies considerably across centers
Weight-loss support	74% offer weight-loss interventions, mainly dietary support (67%), endocrinological evaluation/medications 23% and bariatric surgery 11%	Most centers attempt optimization before excluding overweight donors
Diabetes screening	Exclusion thresholds include HbA1c ≥ 53 mmol/mol (46%), fasting glucose ≥7 mmol/L (57%), or OGTT glucose ≥11.1 mmol/L (59%)	Strong consensus on excluding overt diabetes
Hypertension	91% exclude uncontrolled hypertension/end-organ damage; 78% exclude candidates using ≥3 antihypertensives	High consensus regarding hypertension-related exclusions
Albuminuria/ Proteinuria	Only 38% assess both spot and 24-h urine	Marked variability in testing strategies and thresholds
Microscopic hematuria	57% accept donors if both urological evaluation and kidney biopsy are normal	Donation often permitted after negative work-up
ApoL1 testing	27% routinely test donors of African ancestry	ApoL1 testing is not standard practice in most European centers
Nephrolithiasis	Most centers accept low-risk stone history; only 2% reject any history of stones	Stone history is acceptable when recurrence risk is low
Risk calculators	54% do not use online ESKD risk calculators	Clinical judgment remains the primary assessment tool
Informed consent	95% obtain written consent for donation; 65% for data registration	Donation consent is nearly universal
Follow-up duration	83% offer lifelong follow-up, usually annually	Long-term donor surveillance is strongly supported
Follow-up components	Includes blood pressure (98%), eGFR (94%), spot urine (75%), medication review (70%)	Focuses on kidney function and cardiovascular risk

reserve capacity to support compensatory hyperfiltration [29, 34]. Long-term studies suggest that eGFR trajectories remain stable or improve over time after donation [35], and that eGFR<50 mL/min/1.72m2 is uncommon [36]. Although donors have a higher incidence of hypertension and diabetes, most studies have not demonstrated increased overall mortality or major cardiovascular events [37–42]. A Norwegian cohort reported higher long-term mortality and cardiovascular risk factors, but these findings should be interpreted cautiously given the ethnically homogeneous population, absence of smoking data, and historical donor selection and management practices [30, 43]. Overall, these findings highlight the importance of long-term follow-up, cardiovascular risk reduction, and healthy lifestyle measures after donation.

Women with CKD are at risk of adverse pregnancy outcomes. In living kidney donors, a systematic review found that the risk of preeclampsia increased from 1% to 4%; however, despite the relative increase, the absolute risk remains low and comparable to that of the general obstetric population, with higher BMI and pre-existing hypertension increasing risk [44]. Importantly, there is limited evidence of increased adverse fetal or neonatal outcomes, and post-donation pregnancy has not been associated with accelerated decline in kidney function compared with pre-donation pregnancy. Women who develop gestational hypertension or pre-eclampsia after donation are at increased risk of future hypertension and should receive long-term follow-up [45, 46]. This represents an important opportunity for the transplant community to lead through accurate, evidence-based risk communication. Pregnancy-related risks should be interpreted in the context of study design and individual donor characteristics, with clear distinction between relative and absolute risk. Improved professional education and collaboration with obstetric specialists are essential to ensure balanced counselling and to avoid unnecessarily discouraging suitable women from living kidney donation.

Research on motivations for living kidney donation has identified themes including altruism, family dynamics, and perceived personal benefit [47, 48]. These findings support structured psychosocial screening to identify potential donors who may require additional support, particularly those with limited social support, financial stress, or major caregiving

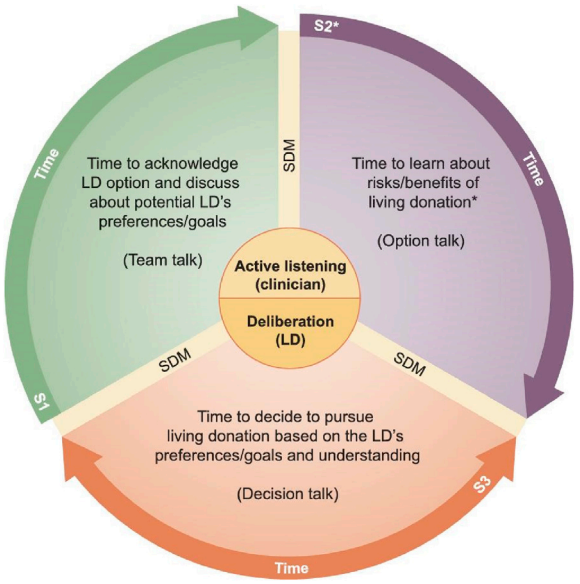

FIGURE 2
Shared decision-making should start with the primary nephrologist prior to the need for kidney replacement therapy or at the local dialysis unit (S1), and, at the transplant center, with transplant clinicians and surgeons throughout the process of evaluation (S2) and prior to nephrectomy (S3). *S2 should not be intended as a single educational session but as a combination of two or more sessions (depending on the LD's health literacy, intellectual capacity, need for information and/or additional clarification) combining the use of various decision aids to improve understanding. S, step; SDM, shared decision-making (reproduced from reference 9, under CC BY 4.0).

responsibilities. Donors reporting poorer outcomes often described inadequate pre-donation information, highlighting the importance of thorough informed consent, appropriate reassurance and ongoing psychological follow-up [49–52].

Reducing inequalities

The UK ATTOM study recruited 2055 patients from all 23 transplant centres in the UK and demonstrated that recipients of living donor kidney transplantation were more likely to be young, white, married, and socioeconomically advantaged, with no sex difference in access [53]. Moreover, broader evidence indicates that women are more likely to donate but less likely to receive living donor transplants, particularly in spousal settings independently of HLA factors [54, 55]. Marked ethnic disparities persist, with non-white patients substantially underrepresented among LDKT recipients in both adult and paediatric populations [56–58]. Older patients may be less likely to be referred because of perceived frailty or assumptions regarding limited benefit, while individuals with obesity may face additional barriers related to eligibility criteria and surgical concerns [1, 59–61].

Barriers to LDKT include cultural, geographic, educational, and financial factors, with ethnic minority patients facing additional challenges such as overseas donors, language barriers, and reported discrimination. Improving access requires culturally competent care, including translation services and peer support within transplant programmes [62–64].

Access to LDKT is reduced among less well-educated patients and is closely linked to lower health literacy. Many patient information leaflets and consent documents exceed the average reading age of 11 years [65]. Improving communication, understanding patient perspectives, and using peer educators from diverse communities may help improve engagement and access to living donation. Financial barriers play an important role and may contribute to sex disparities in living donation, as loss of income may disproportionately affect men in some households. Effective reimbursement policies for living donors are therefore essential and economically justified given the long-term cost savings of transplantation over dialysis.

Against this backdrop of inequality, system-level innovations offer opportunities to improve access. Kidney exchange programmes are among the most effective strategies, enabling incompatible donor-recipient pairs to swap donors with other pairs. In Europe, these programmes are typically coordinated by national transplant organisations with multidisciplinary teams responsible for donor-recipient matching, immunological assessment, registry management, logistics, and regulatory oversight. Building on the 2023 Global Convergence in Transplantation recommendation to expand paired donor exchange, the EURO-KEP program was developed, aiming to support national programmes by harmonising eligibility criteria, matching algorithms, and governance frameworks with the goal to establish a pan-European kidney exchange network under common rules [66]. A European exchange programme is considered feasible through stepwise harmonisation of clinical protocols, legal frameworks, interoperable registries, and pilot cross-border collaborations. By enlarging the donor pool, it could improve access for highly sensitised patients and recipients with uncommon blood groups, thereby reducing inequities in LDKT across Europe.

An additional strategy to increase living donation, adopted particularly in the UK and the Netherlands, is unspecified kidney donation to a stranger [67, 68]. Since legalisation in 2006, over 1,000 such transplants have been performed in the UK, with 83 unspecified donors enabling 119 living donor kidney transplants in 2022/23, accounting for 13% of UK living donor transplant activity [69]. Unspecified donation requires careful psychosocial and ethical assessment, robust informed consent, and appropriate management of donor expectations. The BOUnD study showed outcomes comparable to specified donors, without higher rates of withdrawal, regret, or healthcare costs, and estimated that a 10% increase in unspecified donation could save at least £5 million nationally [70]. Long-term Dutch experience has also demonstrated high donor satisfaction [68]. Wider implementation requires experienced multidisciplinary teams, consistent protocols, and greater public and professional awareness [71]. In highly selected cases, unspecified donation has also been performed by individuals with serious life-limiting illnesses or benign renal conditions requiring nephrectomy, illustrating additional opportunities to expand living donation safely and ethically [72, 73].

Highlighting equity in pediatric transplantation is essential. Paediatric access to transplantation in Europe is limited by capacity, variability, and legislation. Addressing these issues requires local initiatives, advocacy, and consideration of broader

factors [74]. Care models vary across regions, with differences in demand, surgeon availability, and reliance on mobile or virtual teams. Avoiding ongoing inequity for future generations remains a priority.

Surgical influences

Minimally invasive surgery can increase donor willingness not only by offering better cosmetic results and quick recovery, but also by increasing safety after donor nephrectomy. Effective surgeon–donor communication and comprehensive informed consent, including clear explanations of risks (e.g., the low mortality rate (<0.01% in the USA, 0.03% in meta-analysis), morbidity 2.3% (intra-op), 7.3% (post-op)) and available surgical options, are essential for improving transplant quality [75, 76]. Most centers still perform hand-assisted laparoscopic donor nephrectomy (57.4%), followed by laparoscopic donor nephrectomy (40.8%) [77]. Retroperitoneal access is underutilized, even though it avoids contact with intra-abdominal organs and colonic mobilization, which can prevent mesenteric or intra-abdominal organ injuries during surgery, as well as adhesions that can cause intestinal obstruction and possible infertility in the long term [78, 79]. Even though several publications show no significant difference between minimally invasive donor nephrectomy surgical techniques, others focus on the benefit of retroperitoneal access in avoiding intra-abdominal complications [80, 81]. Tailored surgical techniques for nephrectomy can reduce barriers and increase safety and satisfaction while expanding donor eligibility for living-donor kidney transplantation. Some examples are: Hand-assisted surgery to increase safety for donors who are obese or have challenging anatomical variations, while donors with low BMI may benefit from a pure laparoscopic or robotic approach. Vaginal extraction of the kidney or single-port techniques can improve cosmesis [82–85]. Retroperitoneal access can be a good alternative to prevent intestinal adhesions for donors with previous abdominal surgery or gastrointestinal motility complaints. Surgeons can be reluctant to perform a right donor nephrectomy because of technical challenges [86]. Hand-assisted retroperitoneal access may also allow more liberal use of the right kidney due to technical advantages, thereby improving donor safety by always preserving the better kidney [78, 87]. Robotic assistance, offering superior precision and ergonomics, may offer benefits over laparoscopy in nephrectomies involving right-sided or complex vasculature donors [88, 89]. The major indication for kidney transplantation with robotic assistance is improved short- and long-term patient and graft survival by decreased wound complications [90]. Avoiding lower abdominal incisions and improved wound outcome is offering a chance for a kidney transplantation without having to first achieve weight loss and therefore, reducing dropout secondary to dialysis-related morbidity and mortality [91, 92]. Robotic approaches are also focused on offering lower analgesic requirements and a shorter learning curve compared to laparoscopic techniques. Enhanced Recovery After Surgery (ERAS) protocols for kidney transplant donors and recipients are also offering important contributions to daily practice. ERAS protocols in kidney transplantation enable optimizing pain control with minimal opioids and promote early mobilization, which have also contributed to faster recovery and increased satisfaction. ERAS offers similar readmission rates, morbidity, and mortality while reducing length of stay, post-operative complications, and postoperative pain [93–95].

Transplanting incompatible pairs

National opportunities for living donor kidney transplantation for ABO incompatible pairs and highly HLA sensitized patients in Europe differ greatly. Mainly due to a variable access to exchange programs or desensitization strategies.

Although not available everywhere, ABO-incompatible transplantation is widely practiced, with rituximab and antigen-specific immunoadsorption protocols yielding outcomes comparable to ABO-compatible transplants, though infectious complications and higher rejection rates remain concerns [96].

The European Guideline for the Management of sensitized kidney transplant patients proposes a clear approach to a highly sensitized patient [97]. Kidney exchange programs play an important role in this plan.

Successful living donor exchange programs exist on national levels including in the United Kingdom, the Netherlands, South Alliance and Scandiatransplant [98]. In the United Kingdom Living Donor Kidney Sharing Scheme (UKLDKSS) > 70% of the recipients are transplanted making up 23% of the total living donor program. The large number of participants (>250 per run), the inclusion of non-directed altruistic donors (NDAD) and compatible pairs, and allowing ABO incompatible transplants, are, amongst others, contributing to its success. Recent data from the Dutch national kidney exchange programme further support this approach, demonstrating that long-term graft survival after kidney exchange is equivalent to that of direct living donor transplantation, with similar 10-year death-censored graft survival (91.6% vs. 91.9%) [99]. In addition donors participating in KEPs, have similar physical and mental health-related quality of life (HRQoL) outcomes to donors donating directly [100]. These findings support broader adoption of kidney exchange programmes and international collaboration.

Unfortunately, a group of very highly sensitized patients will most probably never receive a graft via these programs and will not be suitable for desensitization strategies. Imlifidase is not available in living donor transplantation. Deceased-donor allocation in acceptable mismatch programs, could offer a solution to these patients yielding long-term graft survival rates comparable to non-sensitized recipients [101], but compromised when compared to LDKT.

Focus on expanding LDKT national exchange programs with more compatible pairs, promoting the participation of NDAD, allowing for ABOi transplantation and by international collaborations (i.e., EURO-KEP), will result in a larger donor pool and a higher chance for the highly sensitized patients to be transplanted in the future [102].

An innovative national strategy in Italy uses deceased-donor initiated chains to overcome immunological incompatibility in living donor kidney transplantation, whereby a deceased-donor kidney enables transplantation for an incompatible pair and triggers a chain of living donor transplants [101]. Early experience demonstrates that, with appropriate ethical oversight and algorithm-based allocation, this approach substantially

increases transplant rates among incompatible pairs, reduces waiting times, and improves the efficiency of paired exchange programmes while benefiting waitlisted patients through high-quality chain-ending grafts.

In summary, the integration of risk stratification, advanced antibody testing, individualized allocation strategies and successful and innovative exchange programs are essential to optimize outcomes for HLA and ABO incompatible LDKT pairs across Europe.

Measuring outcomes in kidney transplantation: New challenges and priorities

The heterogeneous outcomes reported in organ transplant studies prevent comparisons of results across studies and transplant programmes, analysis of international registers and data synthesis in meta-analyses. An increasingly attractive solution that can improve outcome reporting is to use a 'core outcome set' (COS), which is an agreed minimum set of outcomes that have to be measured and reported in all studies of a given disease. For example, the Standardized Outcomes in Nephrology-Kidney Transplantation (SONG-Tx) initiative has established a consensus-based COS in kidney transplantation based on the shared priorities of all stakeholders [103, 104].

In the setting of improving short-term transplant outcomes and declining early graft failure, validated surrogate endpoints are increasingly important to evaluate optimization strategies and inform timely clinical and research decisions. The iBox (integrative box) score [105], which combines functional, immunological, and histological parameters to estimate individualized risk of long-term graft loss, has been qualified by the European Medicines Agency as a secondary endpoint for kidney transplant trials and is undergoing further evaluation in a European randomized controlled study [106]. By enabling early assessment of treatment effects and risk stratification, iBox supports personalized post-transplant care and enhances the efficiency of clinical trials [107], with parallel recognition through the FDA biomarker qualification pathway.

A meta-analysis of studies which used machine learning (ML) models in the prediction of kidney graft survival showed that ML-based models had a significantly higher performance than traditional statistical models [107]. ML methods are able to predict delayed graft function using donor maintenance-related variables [108], graft rejection [109] or the development of *de novo* donor-specific antibodies [110]. An unsupervised learning method integrating clinical, immune, and outcome variables revealed five transplant glomerulopathy associated with distinct causes and allograft survival profiles [111]. ML models in transplantation are limited by data quality, representativeness, interpretability, and overfitting, necessitating high-quality datasets, rigorous external validation, fair evaluation across populations, and further consensus to identify the most reliable and generalizable approaches for clinical use.

Europe hosts multiple national and international transplantation registries, and recent initiatives highlight the need for harmonised, high-quality data collection to support robust clinical and epidemiological research. The EDITH project and Council of Europe recommendations advocate for standardized, prospective datasets across all solid organ transplants, leveraging existing electronic systems to improve data completeness, comparability, and analytical value [112, 113]. The European Health Data Space Regulation, effective from March 2025, provides a major opportunity to enable secure, interoperable, and cross-border data sharing while ensuring data protection and patient control. Complementary initiatives, such as the BRAVEST project [114], further underscore the importance of resilient and coordinated data infrastructures. Established systems like Eurotransplant and Scandiatransplant demonstrate how harmonised, interoperable registries can enhance allocation transparency, cross-border collaboration, and ultimately transplant outcomes across Europe.

Strategies to improve living donation through education and advocacy

From the donor perspective, emotional and psychological barriers often outweigh medical concerns in living donation, including guilt, fear of harm, financial worries, limited knowledge or social networks, and cultural or religious factors. Targeted support and improved education empower patients to engage proactively with potential donors and participate confidently in shared decision-making. Patient organizations help by providing education, support, advocacy, and a sense of community. Established in 2019, the ESOT-ETPO Alliance brings together healthcare professionals and transplant recipients. The ESOT Patient Inclusion Initiative promotes partnership and empowerment to improve knowledge and advocate for patient-centered care [115].

Raising public awareness, building trust among stakeholders, promoting equitable access, removing financial barriers, and encouraging policy changes to improve donation rates, quality, and outcomes for patients and donors drive advocacy initiatives. The European Kidney Health Alliance (EKHA) is a strategic alliance of European non-profit organizations, including patient groups, nephrologists, researchers, and allied health professionals. Its mission is to influence EU health strategies and advocate for harmonized standards of care across Europe [116]. In December 2024, the European Council released conclusions on enhancing organ donation and transplantation, inviting the European Commission to continue work under the proposed action plan to increase donor organ availability and coordinate, promote, and strengthen cooperation between Member States [117]. EKHA and ESOT are working together to achieve this call to action.

Raising awareness about living donor kidney transplantation can be effectively achieved through home outreach programs, like REACH Transplant in the UK [118] and the KRT program in the Netherlands [119]. These initiatives address attendees' understanding of CKD, facilitate open discussion, support advocacy, and provide signposting to appropriate resources. Data from the Scottish Renal Registry illustrates significant socio-economic disparities in access to pre-emptive transplantation, with the most deprived patients markedly less likely to receive such interventions compared to their more affluent counterparts.

TABLE 2 Key recommendations, implementation priorities, and future research directions.

Key recommendations	
Domain	**Recommendations**
A. Harmonise donor evaluation and informed consent	• Develop common minimum standards for donor assessment, risk communication, informed consent, and follow-up • Standardise written information materials and consent processes while allowing individualised donor-recipient decision-making
B. Strengthen donor protection	• Protect donors from unnecessarily prolonged evaluation processes and investigations, particularly invasive, with efficient, timely and well-coordinated assessments • Ensure long-term medical and psychosocial follow-up for all living donors • Prevent financial disadvantage by reimbursing travel, accommodation, childcare, loss of income, and post-donation healthcare costs • Adopt minimally invasive, donor-tailored surgical approaches and enhanced recovery after surgery (ERAS) protocols to improve donor safety, accelerate recovery, and expand access to living donor kidney transplantation
C. Expand kidney exchange programmes	• Support development of national kidney exchange programmes in countries where these are absent or limited • Progressively link national programmes through EURO-KEP or similar frameworks to enable cross-border exchange under shared clinical, legal, ethical, and data-governance standards • Consider developing unspecified kidney donation programmes integrated with kidney exchange schemes and supported by robust psychosocial assessment, informed consent, and multidisciplinary follow-up
D. Reduce inequities in access	• Implement culturally competent education, translation services, peer-support models, and early referral pathways • Prioritise underserved groups, including ethnic minority, socioeconomically disadvantaged, female, paediatric, and geographically remote populations • Promote pre-emptive living donor kidney transplantation through early referral, timely donor evaluation, and targeted interventions to reduce socioeconomic and geographic disparities in access
E. Improve data infrastructure	• Establish harmonised national and European registries for living donor activity, outcomes, and follow-up • Include equity metrics, donor-reported outcomes, and long-term donor safety outcomes in routine data collection
Implementation Priorities	
• Agree on a European core dataset for living donor evaluation and outcomes • Map current reimbursement and donor-protection policies across countries • Expand cross-border kidney exchange between countries with compatible regulatory frameworks • Support countries with low LDKT activity to develop sustainable programmes • Integrate validated risk tools, digital education platforms, and outcome measures into clinical pathways	
Future research directions	
• Define acceptable risk thresholds for expanded donor criteria • Validate donor risk-prediction tools across diverse European populations • Evaluate psychosocial, financial, pregnancy-related, and long-term medical outcomes after donation • Assess the impact of kidney exchange, unspecified donation, genetic testing, digital tools, and minimally invasive surgery on transplant activity, donor safety, and recipient outcomes	

Conclusion

Living donor kidney transplantation remains the most effective renal replacement therapy for many patients with ESKD, yet access across Europe remains highly inequitable. Key priorities emerging from the symposium include harmonisation of donor assessment and informed consent, stronger donor protection and long-term follow-up, expansion of kidney exchange programmes including cross-border and unspecified donation, and targeted strategies to reduce social, financial, ethnic, and gender-based disparities. Advances in surgical techniques, immunological risk stratification, and digital tools offer important opportunities to improve donor and recipient outcomes but must be implemented within equitable and well-resourced systems of care (Table 2).

The EURO-KEP programme and development of a pan-European kidney exchange network represent important opportunities to improve equitable access to living donor transplantation. Achieving sustained progress will require collaboration among clinicians, policymakers, patient organisations, and professional societies, supported by legal reform and investment in education and infrastructure. These priorities align with EKITA's 2026–2027 action plan, which identifies promotion of LDKT as a core European objective.

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

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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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Allograft nephrectomy: a systematic review of immunological consequences and management of immunosuppressants

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Allograft nephrectomy (AN) is a serious complication of kidney transplantation. Beyond surgical morbidity, AN has important immunological implications. We performed a systematic review to synthesize current evidence on the immunological impact of AN and post-allograft failure immunosuppressive strategies. A systematic review was conducted according to PRISMA guidelines. PubMed/Medline® was searched for studies published from 01/2000 to 03/2026 on transplantectomy indications and surgical techniques. Eligible designs included meta-analyses, randomized trials, and prospective or retrospective studies evaluating the immunological impact of AN and/or immunosuppression management before, during, or after graft removal in adult or pediatric kidney transplant recipients returning to dialysis. Consistent evidence indicates that immunosuppression withdrawal is the principal driver of allosensitization after graft failure. Multiple studies demonstrated marked increases in anti-HLA antibodies following the cessation of immunosuppression, regardless of nephrectomy status. When AN was performed under maintained immunosuppression, its independent effect on sensitization and retransplant outcomes appeared limited. Meta-analyses showed comparable survival after retransplantation, although higher PRA levels, delayed graft function, and acute rejection were more frequent in patients with prior nephrectomy. Allosensitization after graft failure is primarily driven by immunosuppression withdrawal/reduction rather than AN itself. Individualized immunosuppressive management balancing immunological and infectious risks is essential.

KEYWORDS
allosensitization, immunosuppression, kidney transplantation, nephrectomy, transplantectomy, kidney embolization, retransplantation

Introduction

Kidney transplantation is the best treatment for patients suffering from end-stage kidney disease, as it provides superior survival, quality of life, and cost-effectiveness while having a lower environmental burden than long-term dialysis [1–3]. Advances in surgical techniques, donor selection, peri-operative management, and immunosuppressive

therapies have improved short- and long-term graft outcomes [4, 5]. Nevertheless, graft loss continues to occur in a substantial proportion of transplant recipients, and management of the failed renal allograft represents a major clinical challenge. In this setting, transplant nephrectomy (also referred as "transplantectomy"), defined as the surgical removal of a renal allograft, constitutes a serious complication of kidney transplantation with important clinical, immunological, and prognostic implications.

Transplant nephrectomy may be required at different timepoints after transplantation and for a wide spectrum of indications. In the immediate postoperative period, nephrectomy is most commonly performed due to surgical complications, including arterial or venous thrombosis [6, 7]. At later stages, transplant nephrectomy is frequently indicated after return to dialysis following chronic graft failure, particularly in patients who develop symptomatic rejections (so-called "graft intolerance syndrome," a condition characterized by graft-related pain, fever, hematuria, anemia, and systemic inflammation reflecting the ongoing immune activation) [8–10], and severe infectious or cancer complications of the graft (such as recurrent pyelonephritis or cancer, depending on the failed graft). More rarely, transplant nephrectomy may be required despite preserved graft function, usually as a consequence of complex vascular, neoplastic, or ureteral complications that are not (or failed to be) amenable to conservative management.

Beyond its indication, transplant nephrectomy is associated with significant morbidity [11]. Infectious complications are among the most frequent and severe adverse events following nephrectomy [12]. Patients undergoing allograft removal often present with multiple predisposing factors, including residual immunosuppression, chronic inflammation related to the failed graft, and malnutrition [13]. Surgical site infections, intra-abdominal abscesses, and sepsis are not uncommon and contribute substantially to early morbidity and mortality [12]. Cardiovascular complications represent another critical concern. Several observational studies have reported increased cardiovascular morbidity and mortality in patients after transplant nephrectomy, although disentangling the independent effects of surgery, graft loss, and dialysis resumption remains challenging [11]. One of the most consequential long-term effects of graft failure and transplant nephrectomy is their role in allosensitization. Removal of the renal allograft has been associated with an increased production of donor specific and non-specific anti-human leukocyte antigen (HLA) antibodies. Several factors, such as the timing of nephrectomy, the duration of graft survival, and the strategy used for immunosuppression withdrawal, have been suspected to influence allosensitization post nephrectomy [6, 14–16]. The immunological consequences of transplant nephrectomy have fueled ongoing debate regarding the optimal management of failed renal allografts. Strategies such as maintaining low-dose immunosuppression have been proposed to mitigate sensitization, but robust evidence remains limited [17, 18]. Furthermore, the balance between reducing immunological risk and minimizing infectious and cardiovascular complications is of paramount importance.

In this systematic review, we aimed to synthesize the evidence regarding the impact of an allograft nephrectomy and the management of immunosuppression.

Methods

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [19]. The protocol for this systematic review was prospectively registered in PROSPERO (International Prospective Register of Systematic Reviews; CRD420251040524).

Evidence acquisition

A systematic literature search was performed in PubMed/MEDLINE® to identify reports (in French or English) on allograft nephrectomy, published between January 2000 and March 2026, in accordance with PRISMA criteria. The full search strategy is provided in Supplementary Table S1. Study selection was based on the PICOS criteria: Population (P): patients with graft failure after a first kidney transplantation, regardless of severity or age; Intervention (I): allograft transplantectomy (transplant nephrectomy), encompassing different surgical techniques; Comparator (C): other surgical approaches, immunosuppression management strategies, dialysis, or embolization; Outcomes (O): morbidity and mortality (including cardiovascular and immunological impact), adverse events (myocardial infarction, congestive heart failure, sepsis, etc.), time or access to retransplantation, anatomical feasibility for retransplantation, quality of life, and acceptability; and Study design (S): meta-analyses, randomized controlled trials, non-randomized prospective studies, or retrospective studies. Bibliographic data were complemented by literature monitoring (up to June 2024), consultation of international society websites (European Association of Urology, American Urological Association, British Transplantation Society, UK Kidney Association, and American Society of Transplantation), a search for systematic reviews in the Cochrane Library database, and suggestions from the working group. The search strategy was designed to address four predefined clinical questions: (1) the indications for kidney allograft transplantectomy and its optimal timing; (2) the immunological impact of transplantectomy and the management of immunosuppression before, during, and after the procedure; (3) surgical techniques for transplantectomy; and (4) alternatives to transplantectomy, including conservative management strategies. The present article reports the results of the literature selection and evidence synthesis related to question 2, focusing on immunological impact and management of immunosuppressants before, during, and after the allograft nephrectomy.

Eligibility criteria and study selection

Inclusion and exclusion criteria were predefined prior to the study. Only studies addressing the immunological impact and management of immunosuppressants before, during, and after the allograft nephrectomy were included. Publications deemed ineligible were (i) health economic studies, as they largely depend on country-specific healthcare systems; (ii) case reports, narrative reviews, editorials, letters, or commentaries; (iii) experimental animal or *in vitro* studies; (iv) studies focusing on laboratory technology aspects; (v) studies on clinical practice patterns; and (vi) out-of-scope studies (e.g., not kidney-specific, public health

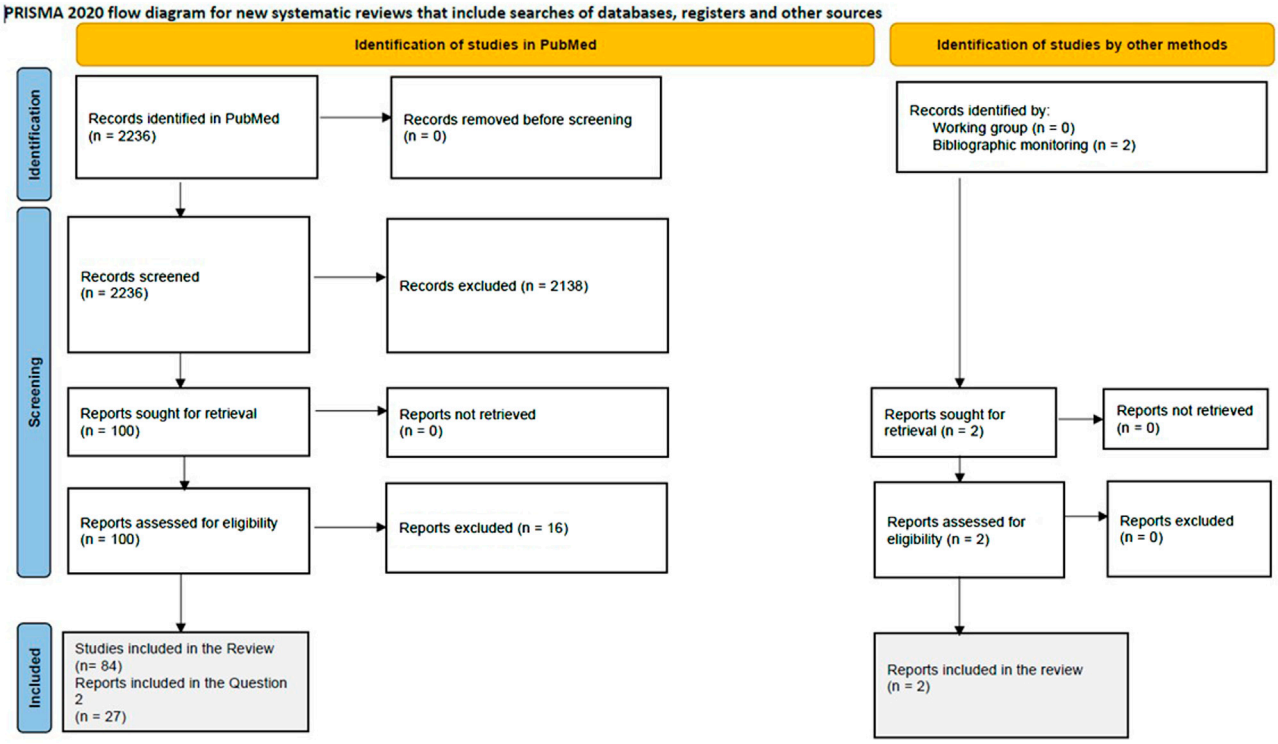

FIGURE 1
PRISMA flow diagram.

topics not specific to kidney transplantation, immunosuppressive therapy efficacy, transplantation technique, donor nephrectomy techniques in living donors, dialysis modality, retransplantation, or primary non-function related to cancer).

Study selection was initially performed by the methodologist (DK) based on these criteria after abstract screenings. The selection was independently validated by the steering committee (TC, AF, AG, TP, and ADB) and subsequently by the full working group. Full texts of selected publications were then reviewed. Following an initial data extraction by the steering committee, the final set of included studies was confirmed by the steering committee, and any disagreements were resolved through discussion with the working group.

Quality assessment

The methodological quality of the included studies was evaluated using validated critical appraisal tools appropriate to each study design (e.g., randomized, prospective non-randomized, or retrospective studies), combining criteria derived from the Haute Autorité de Santé (HAS) evidence appraisal framework [20], the STARD (Standards for Reporting Diagnostic Accuracy Studies) checklist [21], and the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool [22], when applicable. These assessments considered the clinical relevance of the study objectives, representativeness of the selected patients, appropriateness of inclusion and exclusion criteria, relevance of the recruitment period, independence between cohorts, blinding of outcome assessment, identification and adjustment for potential confounding factors, clinical relevance of the compared methods, validity and definition of outcomes, as well as funding sources and conflicts of interest. The level of evidence (LoE) was attributed to each study after taking into account the protocol design and the risk of bias (Supplementary Table S2). The classification of conclusions by LoE (LoE1 is the highest; LoE4 the lowest) was based on the grid proposed by HAS [20]. The risk of bias was assessed independently by two reviewers, and discrepancies were solved by consensus. Randomized and prospective non-randomized studies were prioritized in the analysis, and retrospective studies were included but interpreted with caution. This work was then reviewed by 33 independent experts from all medical and surgical specialties involved in the management of patients with renal graft failure (10 urologists, 4 nephrologists, 4 pediatric nephrologists, 3 immunologists, 3 vascular surgeons, 2 pediatric urologists, 1 pediatric surgeon, 1 infectiologist, and 6 patient representatives). A summary of the methodological analysis of included studies is presented in Supplementary Table S2.

Results

Study selection is detailed in the PRISMA flow diagram (Figure 1). In total, 2,236 records were screened for eligibility and 100 were selected. After full-text review, additional literature checking, and suggestions from the working group, 29 studies were ultimately included for analysis to address the question on

TABLE 1 **Brief summary of the included studies.**

Study	Design	Included Patients	Objectives	Key results
Naini et al [38]	Retrospective observational	85	To define the prevalence of intolerance syndrome requiring an allograft nephrectomy in patients who stopped immunosuppression after return to dialysis	Intolerance syndrome prevalence: 14% after 47 ± 45 months of follow-up
Knight et al. [16]	Retrospective observational	31	To assess the immunization level before and after an allograft nephrectomy	The mean PRA increased from 33.4 to 75.6 in class I ($p < 0.001$) and from 38.9 to 60.6 in class II ($p = 0.002$). This increase was associated with an increase of MESF of DSAs from 33,518 to 121,457 ($p < 0.001$) in class I and from 45,459 to 126,968 ($p < 0.001$) in class II. Rejection episodes and a time between dialysis initiation and graft nephrectomy >10 months were associated with a more important increase of PRA ($p < 0.001$) and MFI DSAs ($p = 0.02$) after multivariate analysis
Johnston et al [11]	Retrospective observational	19,107 (6,213 with an allograft nephrectomy)	To assess the immunological and non-immunological consequences of an allograft nephrectomy	Analysis of a North American registry (MEDICARE), including 6,213 recipients who required an allograft nephrectomy (32.5%), one-third of which experiencing a return to dialysis during the first year post transplantation. A large majority of patients (89; 3%) required an allograft nephrectomy in the year post return to dialysis. In low sensitized recipients at transplantation (PRA< 30%) allograft nephrectomy was associated with higher PRA at repeat transplantation ($p < 0.00001$)
Martinez Diaz et al [39]	Retrospective observational	22	To assess immunization following an allograft nephrectomy during the first week post transplantation	Detection of anti-HLA antibodies is observed in 60.8% in class I and 52.2% in class II. DSA were detected in 91.7% of patients with *de novo* anti-class I HLA antibodies and 100% of patients with *de novo* anti-class II HLA.
Lenaers et al [35]	Retrospective observational	32	To assess immunization following an allograft nephrectomy during the first month post transplantation	Sixteen of the thirty-two patients included developed *de novo* DSAs (50%). Anti-class I antibodies were detected in 15 patients, and anti-class II DSA were detected in 10 patients. In multivariate analysis, donor age was an independent predictive factor of *de novo* DSA development ($p = 0.05$). The median time of *de novo* DSA occurrence was similar regardless the cause of graft failure (immunological vs. non-immunological (67–122 days vs. 9–186 days; $p = 0.31$)

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TABLE 1 Continued

Study	Design	Included Patients	Objectives	Key results
Sener et al [25]	Retrospective comparative	132 (90 with an allograft nephrectomy)	To compare allosensitization between patients who required an early nephrectomy (<6 months) and those who required a late nephrectomy (>6 months)	A decrease of PRA between dialysis initiation and last follow-up was observed in patients who required an early nephrectomy (n = 39): from 46.2% ± 29.7% to 26.8% ± 28.9%, p = 0.02. Conversely the mean PRA increased in patients who return to dialysis rapidly after transplantation but retained their graft (n = 6) (from 36.2% ± 36.8% (pre-transplant) to 82.8% ± 29.4%, p = 0.02), or those who presented a graft failure after 6 months (n = 51) (from 9.0% ± 11.1% (pre-transplant) to 34.2% ± 30.4% at the time of nephrectomy and to 41.9% ± 30.1% at the time of last follow-up (p = 0.002) or without nephrectomy (n = 36): from 4.8% ± 9.0% (pre-transplant) to 17.7% ± 26.2% at time of graft failure and to 27.7% ± 29.4% at the time of last follow-up (p = 0.02)
Billen et al. [40]	Retrospective observational	56	To analyze the incidence of *de novo* anti-HLA antibodies after an allograft nephrectomy	During the follow-up post return to dialysis, 81% of previously non-sensitized patients became sensitized to HLA class I, class II, or both (16% before and 84% after graft nephrectomy). HLA class I antibodies were detected in 84% of patients and class II antibodies in 77%. After accounting for the time interval between transplantation and graft nephrectomy (<1 month, 1–6 months, or >6 months), patients who underwent graft nephrectomy between 1 and 6 months had a higher mean number of HLA class II mismatches and more frequently had a history of acute rejection episodes; all patients in this sub-group were DSA-positive. In multivariable analysis, HLA class I DSA positivity was associated with age (OR = 1.06; 95% CI [1.01–1.12]; p = 0.007) and donor type (donation after circulatory death vs. donation after brain death: OR = 32.08; 95% CI [3.4–571.64]; p < 0.0001). In contrast, HLA class II DSA positivity was associated with age (OR = 1.04; 95% CI [1.00–1.08]; p = 0.03) and the number of HLA class II mismatches (OR = 5.31; 95% CI [1.35–20.81]; p = 0.01)
Adeyi et al [41]	Retrospective observational	27	To characterize the profiles of specificities of circulating anti-HLA antibodies detected before and after the nephrectomy	Circulating DSAs were found in 11% before and 97% after graft nephrectomy. In class I, a molecular analysis by HLA matchmaker™ highlight[28]ed a link between anti-HLA non-DSA antibodies and the HLA of the donor

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TABLE 1 Continued

Study	Design	Included Patients	Objectives	Key results
Schrezenmeier et al [42]	Retrospective observational	111	To assess allosensitization after return to dialysis with or without an allograft nephrectomy	38/111 patients (34.2%) already had anti-HLA non-DSA at the time of graft loss 43/111 patients (38.7%) developed *de novo* DSA after graft loss 30/111 patients (27.0%) did not develop dnDSA during the observation period Among relisted patients, the distribution of HLA sensitization between class I and class II antibodies was comparable to that observed in the overall population of patients experiencing graft loss. Notably, patients who underwent graft nephrectomy had rates of *de novo* DSA comparable to those observed in patients without nephrectomy
Schatchner et al [31]	Retrospective comparative	111 (51 with an allograft nephrectomy)	To determine the T cell pre-sensitization after return to dialysis (with or without an allograft nephrectomy)	Kidney transplant recipients with the previous allograft removed showed significantly higher donor-reactive T cells pretransplantation compared with kidney transplant recipients with the previous allograft retained (p = 0.012). Kidney transplant recipients with the previous allograft removed showed significantly higher rates of acute cellular rejection compared with those who retained their allograft [27/51 (53%) vs. 18/60 KTRs (30%); p = 0.019]. Kidney transplant recipients with the previous allograft removed showed significantly inferior death-censored allograft survival (p = 0.022)
Marrari et al [43]	Retrospective observational	65	To analyze allosensitization before and after the nephrectomy	Allo-sensitivity against the HLA A, B loci was present in 64% before and 87% of patients after the nephrectomy (p = 0.0033); for the DRB1 locus: 57% before and 86% after (p = 0.001); for the DRB3/4/5 loci: 65% vs. 78%; p = 0.22; for the DQB locus:76% vs. 87%; p = 0.18)
Lucisiano et al [33]	Retrospective observational	109	To assess the immunological impact of an allograft nephrectomy	An allograft nephrectomy is a predictive and independent factor of anti-HLA DSA development at 24 months post-surgery (HR = 6.12, 95%CI[1.56; 23.93], p = 0.008), decreasing the chances to get a future compatible transplantation. A tacrolimus therapy with trough levels ≥3 ng/mL was a protective factor for allosensitization
Goral et al [6]	Retrospective observational	73	To assess the immunological impact of an allograft nephrectomy	22 patients were tested before and after nephrectomy: 54% of patients presented DSA at both timepoints, and 34% developed *de novo* DSA after the nephrectomy, while the remaining 14% did not develop *de novo* DSA.

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TABLE 1 Continued

Study	Design	Included Patients	Objectives	Key results
Del Bello et al [28]	Retrospective comparative	95	To assess the immunological impact of an allograft nephrectomy	At last follow-up (538 ± 347 days post return to dialysis), the rate of patients with DSA was higher in case of allograft nephrectomy in comparison with patients who retained their transplant (81% vs. 52%, p = 0.02). Similarly, the rate of patients with detectable anti-HLA antibodies (anti-class I 77% vs. 24%, p = 0.001; anti-class II 62% vs. 43%, p = 0.06). An allograft nephrectomy and the A/B mismatches (0 vs. ≥ 1) were independently associated with anti-HLA DSA development
Del Bello et al [14]	Retrospective observational	35	To assess the immunological impact of an allograft nephrectomy after an early graft failure (<3 months)	The rate of patients with at least 1 detectable class I/II DSA was 9.3%, 22.0%, 26.6%, 50%, 56.6%, 56.25%, at transplantation, day 15, and months 1, 3, 6, 9, and 12 post-surgery. The development of *de novo* DSA was not associated with the use of induction therapy
Khakhar et al [36]	Retrospective observational	81	To assess the immunological impact of an allograft nephrectomy	After an allograft nephrectomy the mean PRA increased from 25% to 40% (p < 0.001) at last follow-up, except for the most sensitized patients who presented a stable mean PRA: 89% ± 7% vs. 76% ± 21%; p = 0.05)
Augustine et al [34]	Retrospective observational	119	To assess the immunological impact of an allograft nephrectomy	24 months après return to dialysis, 56% of patients were hypersensitized (class I or II PRA ≥80%). In multivariate analysis, immunosuppression withdrawal was independently associated with the development of hypersensitization (OR = 14,342; 95%IC [2,334–88,144]; p = 0.004). An allograft nephrectomy for intolerance syndrome was required in 41% of patients after immunosuppression withdrawal, vs. 0% in those who maintained their tacrolimus-based immunosuppression (p < 0.001)
Garcia Montemayor [44]	Retrospective observational	146	To assess the immunological impact of an allograft nephrectomy	Among the 72 patients who required an allograft nephrectomy, 41 presented DSA after they returned to dialysis, including 17 for those DSA was detected only after the nephrectomy Fifty-one patients developed DSA during the follow-up (36 [2; 504] weeks: anti-HLA DSA was detected before immunosuppression withdrawal in 21.6%, and after in 78.4% of cases

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TABLE 1 Continued

Study	Design	Included Patients	Objectives	Key results
Kosmoliaptsis et al [45]	Retrospective observational	131	To analyze the relationship between donor mismatches at each HLA locus and the development of HLA Locus-specific antibodies	After return to the waiting-list, the anti-HLA antibody development was independently associated with waitlist duration (>5 vs. < 1year: OR = 8.4; 95%CI [2.58–31.16]; p < 0.001), the number of HLA mismatches (OR = 1.41; 95%IC [1.15–1.74] par mismatch; p < 0.001), and maintenance of a double immunosuppression (OR = 0.2; 95%IC [0.06–0.61]; p = 0.005), but not with allograft nephrectomy All mismatches loci equally contribute to the development of anti-HLA antibodies (HLA-A: OR = 3.2; HLA-B: OR = 3.4; HLA-C: OR = 2.5; HLA-DRB1: OR = 3.5; HLA-DRB3/4/5: OR = 3.9, HLA-DQ/ OR = 3.0)
Woodside et al [26]	Retrospective, comparative	186	To analyze the role of immunosuppression withdrawal on incidence of the allograft nephrectomy	An allograft nephrectomy was required in 42% of patients who stopped (n = 60/143) and 23% (n = 11/43) of patients who maintained their immunosuppression therapy (p = 0.026)
Piatosa et al [37]	Retrospective observational	14	To analyze the occurrence of anti-HLA sensitization after graft thrombosis in a pediatric population	Of 14 patients, aged from 4 to 18 years (mean age: 10.7 years), 8 lost their transplant in the first week. The remaining six lost their transplant in the 60 days post transplantation. Anti-HLA antibodies were detected in 12 of the 14 patients (85.7%), including 7 patients with *de novo* DSA (50%), 6 cases with *de novo* anti-class I DSA (42.9%), and one anti-class II (7%)
Nimmo et al [29]	Retrospective comparative	71 (29 with an allograft nephrectomy)	To compare the DSA formation in patients who stopped their immunosuppression, with or with a nephrectomy	All patients who required an allograft nephrectomy stopped their immunosuppression at nephrectomy. An increase of the calculated reaction frequency was observed during the follow-up in both groups, independently of the need to perform a graft nephrectomy. In patients who maintained their transplant, cRF increased from 13% before tapering to 40% at withdrawal and 69% at last follow-up. This was associated with a mean R-CoT (relative chance of transplant) of 54%–46% at 5 years, before and after immunosuppression withdrawal. In patients who required a graft nephrectomy, the mean cRF increased from 31% before immunosuppression, tapering to 69% after withdrawal and 89% at last follow-up. The mean R-CoT decreased from 54% to 42% at 5 years before and after immunosuppression withdrawal

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TABLE 1 Continued

Study	Design	Included Patients	Objectives	Key results
Lachmann [30]	Retrospective comparative	54	To compare allosensitization in patients who returned to dialysis and underwent graft nephrectomy with or without immunosuppression withdrawal, or immunosuppression withdrawal without nephrectomy	Anti-HLA antibodies were similarly detectable in the different settings: 100% of patients after nephrectomy post immunosuppression withdrawal, 100% of patients after nephrectomy under immunosuppression and 92% of patients who underwent immunosuppression only
Freist et al [15]	Retrospective comparative	119	To determine the impact of immunosuppression withdrawal on allosensitization	A lower rate of DSA detection was observed in patients who maintained a calcineurin inhibitor-based immunosuppression (30/52 (57.7%) vs. 52/67 (77.6%), p = 0.02), as well as a lower rate of non-DSA allosensitization (17% vs. 38%, p = 0.03). The rate of graft nephrectomy was similar in both groups (36.5% vs. 49.3%; p = 0.17). In multivariate analysis, the rate of hypersensitized recipients was lower in case of maintenance of immunosuppression
Matignon et al [27]	Retrospective Comparative	63	To compare allosensitization before and after nephrectomy and to assess the role of intravenous immunoglobulins on allosensitization	15/63 patients (24%) required an early graft nephrectomy: All of them received immunosuppression at the surgery, which was stopped at nephrectomy in 8 patients (53%) and tapered during the month for the remaining 7 patients (47%). Among the last 48 late nephrectomies 14 (22%) were asymptomatic, 34 (54%) were due to intolerance syndrome. Patients who required early nephrectomy and asymptomatic recipients presented similar levels of allosensitization, but allosensitization increased during the 3 months post surgery. In patients who received intravenous immunoglobulins after the nephrectomy (n = 10), the rate of anti-HLA non-DSA class I increased (p = 0.03), in contrast with a retrospective control group (n = 13) in which anti-HLA DSA and non-DSA increased in class I, II, and MFI.
Martin et al [32]	Retrospective observational	134	To determine the impact of immunosuppression withdrawal on allosensitization	Allosensitization rate was similar whatever the immunosuppression withdrawal strategy tested (<90, 90–180, >180 days after return to dialysis): cPRA (80.06 vs. 81.21 vs. 85.42; p = 0.66). Similar rates of retransplantation were observed:24/31 [77.4%] vs. 21/35 [60.0%] vs. 22/36 [61.1%]; p = 0.13). A lower rate of nephrectomy was observed in patients who stopped later the immunosuppression (10/42 [23.8%] vs. 7/42 [16.7%] vs. 3/43 [7.0%]; p = 0.01)

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TABLE 1 Continued

Study	Design	Included Patients	Objectives	Key results
Achinger et al	Retrospective observational	18,748	To assess whether allograft nephrectomy is associated with reduced future kidney transplantation	9,374 patients requiring an allograft nephrectomy were matched with 9,374 patients who did not. Patients in the allograft nephrectomy group had a higher chance of undergoing a second transplantation as compared with the comparison group (subdistribution hazard ratio: 1.21; 95%CI 1.15–1.28, $p < 0.001$), but a higher risk for death (HR: 1.09; 95%CI 1.05; 1.13, $p < 0.001$)
Leal et al	Retrospective observational (data prospectively collected)	90	To assess the impact of prolonging calcineurin inhibitors after graft loss on allosensitization, graft intolerance syndrome, hospitalization rates, mortality	Patients who prolonged calcineurin inhibitors for at least 6 months had significantly lower allograft nephrectomy rates (4.8% vs. 23%, $p = 0.015$). In multivariate analysis, rapid calcineurin inhibitor withdrawal (OR: 5.9, 95%CI[1.2–32.1), $p = 0.04$) and acute rejection (OR: 5.6, 95%CI[1.1–27.8), $p = 0.04$) were independent risk factors for graft intolerance syndrome during the first year Considering HLA sensitization at 1 year post graft failure, allograft nephrectomy (OR 10.9, [1.1; 112.5], $p = 0.04$), and the number of HLA mismatches (OR: 1.7, 95%CI[1.2–2.5), $p = 0.004$) were independent predictive factors

Abbreviations: PRA, panel reactive antibody; DSA, Donor-Specific Antibodies; MESF, molecular equivalents of soluble fluorochrome.

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"immunological impact and management of immunosuppressants before, during, and after an allograft nephrectomy": 2 systematic reviews/meta-analyses [23, 24], 9 retrospective comparative studies [15, 25–31], and 18 retrospective observational studies [6, 11, 14, 16, 32–45] summarized in the Table 1.

The role of removing the failed graft in the development of allosensitization

The failed graft constitutes a reservoir of donor antigens. In the absence of immunosuppression, ongoing antigen presentation by infiltrating recipient antigen-presenting cells (mainly after late allograft failure) or resident donor-derived cells (in case of early allograft failure) may promote recipient immune activation, leading to antibody formation. The inflammatory milieu surrounding the failing graft may amplify antigen presentation and costimulatory signaling [46–48].

Histopathological data support the role of inflammation. Goral et al [6] reported extensive inflammatory infiltrates in explanted grafts, including plasma cells and tertiary lymphoid structures, which may sustain local antibody production. In such contexts, graft nephrectomy may exacerbate antigen release, immune activation, and *de novo* DSA formation [14, 33].

It was also suggested that the failed graft could adsorb (or regulate) anti-HLA antibody specificities and prevent detection of some anti-HLA antibodies (the so-called "sponge effect") despite the use of highly sensitive tests [43]. According to this hypothesis, removal of the antigen source could lead to an apparent increase in circulating anti-donor antibodies, as antibodies previously sequestered within the allograft become detectable following graft removal [16, 36]. However, this hypothesis has not been substantiated by direct experimental evidence and is instead supported by indirect clinical observations, including the rapid development of donor-specific antibodies following allograft nephrectomy [16]. However, it should be noted that sera considered as pre-allograft nephrectomy were collected several weeks before the surgery, which could represent a major bias. Recent studies have demonstrated that this effect is probably limited. Indeed, Milongo and colleagues [49] investigated the presence of anti-HLA DSA in both the blood and nephrectomy eluates in 17 patients. They observed that all anti-HLA DSA detected in the nephrectomy eluates were also detected in blood at the time of nephrectomy [49].

Immunosuppression withdrawal (more than graft nephrectomy in itself) plays a key role in allosensitization after graft failure

While graft nephrectomy has long been considered a major driver of alloimmunization, accumulating evidence suggests that its immunological impact is largely mediated by the management of immunosuppressive therapy rather than by the surgical removal of the graft itself (Table 3). Several studies consistently demonstrated that cessation of immunosuppressive therapy after graft failure is associated with a rapid and marked increase in anti-HLA antibodies, preceding nephrectomy. In a retrospective comparison study involving 69 patients who returned to dialysis and stopped their immunosuppression, Del Bello and colleagues [28] showed that discontinuation of immunosuppression led to a sharp rise in anti-HLA antibodies detection, regardless of whether nephrectomy was subsequently performed (anti-HLA DSA detected in 52% patients without a history of nephrectomy and 81% in those with nephrectomy). Augustine et al [34] further reinforced this concept by demonstrating in a cohort of 119 patients who returned to dialysis that late sensitization after kidney transplant failure was independently associated with immunosuppression weaning, even in the absence of nephrectomy. Patients who discontinued calcineurin inhibitors and antiproliferative agents experienced a significant increase in panel reactive antibodies (PRA) (Median PRA rose from 0% before transplantation to 57% in class I and 63% in class II, 6–24 months post graft failure), indicating broad alloimmune activation. Similar findings were reported by Nimmo et al. [29], who showed that withdrawal of maintenance immunosuppression was the dominant factor influencing the calculated chance of future transplantation, with nephrectomy exerting only a secondary effect. They observed in 41 patients that immunization (expressed by calculated reaction frequency, cRF) rose from 13% pre-immunosuppression weaning to 62% post immunosuppression withdrawal. In the subgroup of 17 patients who underwent graft nephrectomy, the mean cRF rose similarly to others, from 31% pre-immunosuppression wean to 69%. Kosmoliaptsis and colleagues [45] observed that the development of anti-HLA antibodies after return to dialysis in patients listed for another transplantation was independent of graft nephrectomy but associated with waitlist time and maintenance on dual immunosuppression.

The higher allosensitization observed after graft nephrectomy in comparison with immunosuppression weaning only could be related to the surgical intervention in inflammatory conditions and to the high rate of blood transfusion required during or immediately after the surgery [28, 29, 43]. Lucisano et al [33] conducted a retrospective study evaluating the relative contributions of transplantectomy and immunosuppression management to allosensitization in 109 patients. They found that continued immunosuppression (with tacrolimus levels ≥3 ng/mL) was associated with lower rates of *de novo* anti-HLA antibody formation, irrespective of whether transplantectomy was performed. Schachtner et al [31] extended this concept by demonstrating that graft nephrectomy was associated not only with humoral sensitization but also with presensitization at the T-cell level. They investigated the donor-reactive T cell response by using an IFN-γ ELISPOT assay in a cohort of 111 patients who returned to dialysis (51 with a history of graft removal and 60 without). They observed increased frequencies of donor-reactive T cells responses and inferior outcomes after retransplantation in patients with a history of graft removal in comparison with patients without.

Graft nephrectomy in patients maintained on immunosuppression

Studies focusing on early graft nephrectomy (performed while immunosuppression is ongoing) highlight that sensitization could occur even if the graft nephrectomy is performed only a few minutes after the transplantation. Lenaers et al [35] reported an important

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TABLE 2 **Summary of meta-analyses regarding retransplantation outcomes.**

Study	Included studies/ Sample size	Databases searched (n) Reviewers (n)	Intervention	Outcomes	Results
Wang et al. [11]	8 retrospective studies 1,008 patients	5 databases 2 reviewers	Allograft nephrectomy vs. no allograft nephrectomy	After retransplantation 1-year graft survival 1-year patient survival Acute rejection postoperative complications serum creatinine at 1 year	1-year graft survival OR = 0.74; 95% CI [0.31–1.72]; p = 0.48 1-year patient survival OR = 1.60; 95% CI [0.57–4.46]; p = 0.37 Acute rejection OR = 1.30; 95% CI [0.89–1.91]; p = 0.17 Serum creatinine at 1 year WMD: -0.25; 95% CI [-0.52 to 0.03]; p = 0.08
Gavriilidis et al. [9]	16 retrospective studies 2,256 patients	5 databases 2 reviewers	Allograft nephrectomy vs. no allograft nephrectomy	After retransplantation 5-year graft survival 5-year overall survival %PRA Delayed graft function acute rejection Primary non-function graft loss Cold ischemia time	5-year graft survival HR = 1.11, 95% CI [0.89–1.38]; p = 0.37 5-year overall survival HR = 0.70; 95% CI [0.45–1.10]; p = 0.12 %PRA OR = 1.83; 95% CI [1.20–2.78]; p = 0.005 Delayed graft function 39% vs. 30%; OR = 1.86; 95% CI [1.16–2.98]; p = 0.01 Acute rejection OR = 1.70; 95% CI [1.31–2.22]; p = 0.001 Primary non-function OR = 3.41; 95% CI [1.31–8.89]; p = 0.001 Graft loss OR = 1.51; 95% CI [1.09–2.09]; p = 0.01 Cold ischemia time MD = 1.56; 95% CI [0.28–2.85]; p = 0.02

(*Continued*)

TABLE 2 Continued

Study	Included studies/ Sample size	Databases searched (n) Reviewers (n)	Intervention	Outcomes	Results
Lin et al. [10]	13 studies 1802 patients	3 databases 2 reviewers	Allograft nephrectomy vs. no allograft nephrectomy	After retransplantation 3–5-year graft survival 5-year patient survival PRA >10% Acute rejection Delayed graft function Cold ischemia time	3-year graft survival OR = 0.48; 95% CI [0.34–0.69]; p < 0.001 5-year graft survival OR = 0.65; 95% CI [0.44–0.97]; p = 0.04 5-year patient survival OR = 1.82; 95% CI [1.14–2.90]; p = 0.01 PRA >10% OR = 3.08; 95% CI [2.08–4.56]; p = 0.000 Acute rejection OR = 1.59; 95% CI [1.21–2.09]; p = 0.0009 Delayed graft function OR = 1.66; 95% CI [1.20–2.03]; p = 0.002 Cold ischemia time MD = 1.84; 95% CI [0.90–2.79]; p = 0.0001

(50% of patients) donor-specific alloimmunisation in 32 patients who lost their graft and underwent a nephrectomy during the first 4 months post transplantation. Similarly, Del Bello et al. [14] specifically examined early allograft nephrectomy (<3 months post transplantation) performed under immunosuppression and observed significant anti-HLA immunization (57% of patients after 9 months post nephrectomy). Similarly, when immunosuppression is maintained until nephrectomy in patients with late graft failure, allosensitization is frequent. In a retrospective study of 41 patients (17 with graft nephrectomy, all of whom were maintaining immunosuppression until the surgery), Nimmo and colleagues [29] found high allosensitization (the cRF rose from 31% pre-immunosuppression wean to 69% post-immunosuppression wean and 89% post-immunosuppression cessation). Similarly, Lachmann and colleagues [30] retrospectively compared the allosensitization rate in 28 patients who received a nephrectomy after immunosuppression discontinuation, in 14 patients who received a nephrectomy under immunosuppression (stopped immediately after), and 12 patients who stopped their immunosuppression without nephrectomy. They observed similar allosensitization rates (100% of patients after nephrectomy post immunosuppression withdrawal, 100% of patients after nephrectomy under immunosuppression, and 92% of patients who underwent an immunosuppression only). Matignon and colleagues observed that immunosuppression tapering in the month after the nephrectomy had limited impact on the development of allosensitization, as well as the use of high doses of intravenous immunoglobulins [27]. This could be explained by the persistence of some donor tissue after nephrectomy (in vascular patches). Alloimmunisation could then occur in patients who stop their immunosuppression after the surgery due to these residues [28]. Freist and colleagues [15] observed a lower rate of DSA in patients who maintained a calcineurin inhibitor-based immunosuppression (30/52 (57.7%) vs. 52/67 (77.6%), p = 0.02), as well as a lower rate of non-DSA allo-sensitization (17% vs. 38%, p = 0.03) regardless of the need for an allograft nephrectomy.

As expected, the number of HLA mismatches is an important factor leading to allo-sensitization [28, 40, 45]. All mismatched loci contribute to allosensitization in a similar way [45].

Beyond the formation of anti-HLA DSA, a broad allosensitization is frequently observed after immunosuppression tapering/discontinuation. By using HLA matchmaker™ [28, 41] or recombinant single HLA allele–expressing cell lines [30], several authors demonstrated that a majority of these anti-HLA non-DSA antibodies were directed against donor's epitopes at the molecular level.

Graft nephrectomy and impact of retransplantation

The impact of graft nephrectomy on subsequent retransplantation remains a matter of ongoing debate, as its clinical consequences are closely intertwined with alloimmunization and immunosuppression management. In a recent USRDS-based study, Achinger and colleagues observed that patients who underwent an allograft nephrectomy had higher chances of receiving a second transplant (subdistribution HR: 1.21, 95%CI[1.15–1.28, p < 0.001) [50]. When nephrectomy is

performed under continued immunosuppression, its independent effect on retransplantation rates appeared limited (Table 2). In an initial meta-analysis of eight studies (1,008 patients), Wang and colleagues [51] did not observe a difference regarding the retransplant outcome (1 year graft survival: OR = 0.74; 95%IC [0.31–1.72]; p = 0.48, 1 year patient survival: OR = 1.60; 95%IC [0.57–4.46]; p = 0.37), acute rejection rate (OR = 1.30; 95%IC [0.89–1.91]; p = 0.17), post-operative complications (OR = 1.51; 95%IC [0.24–9.43]; p = 0.66), or graft function at 1 year (mean ponderate difference: -0.25; 95%IC [-0.52 à 0.03]). Nonetheless, patients with a history of graft nephrectomy present a prolonged time between dialysis and retransplantation (mean ponderate difference in months 11.23; 95%IC [2.47–19.99]; p = 0.01) and increased PRA of more than >10% (OR = 1.62; 95%IC [1.17–2.23]; p = 0.003). Another meta-analysis [13] that included 16 retrospective studies (2,256 patients) reported similar 5-year graft (HR = 1.11, 95%IC [0.89–1.38]; p = 0.37) and patient survival (HR = 0.70; 95%IC [0.45–1.10]; p = 0.12). Nonetheless, patients who underwent graft nephrectomy presented high PRA at retransplantation (%PRA: 39% vs. 35%; OR = 1.83; 95%IC [1.20–2.78]; p = 0.005), delayed graft function (39% vs. 30%; OR = 1.86; 95%IC [1.16–2.98]; p = 0.01), acute rejection (33% vs. 28%; OR = 1.70; 95%IC [1.31–2.22]; p = 0.001), and primary non-function (8% vs. 1.7%; OR = 3.41; 95%IC [1.31–8.89]; p = 0.001).

Collectively, these data suggest that graft nephrectomy in itself does not seem to have a detrimental effect on the outcomes of retransplantation.

Discussion

This systematic review on the immunological impact of AN and post-allograft failure immunosuppressive strategies has been conducted to inform the 2025 French guidelines on Allograft nephrectomy: Indications and surgical techniques [52].

The optimal management of immunosuppressive therapy following graft failure and nephrectomy remains controversial. Limiting the time between graft failure and retransplantation was recently underscored by Kainz and colleagues [53], and allosensitization is a major pitfall for retransplantation. Continuation of low-dose immunosuppression has been proposed to limit alloimmunization, particularly in patients who are candidates for retransplantation. Several studies recently highlighted lowered sensitization rates in [15] patients who maintained immunosuppression after graft failure compared with those who underwent rapid withdrawal [15, 54–56]. García Montemayor et al. [44] similarly observed increased development of donor-specific antibodies after reinitiation of dialysis when immunosuppression was discontinued. Leal and colleagues found that patients who maintained a calcineurin inhibitor after return to dialysis presented a lower rate of graft intolerance syndrome [57]. In a recent meta-analysis of 13 studies comprising 1,531 patients, Fragoso and collegues [54] found that maintaining immunosuppression more than 3 months (with at least two immunosuppressants) was associated with significantly lower odds of graft nephrectomy or embolization (OR:0.41, 95% CI[0.27.0.64]), with no significant impact on hospitalization rates, mortality, or retransplantation. These findings suggest that maintaining some degree of immune modulation may attenuate humoral responses, especially in patients with low baseline immunization. The ideal regimen to propose for patients in dialysis still remains to be identified. The importance of calcineurin inhibitors was highlighted, along with the functioning graft period. Lucisiano and colleagues [33] observed that patients who underwent a nephrectomy under tacrolimus and for whom the treatment was prolonged after the surgery presented a low rate of alloimmunization in comparison with patients who stopped their treatment at nephrectomy. The frequent need for blood transfusions following return to dialysis and in the perioperative period of allograft nephrectomy should also be considered as a potential contributor to HLA sensitization. Given the well-established association between transfusion exposure and alloantibody formation, this factor may partly account for the increase in sensitization observed after graft failure and provides an additional rationale for maintaining immunosuppression in candidates for retransplantation [58, 59]. However, the benefits of prolonged immunosuppression must be weighed against its risks. Woodside et al [26] reported increased rates of infection, fever, and hospitalization in patients who remained on immunosuppressive therapy after graft failure.

This finding supports a tailored approach in which immunosuppression continuation is considered in patients with a realistic prospect of retransplantation and low infectious risk. Dynamic approaches with minimization periods during infection complications and an increase of immunosuppression thereafter need to be assessed. Two studies are now open to assess the effect of controlled immunosuppression to reduce the risk of allosensitization after graft failure: in the PREVSENSI study (NCT06676696), the authors investigate the impact of maintaining a low dose of tacrolimus for 2 years in patients who returned to dialysis for late graft failure (>3 months post transplantation). A nationwide prospective study (TACITE) investigating the impact of maintaining a combination of immunosuppression containing tacrolimus is expected to start soon in France. Finally, a pilot study aiming to reduce allosensitization after an early allograft nephrectomy (RAIPONS study, NCT04779957) suggested that anti-IL6 receptor blockers infusion could limit allosensitization in this setting.

Decision-making regarding immunosuppression after return to dialysis should be individualized, integrating different parameters. The likelihood of retransplantation and baseline sensitization status should be assessed. Highly sensitized patients may derive limited benefit from continued immunosuppression, whereas non- or low sensitized patients may experience substantial harm from immunosuppression withdrawal. This is well illustrated by seminal studies in which PRA before and after transplant nephrectomy remain stable, while an increase was observed in low sensitized patients [36]. Since HLA mismatches burden strongly influences antibody development [45], this parameter should be taken into account. Moreover, the risk of infection should be assessed regularly in immunosuppressed dialysis patients.

Embolization of the failed graft has emerged as a possible less invasive alternative to transplantectomy, particularly in patients

with graft intolerance syndrome. Although the immunological impact of embolization in comparison with graft nephrectomy remains to be assessed, we can suppose that embolization could reduce the risk of sensitization by reducing the need for blood transfusion, which is regularly needed after graft nephrectomy.

Finally, our group concluded the following, based on the literature data:

1. After early transplant nephrectomy, the type of induction therapy used does not appear to influence morbidity and mortality [60] or alloimmunization at 1-year post-surgery [14].
2. In patients with late graft failure, systematic transplant nephrectomy before stopping immunosuppression does not seem to prevent anti-HLA immunization after the return to dialysis [29] (LoE4).
3. The rate of anti-HLA immunization (PRA rate >50%) is higher in recipients who underwent transplant nephrectomy than in those who did not [30, 51, 61] (LoE4).
4. After late graft failure, immunosuppressive treatment continuation appears to be well tolerated (at least in the early years after return to dialysis) concerning infection or tumor development [15, 32] (LoE4).

Conclusion

Our systematic review shows that the immunological impact of graft nephrectomy after kidney allograft failure is largely determined by the timing and manner of immunosuppression withdrawal and by the inflammatory context in which graft removal occurs. Evidence consistently shows that immunosuppression cessation is the principal driver of alloimmunization, often preceding and overshadowing the effects of nephrectomy. When performed while prolonged post-operative immunosuppression is maintained, graft nephrectomy appears to have a limited impact on allosensitization and retransplantation outcomes. Despite the inherent limitations of systematic reviews, we propose that management strategies should therefore prioritize individualized immunosuppression protocols to reduce the need for graft nephrectomy and limit subsequent allosensitization following graft failure.

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

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

DK performed the study selection TC, AF, AG, TP, and AD validated the selection and reviewed the papers, performed the critical analysis. AD wrote the paper. TC, AF, AG, TP, and DK reviewed the paper. 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.

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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.2026.16661/full#supplementary-material

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Surgical residents' career interests in transplantation surgery in Germany – a nationwide survey

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The sustainability of transplantation surgery (TS) relies on the ability to attract and retain the next generation of surgeons. This study aims to assess how surgical residents perceive TS as a career pathway in Germany, and to identify barriers in choosing TS as a career. An anonymous 30-item online survey was distributed to surgical residents at all transplant centers registered with the Deutsche Stiftung Organtransplantation (DSO, German Organ Procurement Organization). Quantitative data were analyzed using SPSS (version 29), free-text responses underwent thematic content analysis. Sixty-eight complete surveys were analyzed. TS was considered by 25% of respondents as a subspecialty training. Transplant-specific education was occasional or absent, though desired by >80%. Motivators included personal interest, patient care, and career development, while barriers were structural: lack of defined fellowship programs and limited autonomy during residency. Structured fellowship programs (46%), mentorship (27%) and enhanced operative autonomy (25%) were identified as key factors to encourage recruitment of surgeons in their early career stages. Surgical residents in their early career stages in Germany regard TS as an appealing career option. A structured training framework is a perceived unmet need to enhance recruitment to TS. Transplantation surgery, workforce sustainability, medical education

KEYWORDS
medical education, surgical residents, training pathways, transplantation surgery, workforce sustainability

Introduction

The future of transplantation surgery (TS) depends not only on scientific and technical advances but also on the ability to attract, train, and retain the next-generation of surgeons. Globally, TS faces unique challenges in workforce development due to its complexity, demanding schedules [1, 2], and lack of standardized training pathways in many countries. These challenges are also evident in the German context [3]. Contributing factors include low workforce retention and comparatively modest procedural volumes within the subspecialty [3, 4]. The median caseload per surgeon remains limited, with 16 liver transplants performed annually, and fewer than 20% of these surgeons having completed formal subspecialty training. Loss of early-career surgeons to alternative subspecialties further underscores the systemic difficulties, as most surgeons involved in

GRAPHICAL ABSTRACT

liver transplantation exit the field after a median of just 3.5 years [4]. This trend potentially compromises the continuity and quality of surgical care.

Beyond structural deficits, gender-specific and generational differences also appear to influence interest and persistence in TS [5]. In Germany, despite increasing numbers of women entering surgical residency, they remain significantly underrepresented in leadership roles and high-complexity subspecialties such as transplantation [6, 7]. To date, however, there has been no systematic national assessment on the sustainability of the transplantation's workforce, which translates to how surgical residents in Germany perceive TS as a potential career path. Understanding their motivations, barriers, and expectations is critical to informing structural reforms, amid a perceived static or declining interest from trainees.

To assess these perceived challenges and the attitude of young surgical trainees, we conducted a nationwide survey with surgical residents in Germany. Specifically, we sought to (1) evaluate the level of interest in transplantation as a career, (2) identify structural and perceived barriers to pursuing TS, and (3) determine which supportive measures could enhance recruitment and retention. In doing so, we hope to provide a data-driven assessment that allows to form recommendations for strengthening the future transplant surgical workforce in Germany.

Materials and methods

An anonymous online survey was generated using the LimeSurvey platform[1]. The questionnaire was developed and drafted by two of the authors (AJP, PH). A review of the literature was conducted to identify existing frameworks and validated items that could be adapted to our context. The survey comprised 30 items designed to quantify the prevalence and relative importance of predefined motivators and barriers across a nationwide cohort of surgical residents, and to provide a broad, policy-relevant snapshot of which factors occur most frequently and are perceived as most limiting. To ensure clarity and relevance, the questionnaire was reviewed by experts in the field, including transplant surgeons, educators, and researchers, to validate the questions prior to distribution. The questionnaire was then piloted with 25 medical students rotating in our center. Their feedback, combined with input from experts, helped ensure the instrument's effectiveness in capturing the intended data and also eliminated any overlap with the targeted resident as samples. The final survey is available in *Supplementary Material 1*. The survey was then disseminated to all university hospitals and transplant centers registered with the *Deutsche Stiftung Organtransplantation* (DSO) across Germany. Contact information were obtained from publicly accessible institutional websites. In cases where individual contact information was unavailable, the survey was distributed via the head of department or the responsible program director. Participants were provided with an informed consent form *prior to* completing the survey, outlining the study's objectives, voluntary participation, and the use of anonymized data.

Any survey with incomplete responses was excluded prior to analysis to ensure consistency across all reported variables. Quantitative data were analyzed using IBM SPSS Statistics (version 29, IBM Inc., Armonk, New York, USA), with a p-value <0.05 considered statistically significant. The free-text responses are presented as a complementary component to contextualize and illustrate the quantitative findings, which were analyzed using thematic content analysis with iterative coding. All

1 www.limesurvey.org

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TABLE 1 Characteristic of respondents.

Variables	Sex			All	p
	M (n = 29)	F (n = 38)	Neutral (n = 1)		
Year of residency					0.20
Years 1–3	18 (60)	12 (31)	0 (0)	30	
Years 4–6	11 (40)	26 (69)	1 (100)	38	
Academic degree					0.44
No academic degree	13 (45)	19 (50)	0 (0)	32	
Dr. med	14 (48)	19 (50)	1 (100)	34	
Privatdozent	2 (7)	0 (0)	0	2	
Employment status					0.44
Full-time	29 (100)	36 (95)	1 (100)	66	
Part-time (≥75%)	0 (0)	2 (5)	0 (0)	2	
Interest in pursuing a surgical fellowship					**0.001**
Transplant surgery	10 (35)	7 (18)	1 (100)	18	
Other surgical fellowship	16 (55)	26 (68)	0 (0)	42	
Not interested	3 (10)	5 (14)	0 (0)	8	
Presence of mentor					0.77
Mentored by a Tx surgeon	12 (41)	14 (37)	0 (0)	28	
Mentored by a non-Tx surgeon	8 (28)	10 (26)	0 (0)	18	
No mentor	9 (31)	14 (37)	1 (100)	24	
Relationship status					**0.001**
Single	7 (24)	16 (42)	0 (0)	23	
Committed	22 (76)	20 (53)	0 (0)	42	
Prefer not to say	0 (0)	2 (5)	1 (100)	3	
Parental status					0.45
Parent	4 (14)	2 (5)	0 (0)	6	
Non-parent	25 (86)	36 (95)	1 (100)	62	

responses were reviewed, coded inductively, and refined into final themes. The study was conducted and reported in accordance with the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines (see *Supplementary Material 2*). In accordance with institutional guidelines, formal ethics approval was not required for this anonymous, non-interventional survey study involving healthcare professionals. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Characteristics of the respondents

A total of 96 responses were received. Out of these, eleven were excluded due to the respondents having already completed their surgical residency training, while another 17 submissions were incomplete and therefore excluded. The mean age of survey participants was 32 years (SD = 0.803), with 93% of respondents being under the age of 35. Of the respondents, 60% (n = 38) identified as female, 40% (n = 29) as male, and one respondent identified as gender neutral. More than half of the respondents (56%) held a German academic title (i.e., *Dr. med.*), and nearly all were employed in full-time clinical positions. The respondents represented all levels of residency training, with the majority being in their fourth year of training. Importantly, 90% of respondents expressed interest in pursuing a subspecialty fellowship in visceral surgery, with 25% of those (*n* = 17) specifically indicating an interest in TS. A higher proportion of men indicated interest in pursuing a TS certification (34.5% of men vs. 18.4% of women), whereas women were slightly more represented among those not interested in any additional

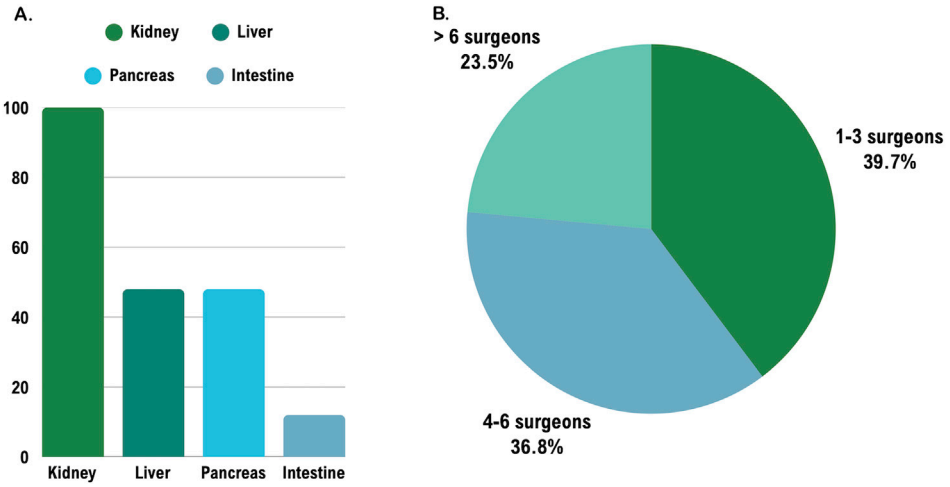

FIGURE 1
Percentage of **(A)** transplant procedures and **(B)** transplant surgeons at respondents' training centers.

certification (13.2% of women vs. 10.3% of men). Among the 68 respondents, 38.2% (n = 26) reported having a mentor who is a transplant surgeon. Another 26.5% (n = 18) indicated they had a mentor, but not in the field of TS, while 35.3% (n = 24) reported having no mentor at all. Regarding the personal characteristics, a significantly higher proportion of male respondents reported being in a committed relationship compared to female respondents (75.9% of men vs. 52.6% of women, p 0.001). Conversely, female residents were more likely to report being single (42.1% of women vs. 24.1% of men, p 0.001). Only 9% of respondents (n = 6) reported having children (Table 1).

Characteristics of the respondents' training centers

Respondents were asked to report which types of solid organ transplantation were actively performed at their respective training centers (Figure 1). Kidney transplantation was the most widely available, performed at all participating centers. Liver and pancreas transplantation were each reported as active programs at 71% of respondents' centers (n = 48), while intestinal transplantation was reported at 12% of respondents' centers (n = 8). Twenty-seven of respondents reported having 1–3 transplant surgeons in their center, and 25 respondents reported of having 4–6 transplant surgeons. Notably, 23.5% (n = 16) of respondents were based at institutions with more than six transplant surgeons. With regard to research involvement, only 23.5% of respondents (n = 16) reported active participation in transplantation-related research activities.

When asked about the availability of transplant-specific continuing education (i.e., seminars and courses) at their training centers, two-thirds of respondents indicated that such opportunities were offered only occasionally. Around one third reported no transplant-related educational activities, like seminar and workshop, at their institution, and only one respondent (1.5%) reported that such training occurred regularly. Despite this limited institutional provision, a strong majority (80.9%, n = 55) expressed a desire for more transplant-specific seminars or courses.

Involvement of surgical residents in transplant surgery

The level of surgical resident involvement varied considerably across different types of transplant procedures. In liver transplantation, half of the respondents (50%, n = 34) reported serving as second assistants, while 16.2% (n = 11) were involved as first assistants. Only 10.3% (n = 7) were not involved at all. Notably, 23.5% (n = 16) stated that liver transplantation was not performed at their center. In kidney transplantation, resident involvement was more evenly distributed. The largest proportion (44.1%, n = 30) served as first assistants, while 33.8% (n = 23) reported serving as second assistants. A smaller subset (5.9% each, n = 4) reported either leading the operation under supervision or performing the procedure independently. No involvement was reported by 10% (n = 7). In pancreas transplantation, involvement was less pronounced: 48.5% (n = 33) reported assisting as second assistants, 27.9% (n = 19) as first assistants, and 14.7% (n = 10) were not involved. Regarding organ procurement, 45.6% (n = 31) had assisted, and 5.9% (n = 4) had taken on an active operative role under supervision in the procurement process.

Resident independence in back table or bench preparation was minimal across all organ types. In liver transplantation, 98.5% (n = 67) of respondents reported no independence during back table preparation, with only one respondent (1.5%) being able to do the procedure independently. Similarly, for kidney transplantation, only 7.4% (n = 5) did the back table work independently. None of the respondents (n = 68) had independence in back table preparation for pancreas transplantation.

Factors influencing the pursuit of a formal fellowship training

Respondents were asked to rate the importance of various factors in their decision to pursue additional subspecialty training using a 5-point Likert scale (1 = not important at all; 5 = very important). The most influential factor was personal interest in

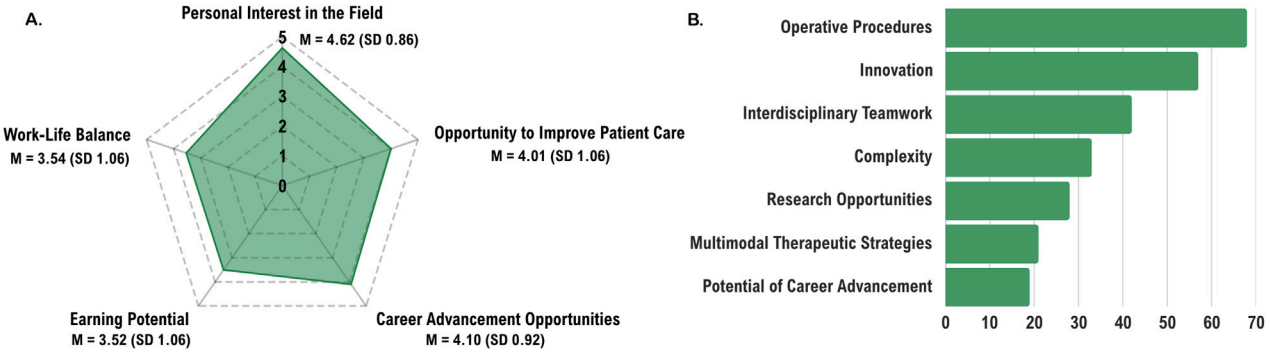

FIGURE 2
Factors influencing interest in fellowship **(A)** overall **(B)** in transplantation surgery.

the subject matter itself, with a mean score (M) of 4.62 (SD = 0.86), followed by the perceived opportunity to improve patient care (M = 4.01, SD = 1.06) and career advancement prospects (M = 4.10, SD = 0.92). Earning potential (M = 3.53, SD = 1.06) and work-life balance (M = 3.54, SD = 1.06) were rated moderately important (Figure 2A). Further analysis by gender revealed no statistically significant differences between male and female residents regarding the factors influencing their decision to pursue a fellowship.

Factors influencing the pursuit of transplant surgery as a career option

With regards to which aspects of transplant surgery the respondents found appealing, the operative procedures itself were universally regarded as engaging, with all respondents expressing interest in the surgical aspects of the field (Figure 2B). A substantial majority reported enthusiasm for innovation (83.8%, n = 57), followed by interest in interdisciplinary teamwork (61.8%, n = 42). About 48.5% (n = 33) were drawn to the intellectual and clinical complexity of the specialty while 41.2% (n = 28) expressed interest in the field's research opportunities. Multimodal therapeutic approaches appealed to 30.9% (n = 21) of respondents. In contrast, only 27.9% (n = 19) viewed career advancement prospects as a motivating factor. No statistically significant gender differences were observed in the distribution of these responses. When asked about their geographic willingness to relocate in order to receive formal training, i.e., fellowship in TS, the majority of respondents (55.9%, n = 38) indicated openness to training opportunities anywhere in the world. An additional 16.2% (n = 11) preferred to remain within Germany, while 11.8% (n = 8) expressed willingness to relocate within the European Union. Only 16.2% (n = 11) reported unwillingness to relocate for a transplant fellowship, mostly due to personal reasons.

Mentorship was identified as a motivating factor by 14.7% (n = 10), who indicated that their interest in TS was inspired by their mentor. Eight respondents (11.8%) reported that they were already interested in TS and intentionally sought out a mentor in the field. A considerable proportion (38.2%, *n* = 26) remained undecided about the mentor's influence, and 35.3% (*n* = 24) felt that their mentor did not impact their interest in TS.

Barriers and opportunities: resident perspectives on advancing a career in transplant surgery

In examining the perceived feasibility to have a career in TS, the majority of respondents expressed a positive inclination (Figure 3A). Specifically, 42.6% (*n* = 29) responded "probably yes" and 30.9% (*n* = 21) selected "definitely yes," together representing nearly three-quarters (73.5%) of all respondents. Conversely, 23.5% (*n* = 16) indicated "no," and only a small minority (2.9%, *n* = 2) stated they could not imagine pursuing a career in TS at all. The surgical residents then rated the potential barriers to pursuing a career in TS on a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree) (Figure 3B). The most strongly endorsed barrier was the lack of a structured training pathway (M = 3.97, SD = 0.36) and unclear training duration (M = 3.93, SD = 0.46), followed by a limited operative autonomy during residency (M = 3.68, SD = 0.74). Work-life balance factors also featured prominently, with lack of free time (M = 3.71, SD = 0.75). Additional concerns included the absence of protected operating time for transplant cases (M = 3.66, SD = 0.92) and the perceived constraint of being tied to a transplant center (M = 3.61, SD = 1.06). High stress levels (M = 3.62, SD = 0.88) identified as relevant obstacles. Personal or perception-based factors were viewed as less limiting: private reasons scored lowest (M = 2.92, SD = 0.87), followed by the technical complexity of transplant surgery (M = 2.80, SD = 0.74). The intrinsic challenges of the field itself were not major deterrents for most respondents. No significant gender differences were observed in the perception of these barriers. These findings highlight that structural and systemic barrier, rather than personal preferences or technical concerns, are the predominant deterrents to pursuing a career in transplant surgery.

Residents predominantly emphasized the need for structured training programs encourage them to pursue a career in TS. Specifically, 45.6% (*n* = 31) selected clear and standardized subspecialty program, such as defined fellowships, as the most critical pulling factor. Mentorship was also highlighted to be important, with 26.5% (*n* = 18) of respondents emphasizing the need for guidance from experienced transplant surgeons. A comparable proportion (25.0%, *n* = 17) underscored the importance of gaining hands-on operative experience during residency, particularly through involvement in smaller

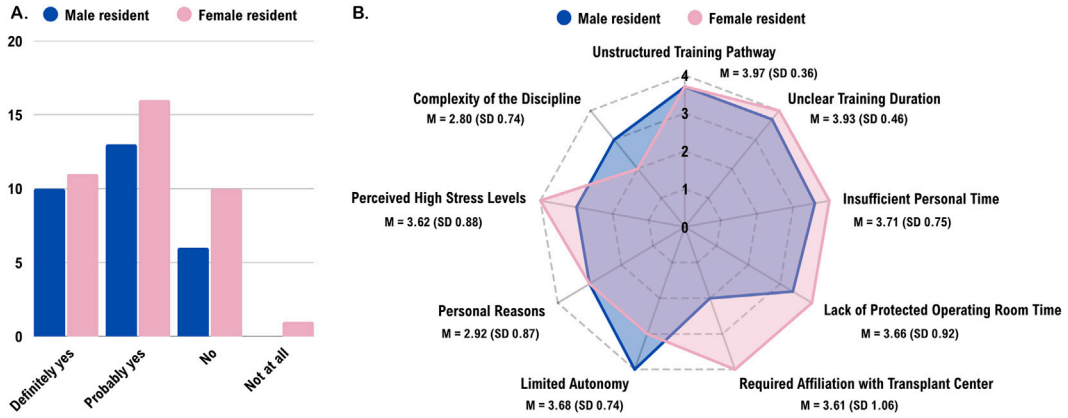

FIGURE 3
(A) Perceived feasibility in having career in transplant surgery **(B)** perceived barriers to residents' engagement in transplant surgery.

FIGURE 4
Key drivers of resident engagement in transplant surgery.

procedures such as colorectal surgery or participation in specific steps of hepatopancreatobiliary (HPB) operations. Such exposure was viewed as essential for developing a comprehensive surgical perspective and operative autonomy, thus confident in thinking about career in TS. In contrast, opportunities for research and publication were considered less critical at this stage of training, with only 2.9% ($n = 2$) identifying them as a primary support need. Qualitative responses further emphasized the central role of training structure and autonomy. Several respondents expressed concerns regarding a lack of operative autonomy during training ($n = 6$) and cited this as a deterrent to pursuing the specialty (Figure 4). Other recurring themes included the need for improved working hours and work-life balance ($n = 5$), direct intraoperative teaching ($n = 5$), and greater involvement in perioperative decision-making, including organ allocation decisions ($n = 5$). Further, the absence of engagement from their institutions also serves as a barrier to professional development in TS. Nearly half of the respondents (47.1%, $n = 32$) reported lacking support in pursuing a career in TS from their institutions, while 45.6% ($n = 31$) indicated having partial support. A small minority (7.4%, $n = 5$) felt fully supported in this career path. Notably, a statistically significant association was found between gender and the aspiration to hold a leadership position in transplant surgery ($p = 0.018$). Overall, 75% (n = 51) of respondents expressed a desire to assume leadership roles. When stratified by gender, 89.7% of male respondentsindicated interest in leadership positions, compared to 65.8% of female respondents.

Discussion

This national survey provides updated insights into the attitudes, exposures, and perceived barriers faced by surgical residents in Germany with respect to having a career in TS from the last decade [3]. Our findings reveal both significant latent interest in the field and notable structural and educational shortcomings that hinder the translation of this interest into formal career progression. These results mirror, and in some aspects update, findings from previous workforce assessments among transplant surgeons and trainees in Germany and across Europe [8, 9]. The data increasingly suggest that Germany is facing a pipeline crisis. A national survey among over 1,000 German medical students revealed that only 14% planned to enter a surgical specialty of any kind. Among female students, this number drops even further to just 11%, which is especially notable considering they comprise 64% of the student population [10]. The translation from surgical residency to a transplant surgeon represents the next critical hurdle [4]. Importantly, this concern is not confined to Germany. Both the United States and the United Kingdom, despite having more structured surgical

training pathways, are facing mounting challenges in sustaining a robust transplant workforce [8, 11, 12].

Nearly three-quarters of respondents expressed a willingness to consider a career in TS. This level of expressed interest is encouraging and suggests that TS continues to exert a meaningful appeal among trainees. Operative procedures, innovative techniques, and interdisciplinary teamwork were ranked among the most appealing aspects of the specialty, consistent with prior research on motivational factors in both general and TS. However, the observed enthusiasm sharply contrasts the actual structural environment in which residents are trained. Exposure to transplant procedures remains highly dependent on institutional setting and mentorship [2]. Operative autonomy during residency remains a critical issue in surgeon's attrition, not limited to transplant procedures alone [3, 13, 14]. Back table preparation, an essential component of the transplant surgical process and a proxy for procedural trust and responsibility, was seldom performed independently. Only one respondent reported independent performance for liver grafts, and none for kidney and pancreas. This echoes previous concerns regarding limited hands-on exposure among trainees and reflects a training environment that continues to prioritize technical performance by senior staff, often at the expense of skill transfer. Interest, and thus, attrition in TS was associated with lower operative volumes, a narrower case mix, and worse patient and graft survival after liver transplantation [2, 9, 15].

To enhance early exposure during residency, it would be beneficial to partially integrate a transplant surgery curriculum. While this is challenging due to the limited number of transplant centers and the constraints of the existing Facharzt training structure in Germany, a structured transplant rotation for those training at the DSO-registered transplant centers should be encouraged, similar to models in the United States. Such rotations would standardize baseline exposure across institutions and ensure all surgical residents acquire essential competencies in transplant surgery, including perioperative management, pre-transplant evaluation, waiting-list processes, complication management (e.g., hyponatremia, spontaneous bacterial peritonitis, refractory ascites), and participation in multidisciplinary kidney and liver selection committee meetings. Programs should promote progressive operative autonomy through staged responsibility models to enhance motivation, skill development, and retention. Additionally, virtual simulation tools and targeted workshops could enhance exposure to transplant scenarios, including operative procedures and management related to the waiting list. These solutions would be particularly beneficial in centers with lower case volumes, aiming to increase hands-on experience and decision-making autonomy for residents.

It has been shown that an effective transplant surgery fellowship should offer substantial case volume, high procedural complexity, and operative autonomy, enabling trainees to independently manage both surgical and nonsurgical aspects of transplant patient care. This educational triad has been repeatedly emphasized as essential for skill maturation and professional identity formation in surgical subspecialties such as transplant and HPB surgery [11, 14]. These concerns are corroborated by prior national studies showing that only a minority of German transplant surgeons dedicate more than 10% of their operative time to transplantation, with most maintaining broader clinical identities in HPB or general surgery [2, 3, 6].

A potential framework for a transplant fellowship could involve a structured, stepwise educational curriculum. The initial 6 months could focus on donor procedures, including multi-visceral deceased donor organ procurement and first-assist roles in transplant cases. This foundational phase would be complemented by research projects, journal clubs, and literature review sessions led by senior staff members, aimed at providing in-depth preparation for the subsequent rotations. These rotations would include living donor procedures, as well as kidney, pancreas, and liver transplants, with fellows ultimately performing these procedures as the lead surgeon. To ensure comprehensive skill development and exposure, the fellowship training should be completed over two consecutive years. Fellows would progress from "junior" status in the first year to "senior" status in the second year, providing a clear structure for training progression. A two-year timeframe would establish a practical and focused training period, addressing the current lack of a defined fellowship pathway in Germany, where training is often unstructured and lacks consistency across institutions. Furthermore, identifying "certified" training centers, typically the largest and most experienced institutions in the country, would ensure that fellows receive maximum exposure to high-volume cases within this structured period. In France, the cardiovascular surgical residency program exemplified how early, dedicated exposure combined with structured mentorship can effectively promote operative autonomy and interest among residents, including in TS [16]. Here, the DSO could also play a role in establishing a national minimum framework for transplant training by defining standardized exposure requirements for trainees at accredited centers. In addition, the DSO is well positioned to develop and facilitate transplant-related educational courses, such as those focused on organ donation processes and the associated logistical infrastructure, to further support uniform, high-quality training across institutions.

Work-life balance and emotional workload were also noted as barriers, although they appeared to be secondary to the structural constraints. This is an important distinction. While lifestyle factors have traditionally been assumed to deter younger physicians from demanding specialties such as transplantation [2, 17, 18], our findings suggest that these factors play a comparatively smaller role. The interest is clearly present, yet a discrepancy persists, including academically [18]. While 41.2% of respondents indicated an interest in research opportunities within TS, only 23.5% were actively involved in transplantation-related research. This mismatch is not unique to transplant surgery and reflects broader trends in surgical training. It is important to note that protected research time and mentoring consistently shown to yield significant long-term academic benefits. It is strongly associated with higher publication productivity, a greater likelihood of obtaining external funding, an increased probability of pursuing a career in academic surgery, and improved progression into leadership roles [19].

Our study identifies a significant gender gap in leadership aspirations (89.7 percent among male residents versus 65.8 percent among female residents), consistent with findings

from previous studies. Addressing this disparity requires structured mentorship and active sponsorship, transparent leadership pathways, systematic monitoring of operative autonomy, early leadership development during residency, family-compatible training structures without career penalty, and greater visibility of female role models in transplantation surgery.

Mentorship, widely recognized as a key driver of career development, was inconsistently available as per our analysis. In contrast, in systems with well-established fellowship structures, such as the ASTS model in the United States, mentorship has been shown to play a formative role in guiding young surgeons toward transplant careers [1, 2, 18]. Our data suggest that while mentorship does occur, it is neither systematic nor sufficient to guide career formation in transplantation in the current German context.

A critical aspect, and a limitation of this survey, is the fact that it is aimed at residents only. While the overall interest and motivation to pursue a career in TS is there, a survey to follow up on the development of this motivation at a later age would be equally important in order to see how perceptions develop following graduation from a residency program, which will translate to more operative autonomy after becoming a surgeon (*Facharzt/Fachärztin*). A wide range of trainees at institutions without a transplant program were not addressed here, even though their interest in pursuing a career in transplant surgery or their interest in exposure or rotations to transplant programs would be of interest.

Conclusion

In summary, this study highlights a critical tension between the enduring appeal of TS to surgical residents in Germany and the structural improvement options of the current training environment. When surgical training does not consistently translate into long-term commitment to subspecialties like TS, the field faces a serious challenge. Transplant surgery, by its nature, demands high levels of skill, dedication, and institutional support. Yet without structural improvements, its future workforce may remain vulnerable. Systematic educational reforms during residency, implementation of structured fellowship programs, and improved mentorship are possible ways to enhance recruitment to transplant surgery and positively influence workforce sustainability.

Data availability statement

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

Ethics statement

In accordance with institutional guidelines, formal ethics approval was not required for this anonymous, non-interventional survey study involving healthcare professionals. The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was not required.

Author contributions

AP and PH: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis; AP: Visualization, Writing; KB, AO, SN, MG, and CM: Review and Editing; PH: Review and Editing, Supervision. 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.2026.15736/full#supplementary-material

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Prepared or at-risk? Evaluating live viral vaccine coverage and vaccine immunogenicity before pediatric solid organ transplantation

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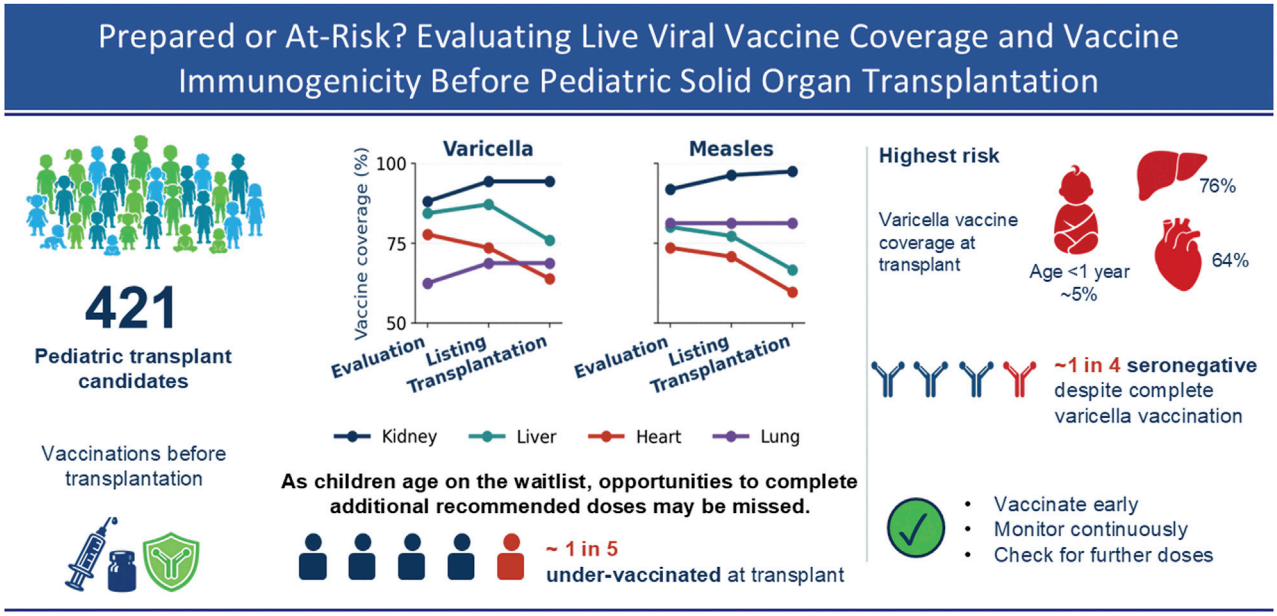
Pediatric solid organ transplant recipients are at high risk for complications from vaccine-preventable diseases, yet pre-transplant vaccination coverage is often inconsistent. We conducted a retrospective cohort study of 421 pediatric transplant recipients between 2018 and 2024 to evaluate vaccination status and serologic immunity for varicella and measles at the time of initial evaluation, listing, and transplantation. At the time of transplant, 19.2% of patients for varicella and 21.6% for measles were under-vaccinated, with infants having the highest rates of incomplete vaccination. A portion of patients (7.1% for varicella, 8.6% for measles) transitioned from full to incomplete vaccination status during the pre-transplant period, a change associated with a shorter time from evaluation to listing. Kidney recipients had the highest completed vaccination rates (>94%), whereas rates for liver and heart recipients were substantially lower (58%–72%). Among fully vaccinated patients, seronegativity was observed for varicella (23.6%) and measles (13.0%). In conclusion, many pediatric transplant candidates, particularly infants and those awaiting liver or heart transplant, are incompletely vaccinated. A dynamic change in vaccination status from evaluation to transplant highlights an urgent need for continuous monitoring and improved strategies to protect these vulnerable children.

KEYWORDS
Measles, pediatric solid organ transplantation, serology, vaccination before transplantation, varicella



Introduction

Pediatric solid organ transplant (SOT) recipients are at increased risk for severe complications from vaccine-preventable diseases such as measles, mumps, rubella, and varicella [1]. Because live viral vaccines are often avoided after transplantation, pre-transplant vaccination is essential to protect patients in the vulnerable post-transplant period [2].

Despite recommendations, studies have shown that many SOT candidates remain incompletely vaccinated or are seronegative at the time of transplantation [1, 3]. Contributing factors include early transplantation before completion of routine immunizations, missed opportunities for catch-up vaccination, and inconsistent implementation of pre-transplant vaccination protocols across centers [4]. This gap in protection is especially concerning in light of recent outbreaks of measles and varicella, which can be attributed in part to declining vaccination rates during the COVID-19 pandemic [5, 6]. Transplant recipients are particularly vulnerable during such outbreaks, underscoring the need for optimized pre-transplant immunization strategies [7, 8].

While prior reports have provided valuable cross-sectional assessments, the specific vulnerabilities and dynamic changes in vaccination status during the pre-transplant period remain poorly defined. In this study, we retrospectively evaluated pre-transplant vaccination status and serologic immunity against measles and varicella in a large pediatric SOT cohort to identify gaps in protection and provide insight into modifiable, system-level practices that could sustain high vaccine coverage. Unlike prior cross-sectional reports, this study offers a longitudinal, organ-specific assessment of vaccination coverage at multiple pre-transplant milestones (evaluation, listing, and transplantation) and integrates serologic data to identify immunity gaps.

Materials and methods

Study overview and patient selection

A retrospective cohort study was conducted at Cincinnati Children's Hospital Medical Center (CCHMC), a tertiary care center with active pediatric SOT programs. The study included recipients of a first liver, kidney, heart, lung, intestinal, or multi-visceral transplant between January 1, 2018, and December 31, 2024. Demographic and clinical data were extracted from the electronic medical records, including age at first transplant evaluation, listing and transplantation dates, sex, underlying diagnosis, type of transplanted organ, vaccination records, and serologic results. Vaccination records were obtained from patients' electronic medical records, which are routinely updated with internal and external vaccine records by the infectious diseases clinic during the standard pre-transplant assessment. Patients were excluded if they lacked vaccination records or were not transplanted at CCHMC.

Abbreviations: AST, American Society of Transplantation; CCHMC, Cincinnati Children's Hospital Medical Center; CKD, Chronic kidney disease; IDCOP, Infectious Diseases Community of Practice; IDSA, Infectious Diseases Society of America; IQR, Interquartile range; IRB, Institutional Review Board; MMR, Mumps, measles, and rubella; SOT, Solid organ transplant; VZV, Varicella-zoster virus.

Vaccination status

Vaccination status was determined for measles and varicella based on documented vaccination records. *Completed vaccination* was defined separately for measles and varicella as meeting the following criteria for different age groups:

Measles

- 6 – <12 months of age: One dose of mumps, measles, and rubella (MMR) vaccine (accelerated regimen)
- ≥12 months - <4 years of age: At least one dose of MMR
- ≥4 years of age: Two or more doses of MMR

Varicella

- 9 – <12 months of age: One dose of varicella-zoster virus (VZV) vaccine (accelerated regimen)
- ≥12 months - <4 years of age: At least one dose of vaccine
- ≥4 years of age: Two or more doses of vaccine

The vaccination status of each patient was assessed at three separate time points: initial evaluation, listing for transplant, and date of transplant. Patients could transition from one age group to another between these time points affecting their immunization status. This temporal approach aimed to determine patients' complete vaccination needs as they aged in the pre-transplant period. The lower age limits for starting MMR and VZV vaccinations in patients (≥6 months for MMR and ≥9 months for VZV) were defined according to the guidelines of the American Society of Transplantation Infectious Diseases Community of Practice (AST IDCOP) [2]. Patients younger than the lower age limits at one of the assessment points were accepted as completely vaccinated for that timepoint. While vaccination status was documented, the specific reasons for incomplete vaccination, such as patient or parental vaccine refusal, were not routinely collected in the medical record and thus could not be analyzed. For the one to <4 years age group, completed vaccination was defined as at least one dose of MMR or varicella vaccine to align with age-based eligibility at the time of assessment. While clinical practice at our center aims to administer a second dose if the pre-transplant window allows for the recommended interval between doses, the one-dose threshold was maintained for this analysis to provide a standardized metric of basic coverage. In a sensitivity analysis, complete vaccination for the 1–<4 years group was redefined as two doses and the multivariable models repeated. Pre-transplant seropositivity in this group was also compared between one- and two-dose recipients at the time of testing.

Vaccine immunogenicity

Pre-transplant vaccine immunogenicity was assessed using commercial chemiluminescent immunoassays (LIAISON, DiaSorin) in routine clinical practice: varicella-zoster virus IgG qualitatively at our institutional laboratory (seropositive >1.0 S/CO) and measles (rubeola) IgG at a reference laboratory (ARUP Laboratories, Salt Lake City, UT; positive ≥16.5 AU/mL, with equivocal results [13.5–16.5 AU/mL] classified as seronegative). Serologic status was analyzed dichotomously (seropositive vs. seronegative); numerical titers were not included. If testing was not performed, immunity status was recorded as unknown.

Data analysis

Descriptive statistics were used to summarize the data. Categorical variables were expressed as counts and percentages, while continuous variables were summarized using medians and interquartile ranges (IQRs). Comparisons between groups were performed using Chi-square or Fisher's exact test for categorical variables and Mann–Whitney U or Student's t-test for continuous variables. A two-sided p-value <0.05 was considered statistically significant. Analyses were conducted using IBM SPSS Statistics (Version 30).

Ethical approval

This study was approved by the CCHMC Institutional Review Board (IRB ID:2023-0334). Due to the study's retrospective nature and the use of de-identified data, the requirement for informed consent was waived in accordance with institutional policy.

Results

Study cohort

During the 7-year study period, a total of 457 patients were evaluated for solid organ transplantation at CCHMC. Twenty patients who were not transplanted at CCHMC and 16 patients who had second or subsequent transplantations were excluded from the study, leaving a total of 421 SOT recipients in the analysis (Figure 1). The distribution of the transplants in the study cohort was 38.0% kidney (160/421), 33.5% liver (141/421), 17.1% heart (72/421), 3.8% lung (16/421), 2.6% heart-dual organ (11/421), and 5% abdominal multi-visceral and intestinal transplant (21/421). The number of transplants per organ type for each calendar year is shown in Supplementary Figure S1.

Patient demographics

Among 421 patients, 53.7% (226/421) were male. The median age at transplantation was 8 years (range 0.6–38.4 years). Most patients (60.3%, 254/421) were >4 years old, while infants (<12 months) and toddlers (1–<4 years) comprised 13.3% (56/421) and 26.4% (111/421), respectively. Median times between evaluation and listing for transplantation, and between listing and operation were 42 and 114 days, respectively (Table 1).

Vaccination status of the patients

Vaccination status was assessed for the same cohort of 421 recipients at all three time points (evaluation, listing, and transplantation), reflecting longitudinal follow-up of one population rather than separate groups. As age-based eligibility was reassessed at each milestone, the number of completely vaccinated patients could increase through catch-up vaccination or decrease as patients aged into categories requiring additional doses.

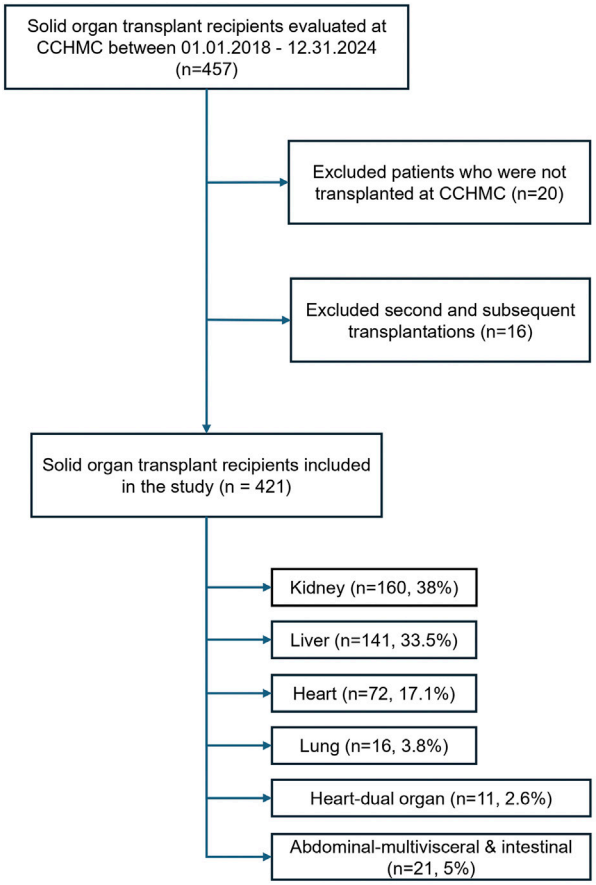


FIGURE 1
Study cohort and subgroups. The flow diagram illustrates the application of exclusion criteria to define the final study population and shows the distribution by transplanted organ.

Varicella

In the cohort, at the time of evaluation, listing, and transplantation, 83.1% (350/421), 86.5% (364/421), and 80.8% (340/421) were fully vaccinated against varicella, respectively (Table 2). Vaccination coverage varied significantly by age. The lowest coverage rates were observed in the 9 – <12 months age group, where none of the 13 patients were vaccinated at evaluation (0/13). Among patients who were 9–<12 months of age at the time of listing and transplantation, only 7.69% (1/13) and 5% (1/20) had received complete vaccination, respectively. Among children aged 1–<4 years, the complete vaccination rate declined from 82.7% (81/98) at initial evaluation to 74.6% (82/110) at the time of transplantation. In contrast, patients aged 4 years or older demonstrated high and improving coverage, with 82.8% (197/238) vaccinated at evaluation and 86.6% (220/254) at transplantation. Despite these rates, 19.2% of the study population (81/421) ultimately underwent transplantation without the recommended age-specified varicella vaccination. Organ-specific analyses revealed that kidney transplant recipients had the highest proportion of completely vaccinated patients regarding varicella (94.4%, 151/160), while the lowest rates were observed among lung (68.8%, 11/16) and heart (63.9%, 46/72) recipients.

Measles

Complete measles vaccination rates at the time of evaluation, listing, and transplantation were 83.1%, 83.6%, and 78.3%, respectively (Table 2). The lowest rates of coverage were observed in the 6 – <12 months age group, with only 3.3% (1/30) fully vaccinated at evaluation. In patients who were 6 - <12 months of age at listing and transplantation time, only 11.1% (4/36), and 7.1% (3/42) of them had received complete vaccination, respectively. Among children aged 1 – <4 years, the rate of complete vaccination declined from 82.7% (81/98) at initial evaluation to 75.45% (83/110) at the time of transplantation. In contrast, patients older than 4 years consistently had high coverage rates, with 89.9% (214/238) and 87.4% (229/254) at evaluation and transplantation, respectively. Notably, 21.6% of the entire study population (91/421) underwent transplantation without receiving the complete recommended measles vaccination. The highest pre-transplant measles vaccination rate was found among kidney recipients (97.8%, 156/160), whereas patients undergoing liver (66.7%, 94/141) and heart (59.7%, 43/72) transplants exhibited the lowest vaccination rates.

Changes in vaccination status from the first evaluation to transplantation

During follow-up, changes in pre-transplant vaccination status were observed in a subset of patients (Figure 2). For varicella, 7.1% (30/421) of patients transitioned from full to incomplete status, most frequently among heart transplant recipients (10/72, 13.9%) and liver transplant recipients (17/141, 12.1%), primarily based on changes in age category. Conversely, 4.8% (20/421) improved from incomplete to complete, primarily among kidney (11/160, 6.9%), liver (5/141, 3.5%), and lung (1/16, 6.3%) candidates, with no improvement observed in heart and heart-dual organ recipients. Similarly, for measles, 8.6% (36/421) transitioned to incomplete vaccination status, with the highest rates among liver (25/141, 17.7%) and heart (10/72, 13.9%) recipients. Improvement occurred in 3.8% (16/421), most commonly among kidney (9/160, 5.6%) and liver (6/141, 4.3%) transplant candidates, while no improvement was noted in lung, heart, or heart-dual organ recipients.

Factors for incomplete vaccination

To identify patient characteristics associated with the risk of incomplete vaccination status at the time of transplantation, we compared demographics and clinical factors (Table 3). In this analysis, only cases exceeding the lower age limit of the relevant vaccine were included as vaccine-eligible (384 patients for varicella, and 406 patients for measles vaccination).

The distribution of organ types differed significantly for both varicella and measles ($p < 0.05$ for both). For varicella, liver and heart candidates were disproportionately represented in the incompletely vaccinated group, accounting for 42.0% (34/81) and 32.1% (26/81) of

TABLE 1 Demographics of the pediatric solid organ transplant recipients.

Characteristics	All recipients (n = 421)
Age groups at transplant *(n, %)*	
0 – <12 months	56 (13.3%)
1 – <4 years	111 (26.4%)
≥4 years	254 (60.3%)
Transplanted organ *(n, %)*	
Kidney	160 (38.0)
Living donor (kidney)	60 (37.5)*
Liver	141 (33.5)
Living donor (liver)	11 (7.8)*
Heart	72 (17.1)
Lung	16 (3.8)
Heart-dual organ	11 (2.6)
Abdominal – multivisceral and intestinal	21 (5.0)
Age at transplant, *median (IQR), years*	8 (2.2–15.7)
Kidney	11.4 (3.8–16.2)
Liver	2.9 (0.9–11.3)
Heart	6.1 (1.3–15.1)
Lung	15.2 (10.1–17.4)
Heart-dual organ	20.7 (15.2–22.2)
Abdominal – multivisceral and intestinal	3.5 (2.2–9.8)
Sex (n,%)	
Male	226 (53.7)
Female	195 (46.3)
Duration between time points, *median (IQR), days*	
Starting of evaluation to listing for transplantation	42 (20–109.5)
Listing for transplantation to the operation	114 (37.5–267.5)

IQR: interquartile range.
*Living-donor frequencies are shown for kidney and liver recipients with percentage within each organ group; the remainder received deceased-donor transplants.

this cohort, respectively. In contrast, kidney recipients comprised nearly half of the fully vaccinated group (49.8%, 151/303) but only 11.1% (9/81) of the incompletely vaccinated group.

For measles, the disparity between organ groups was even more pronounced. Liver and heart candidates together constituted 83.5% of the incompletely vaccinated cohort (51.6% [47/91] and 31.9% [29/91], respectively). Conversely, kidney recipients accounted for 49.5% (156/315) of fully vaccinated patients but only 4.4% (4/91) of those who were incompletely vaccinated, highlighting a strong association between organ type and the likelihood of completing the recommended measles vaccination series before transplantation. While the lung transplant group had the second-lowest observed rate of complete vaccination (68.8%) for varicella, due to the small number of lung transplants, the difference between their vaccination rates in vaccine-eligible patients was not statistically significant.

Age was also a significant factor; children under 1 year of age at the first evaluation accounted for nearly half of those incompletely vaccinated for varicella (48.1%) and the majority of those incompletely vaccinated for measles (64.8%) at the time of transplantation. Consequently, the median ages at evaluation, listing, and transplant were all significantly lower in the incompletely vaccinated groups ($p < 0.001$ for all, Table 3). The duration between initial evaluation and listing was significantly shorter for patients in the incompletely vaccinated groups for both varicella (median 28 vs. 58 days; $p < 0.001$) and measles (median 23 vs. 59 days; $p < 0.001$). In multivariable analysis (Supplementary Tables S1, S2), non-kidney candidates and younger patients had significantly higher odds of incomplete vaccination ($p < 0.05$). Conversely, the evaluation-to-listing interval lost significance after adjustment. This suggests organ type captures the clinical urgency driving shorter timelines, while young age remains a distinct, independent barrier. In a sensitivity analysis applying a stricter two-dose definition for the 1–<4 years group, non-kidney organ type and younger age remained independent predictors for both vaccines (Supplementary Tables S3, S4). No significant differences were observed based on sex, year of transplantation, or the duration from listing to transplantation.

Vaccine immunogenicity

Serological tests were not performed on all patients at each assessment point or vaccination. Overall, varicella and measles serology were available for 94.3% (397/421) and 57.9% (244/421) of patients, respectively. To minimize the effect of passive maternal antibodies, all tests from patients under 12 months of age were excluded from comparative analysis. In completely vaccinated recipients, pre-transplant seropositivity was 76.4% (217/284) for varicella and 87.0% (167/192) for measles.

Among 1–<4-year-olds with serology, most had received one dose (74.7% varicella, 81.5% measles). Varicella seropositivity was lower after one than two doses (67.7% [44/65] vs. 95.5% [21/22]; $p = 0.010$), with 9 of 10 initially seronegative children seroconverting after the second dose; measles was already immunogenic after one dose (95.5% vs. 100%; $p = 1.0$). Among fully vaccinated older children (≥4 years), differences in seropositivity rates for measles were observed across the organ groups ($p = 0.007$, Table 4). Post-hoc analysis revealed that the seronegativity rate in kidney recipients (25.4%) was significantly higher than the rates in both liver (0.0%) and heart (5.0%) recipients ($p < 0.05$). Additionally, older kidney recipients were significantly more likely to be seronegative than their younger counterparts (93.1% vs. 74.6%, $p < 0.05$). For varicella, a trend toward higher seropositivity was observed in liver recipients (88.9%) compared to kidney (72.9%) and heart (66.7%) recipients; however, this difference was not statistically significant ($p = 0.057$).

Discussion

In this study, we assessed the vaccination status and serologic response against measles and varicella in a large group of pediatric SOT recipients. Ensuring immunization before transplantation is important to minimize the risk of vaccine-preventable infections in immunocompromised children [2, 9]. Our cohort demonstrated high overall pre-transplant vaccination rates compared to previously reported studies. For instance, our completion rates for varicella (80.8%)

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TABLE 2 Varicella-zoster virus and measles vaccination status of the recipients at different time points.

Complete vaccination rates for varicella						
Study cohort	Evaluation		Listing		Transplantation	
(n = 421)	350/421	(83.1%)	364/421	(86.5%)	340/421	(80.8%)
Age group						
0 – <9 months	72/72	(100%)*	65/65	(100%)*	37/37	(100%)*
9 – <12 months	0/13	(0%)	1/13	(7.7%)	1/20	(5%)
1 – <4 years	81/98	(82.7%)	87/100	(87%)	82/110	(74.6%)
≥4 years	197/238	(82.8%)	211/243	(86.8%)	220/254	(86.6%)
Transplanted organ						
Kidney	141/160	(88.1%)	151/160	(94.4%)	151/160	(94.4%)
Liver	119/141	(84.4%)	123/141	(87.2%)	107/141	(75.9%)
Heart	56/72	(77.8%)	53/72	(73.6%)	46/72	(63.9%)
Lung	10/16	(62.5%)	11/16	(68.8%)	11/16	(68.8%)
Heart-dual organ	9/11	(81.8%)	9/11	(81.8%)	9/11	(81.8%)
Abdominal-MV. and intestinal	15/21	(71.4%)	17/21	(81.0%)	16/21	(76.2%)
Complete vaccination rates for measles						
Study cohort	Evaluation		Listing		Transplantation	
(n = 421)	350/421	(83.1%)	352/421	(83.6%)	330/421	(78.4%)
Age group						
0 – <6 months	54/54	(100%)*	42/42	(100%)*	15/15	(100%)*
6 – <12 months	1/30	(3.3%)	4/36	(11.1%)	3/42	(7.1%)
1 – <4 years	81/98	(82.7%)	88/100	(88%)	83/110	(75.5%)
≥4 years	214/238	(89.9%)	218/243	(89.7%)	229/254	(87.4%)
Transplanted organ						
Kidney	147/160	(91.9%)	154/160	(96.3%)	156/160	(97.5%)
Liver	113/141	(80.1%)	109/141	(77.3%)	94/141	(66.7%)
Heart	53/72	(73.6%)	51/72	(70.8%)	43/72	(59.7%)
Lung	13/16	(81.3%)	13/16	(81.3%)	13/16	(81.3%)
Heart-dual organ	9/11	(81.8%)	9/11	(81.8%)	9/11	(81.8%)
Abdominal-MV. and intestinal	15/21	(71.4%)	16/21	(76.2%)	15/21	(71.4%)

The same 421 recipients were assessed at all time points; counts may rise with catch-up vaccination or fall as patients age into categories requiring additional doses.
*For each assessment at a given time point, patients who were not eligible for the vaccine because of age were defined as having a complete vaccination status.
MV: multivisceral.

and measles (78.4%) are high compared to findings from a single-center cohort (54.9% and 69.2%, respectively) and a larger multicenter study (34% and 36%, respectively) [1, 3]. These results may reflect institutional policies that emphasize early consultation with infectious disease specialists and structured vaccine tracking for all transplant candidates.

Despite longstanding recommendations to complete live viral vaccinations prior to transplantation, our study found that a considerable proportion of pediatric candidates remained incompletely vaccinated at the time of transplantation. Our results are consistent with a broad body of evidence documenting similar, and in some cases more pronounced, gaps in care across various pediatric transplant populations. A multicenter European reference network survey revealed a systemic challenge, with complete immunization coverage of at least 80% of patients being achieved in only 57% of participating pediatric SOT programs [10]. A study from the US showed that only about half (54.9%) of pediatric transplant candidates had a complete varicella vaccination history, and only 69.2% had completed their age-appropriate measles vaccinations [1]. A study focused on European pediatric liver transplant programs reported that nearly 35% of the candidates were under-vaccinated for varicella [11]. A key reason identified for these gaps is often the insufficient time available for vaccination before a transplant is required.

The dynamic changes in pre-transplant vaccination status

A distinctive strength of our study lies in its organ-specific analysis and longitudinal tracking of vaccination status from

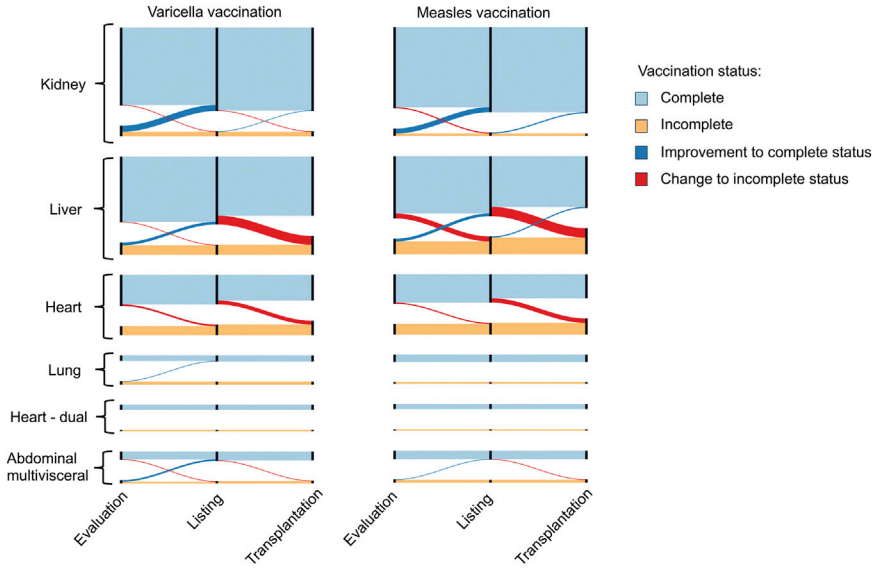

FIGURE 2
Sankey diagram illustrating changes in vaccination status for varicella and measles from evaluation to transplantation, stratified by organ group. Blue bands represent patients with complete vaccination status, while orange/red bands indicate incomplete status. The width of each flow is directly proportional to the number of patients at each time point, including evaluation, listing, and transplantation. Darker shades highlight transitions, where individuals change from complete to incomplete (dark red) or from incomplete to complete (dark blue). Substantial transitions in complete vaccination were particularly evident among liver and heart transplant recipients, for both varicella and measles.

initial evaluation to the time of transplantation. While other reports have provided valuable snapshots of incomplete vaccination across SOT populations, our longitudinal analysis, to our knowledge, is the first to document the transition of status systematically. This longitudinal approach revealed that overall vaccine coverage declined during the pre-transplant period, with a notable subset of patients—7.1% for varicella and 8.6% for measles—transitioning from complete to incomplete status rather than progressing toward schedule completion (Figure 2). As status was re-evaluated by age at each milestone, completely vaccinated counts could rise with catch-up vaccination or fall as patients aged into stricter requirements; the net decline thus reflects reclassification rather than loss of previously administered vaccines. The transition in vaccination status was most prominent in liver and heart transplant candidates. These shifts were primarily driven by age-based eligibility changes, highlighting the importance of continued, dynamic assessment of immunization status throughout the waitlist period.

Effects of patient age on incomplete vaccination

Notably, the lowest vaccination rates in our cohort were observed among infants aged 9 to <12 months. These low rates highlight a critical vulnerability in the youngest candidates, a finding that is strongly corroborated by other research. One study found that a staggering 81% of infants aged 6–11 months with documented vaccination status had not received the first dose of the varicella vaccine prior to transplantation [12]. The same study concluded that this specific age group accounted for nearly half (47%) of missed immunization opportunities for the first vaccine dose. Crucially, our multivariable analysis confirmed that younger age is an independent predictor of incomplete vaccination, distinct from the type of organ transplant. Although our criteria for toddlers (1 to <4 years) required only one dose for 'complete' status, the decline in coverage observed as patients age underscores the difficulty of completing the full two-dose series. This definition did not affect our conclusions on sensitivity analysis, but its serologic impact was vaccine-specific: a single varicella dose was seroprotective in only 67.7% (vs. 95.5% after two doses), whereas one measles dose sufficed (95.5%), supporting prioritization of two-dose varicella completion before transplantation. Nonetheless, where sufficient time exists before transplantation, these candidates should still complete the full two-dose measles schedule recommended by AST IDCOP [2]. Guidelines for transplant candidates suggest accelerating vaccination, including early initiation (MMR from 6 months, varicella from 9 months) and early completion (second dose before age 4). Our data, and those of others, demonstrate that uptake of the early first dose is lagging. Low vaccine uptake in this population is further demonstrated by the European network survey, which found that 39% of transplant programs reported never prescribing an accelerated schedule for live-attenuated vaccines to infants [10].

Specific reasons for incomplete vaccination were not systematically recorded; however, the decline among younger candidates likely reflects urgent transplantation, temporary medical contraindications, and missed opportunities for accelerated dosing. Broader implementation of accelerated schedules, both early initiation and completion, improved documentation and standardized tracking could help clarify these barriers and enhance preparedness.

TABLE 3 Comparison of characteristics among vaccine-eligible transplant recipients by vaccination status at the time of transplantation.

Variables	Varicella (n = 384)*					Measles (n = 406)**				
	Completely vaccinated (n = 303)		Incompletely vaccinated (n = 81)		P Value	Completely vaccinated (n = 315)		Incompletely vaccinated (n = 91)		P Value
Sex [*n,(%)*]					0.529					0.056
Male	171	(56.4)	42	(51.9)		179	(56.8)	41	(45.1)	
Female	132	(43.6)	39	(48.1)		136	(43.2)	50	(54.9)	
Organ group [*n, (%)*]										
Kidney	151	(49.8)	9	(11.1)	**<0.05**	156	(49.5)	4	(4.4)	**<0.05**
Liver	81	(26.7)	34	(42.0)	**<0.05**	84	(26.7)	47	(51.6)	**<0.05**
Heart	36	(11.9)	26	(32.1)	**<0.05**	38	(12.1)	29	(31.9)	**<0.05**
Lung	11	(3.6)	5	(6.2)		13	(4.1)	3	(3.3)	
Heart-dual	9	(3.0)	2	(2.5)		9	(2.9)	2	(2.2)	
Abdominal-MV. and intestinal	15	(5.0)	5	(6.2)		15	(4.8)	6	(6.6)	
Age [median years, (IQR)]										
Evaluation	10.3	(2.8–15.3)	1.1	(0.5–13.5)	**<0.001**	10.4	(2.8–15.4)	0.7	(0.4–3.6)	**<0.001**
Listing	10.5	(3.1–15.6)	1.2	(0.6–14.1)	**<0.001**	10.7	(3.1–15.8)	0.8	(0.5–4.0)	**<0.001**
Transplant	10.9	(3.6–16.2)	1.7	(1.0–14.9)	**<0.001**	11.1	(3.6–16.3)	1.2	(0.8–4.3)	**<0.001**
Age group at evaluation [*n, (%)*]										
<1 year	9	(3.0)	39	(48.1)	**<0.05**	11	(3.5)	59	(64.8)	**<0.05**
1 – <4 years	87	(28.7)	11	(13.6)	**<0.05**	88	(27.9)	10	(11.0)	**<0.05**
≥4 years	207	(68.3)	31	(38.3)	**<0.05**	216	(68.6)	22	(24.2)	**<0.05**
Duration [median days, (IQR)]										
Evaluation to listing	58	(26.0–144.0)	28	(15.0–78.0)	**<0.001**	59	(26.0–140.0)	23	(12.0–43.0)	**<0.001**
Listing to transplant	138	(39.0–297.0)	107	(51.5–213.0)	0.370	136	(40.0–298.0)	97	(41.0–169.0)	0.057

*Patients who were transplanted before 9 months of age are excluded from varicella vaccination-related analysis in this table.
**Patients who were transplanted before 6 months of age are excluded from the measles vaccination-related analysis in this table.
IQR, interquartile range; MV, multivisceral. Bold values indicate statistically significant differences ($p < 0.05$).

Organ-specific considerations for incomplete vaccination

In contrast to the kidney group, where we saw rates of full vaccination exceeding 94% for both measles and varicella, rates at transplant were considerably lower for liver (66.7% for measles, 75.9% for varicella) and heart recipients (59.7% for measles, 63.9% for varicella). One of the key findings of our study was the unique vulnerability of heart transplant candidates as the existing literature is limited by publication era or study design [1, 13, 14]. In the multicenter observational study from Europe that included 430 pediatric liver transplant recipients, varicella and measles vaccination coverage rates before transplantation were reported as 65.2% and 81.1% respectively [11]. Again, a multicenter cohort of 281 pediatric SOT recipients (96% liver) from the US reported similarly low pre-transplant vaccination rates of 36% for MMR and 34% for varicella [3].

The underlying reason for increased risk in liver and heart candidates appears to be the urgency of their clinical course. The challenge of a shortened timeline is directly supported by the survey of European transplant centers, where "insufficient time before transplant" was cited by 86% of programs as the primary reason for incomplete immunization [10]. In contrast, the relative stability and higher vaccination rates we observed among kidney transplant recipients may reflect their longer and more predictable pre-transplant course afforded by the availability of dialysis. In our analysis, the evaluation-to-listing interval lost significance after adjustment, suggesting organ type effectively proxies for the clinical urgency and limited vaccination window characterizing liver and heart transplantation. Liver candidates lack a comparable bridging therapy, and while pediatric heart candidates may be stabilized with mechanical circulatory support devices, their clinical course often remains urgent. This fundamental difference in pre-transplant management directly impacts the window of opportunity for completing immunization schedules, positioning kidney recipients at a distinct advantage for vaccination administration.

Vaccine immunogenicity in the patients

Our cohort's overall seropositivity rates in completely vaccinated children—76.4% for varicella and 87.0% for measles—appear more favorable but still demonstrate that a significant percentage of children who are up to date on vaccinations lack detectable antibodies. This discordance between vaccination records and humoral immunity is a well-documented challenge in transplant populations with one study of pediatric kidney candidates reporting seropositivity rates were as low as 59.0% for measles and 43.6% for varicella despite being fully vaccinated [15]. Another study found 50% seropositivity among children aged 7 years or older with two documented varicella vaccine doses [1].

TABLE 4 Comparison of the most recent pre-transplantation serological immunity and vaccination status at the time of the test.*

		Varicella (n = 305)						Measles (n = 201)					
Age group at the test time		1 – <4 years (n = 87)		≥4 years (n = 21)		≥4 years (n = 197)		1 – <4 years (n = 54)		≥4 years (n = 9)		≥4 years (n = 138)	
Vaccination status at the test time		Completely vaccinated (≥1 dose)		Incompletely vaccinated (1 dose)		Completely vaccinated (≥2 doses)		Completely vaccinated (≥1 dose)		Incompletely vaccinated (1 dose)		Completely vaccinated (≥2 doses)	
Transplanted organ		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Kidney	SN	15	(28.3)	4	(50)	26	(27.1)	2	(6.9)	0	(100)	16	**(25.4)**†
	SP	38	(71.7)	4	(50)	70	(72.9)	27	**(93.1)**‡	2		47	**(74.6)**‡
Liver	SN	6	(26.1)	2	(28.6)	5	(11.1)	0	(100)	0	(100)	0	**(100)**§
	SP	17	(73.9)	5	(71.4)	40	(88.9)	14		3		25	
Heart	SN	1	(16.7)	1	(50)	10	(33.3)	0	(100)	0	(100)	1	(5)
	SP	5	(83.3)	1	(50)	20	(66.7)	6		3		19	(95)
Other	SN	0	(100)	1	(25)	4	(15.4)	0	(100)	0	(100)	6	(20)
	SP	5		3	(75)	22	(84.6)	5		1		24	(80)
Overall	SN	22	(25.3)	8	(38.1)	45	(22.8)	2	(3.7)	0	(100)	23	(16.7)
	SP	65	(74.7)	13	(61.9)	152	(77.2)	52	(96.3)	9		115	(83.3)

*This analysis excludes two groups: patients who had never received the relevant vaccine and any serology tests performed before 12 months of age.

SN, seronegative; SP, seropositive. Bold values indicate proportions that differed significantly in the comparisons specified in footnotes †, ‡, and §.

†p = 0.007 for the comparison of kidney vs. all other organ recipients (including liver and heart) for measles seronegativity among completely vaccinated patients aged ≥4 years.

‡p = 0.048 for the comparison of measles seropositivity in completely vaccinated kidney recipients aged 1–<4 years (% 93.1%) vs. ≥4 years (74.6%).

§p = 0.007 for the comparison of liver recipients vs. all other organ recipients for measles seropositivity in that age group.

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This seropositivity gap was influenced by organ type and other clinical factors. In a multicenter study focused on pediatric liver transplant candidates, 53.1% were seropositive for varicella and 62.9% for measles before transplant [11].

In our cohort, older, completely vaccinated kidney recipients showed lower measles seropositivity than other organ groups. Although we did not collect renal-function laboratory values or dialysis data and did not perform any analysis relating these factors to serologic status, prior literature offers a plausible context: chronic kidney disease (CKD) and the uremic state have been associated with immune dysfunction and impaired vaccine responses [16]. Furthermore, factors such as the dialysis modality and a more rapid waning of vaccine-induced antibodies are documented challenges in this population [15, 16]. This observation is not limited to pediatrics, as studies in adult transplant candidates have also found that kidney recipients can be more likely to be seronegative despite vaccination compared to other transplant groups [17]. These mechanisms were not tested here and remain hypotheses for future, appropriately designed studies.

The discrepancy between vaccination history and measurable seropositivity raises critical questions about how best to assess protection before transplant. While national guidelines for the general pediatric population often consider two documented vaccine doses as sufficient evidence of immunity regardless of serology, transplant-specific guidelines recommend a more cautious approach due to the high risks in this population [1, 18]. For instance, the AST IDCOP guidelines recommend considering a third dose of MMR or varicella vaccine for transplant candidates who remain seronegative after completing their initial series [2]. However, the decision to revaccinate based on titers is complex, as serology measures only humoral immunity, and protection may persist through T-cell-mediated responses even with undetectable antibody levels [18, 19]. Ultimately, incorporating serologic screening into pre-transplant evaluations for select patients—especially those in high-risk groups, such as those with CKD—could help mitigate the risk of post-transplant vaccine-preventable diseases. The assessment of cellular immunity—such as Lymphocyte Transformation Testing (LTT)—and benchmarking against antibody persistence for non-live vaccines (e.g., tetanus) in seronegative candidates represent important targets for future research aimed at refining the assessment of pre-transplant vaccination status in children.

Limitations of the study

This study has some limitations. First, its retrospective design carries an inherent risk of information bias, particularly regarding vaccination histories from outside institutions. However, to mitigate this, our center has a standardized practice of collecting and integrating external vaccine records into the patient's electronic medical record. Additionally, we could not account for unmeasured confounders, such as socioeconomic factors, parental vaccine hesitancy, or exposure to blood products or intravenous immunoglobulin—which can temporarily defer live viral vaccination. These unmeasured factors may influence vaccine administration. Our dataset did not include renal function laboratory values or dialysis details (duration or modality), and we did not perform any analyses relating these factors to serologic status. The lower seropositivity observed among kidney recipients is therefore a descriptive finding only; the contribution of the uremic state and dialysis-related factors, while biologically plausible and supported by prior literature, could not be evaluated in this study and should be addressed in future work. Another limitation is the incomplete serologic data for measles, available for only 58% of the cohort. Routine institutional screening for measles was implemented only during the final 2 years of the study period. Despite this, the available data still provides valuable insights into seropositivity gaps. Our reliance on serology provides information solely on humoral immunity, although cellular immunity also plays a protective role. Therefore, seronegativity does not definitively equate to a lack of protection. Nevertheless, serologic testing is currently the clinical standard for assessing the risk of vaccine-preventable diseases and guiding clinical decisions, such as the administration of additional vaccine doses. Finally, as a single-center study at a tertiary referral institution, our results—particularly our higher-than-average vaccination rates—may not be fully generalizable to other settings. However, the consistent protocols at a single center allowed for a detailed longitudinal analysis that is a unique strength of this study. Furthermore, the core challenges identified by this study, such as the impact of clinical urgency on vaccination timelines and the presence of organ-specific immunity gaps, are fundamental issues likely applicable to other pediatric transplant centers.

In conclusion, our longitudinal analysis uniquely reveals that the risk for incomplete vaccination is a dynamic process likely reflecting an overlap in system and clinical barriers. Shifts in care from primary to specialty providers, limited time for vaccination in acutely ill children, and variability in infectious disease involvement may contribute. A patient's vaccination status can change during the pre-transplant period as they age, highlighting the need for continuous monitoring. Early infectious disease consultation and standardized vaccine tracking within transplant workflows could help reduce missed opportunities and improve coverage. We identified infants and those awaiting liver or heart transplantation as the most vulnerable subgroups, where shorter pre-transplant timelines directly correlate with a failure to maintain or complete vaccination schedules. Furthermore, our serologic data confirm that the number of vaccine doses received is not a guarantee for seropositivity. Therefore, these combined challenges underscore the urgent need for proactive, continuous vaccine management, including early implementation of expedited protocols and consideration of serologic screening, to ensure this high-risk population is truly protected.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the datasets analyzed during this study are not publicly available because of patient privacy concerns and institutional data protection policies. Requests to access these datasets should be directed to Lara.Danziger-Isakov@cchmc.org.

Ethics statement

The studies involving humans were approved by Cincinnati Children's Hospital Medical Center Institutional Review Board (IRB ID: 2023-0334). 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

BSC, LD-I, CB, and WO participated in study design; WO, HM-H, MM, GP, TA, EC, KC, KP, and LD-I participated in the clinical management of patients and contributed to data collection; BSC and CB performed data analysis; BSC wrote the first draft of the manuscript; and WO, HM-H, GP, MM, KC, and LD-I critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors of this manuscript have conflicts of interest to disclose. BSC has received research support from Merck/MSD and GSK, paid to his institution, for prior clinical trials that are not related to this manuscript. GP has received research support from Pfizer, Moderna, and Sanofi, paid to his institution, for prior clinical trials that are not related to this manuscript. LD-I has received consulting fees from Astellas and Kamada, not related to this manuscript. LD-I has received research support from AiCuris, Ansun BioPharma, Astellas, Merck, Pfizer, and Takeda, paid to her institution, for clinical trials that are not related to this manuscript.

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.2026.15958/full#supplementary-material

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Blood pressure control after solid organ transplantation: opportunities for optimizing care

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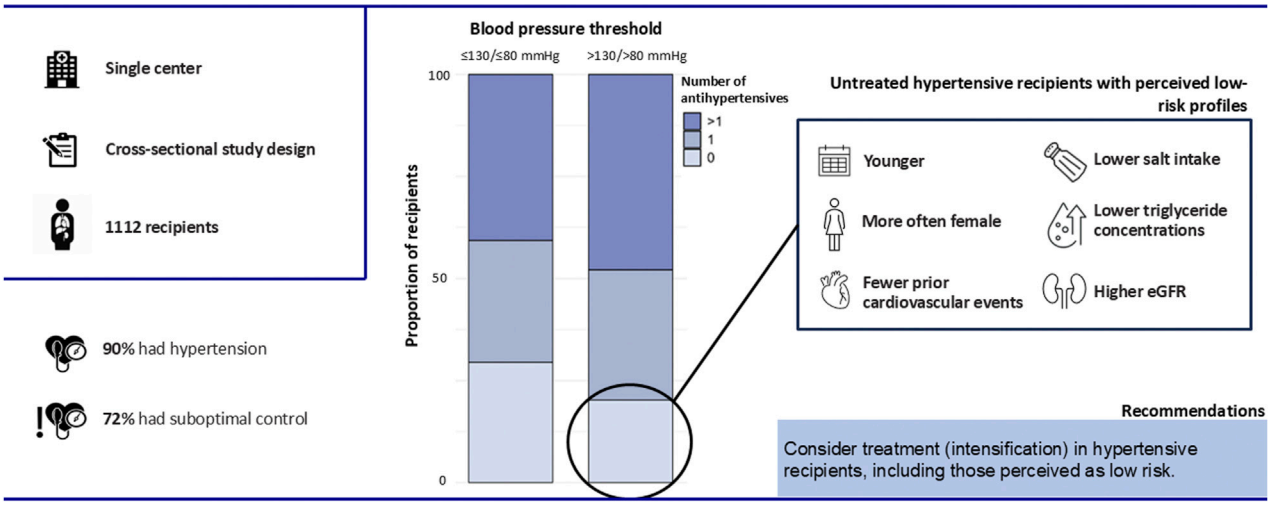
Hypertension affects 50%–90% of solid organ transplant recipients (SOTR) and is a major driver of cardiovascular disease. Nevertheless, hypertension control has received little attention in this population. We assessed blood pressure control 1 year after heart, liver, lung or kidney transplantation using cross-sectional data from 1112 SOTR (39% female, mean age 57 ± 13 years) from the TransplantLines biobank and cohort study. Suboptimal control was defined as systolic blood pressure >130 mmHg or diastolic blood pressure >80 mmHg. Overall, 997 (90%) SOTR had hypertension. Suboptimal control occurred in 721 (72%), including 146 (20%) who received no antihypertensive treatment despite elevated blood pressure. Rates of suboptimal control were consistently high across organ types (71%–84%). Older age (OR = 1.03; 95%CI1.01–1.04), diabetes (OR = 1.99; 95% CI1.18–3.36), and higher cholesterol (OR = 1.23; 95%CI1.01–1.51) were independently associated with suboptimal control. Among treated SOTR, recipients were older (OR = 1.03; 95%CI1.01–1.05), more often male (OR = 1.55; 95%CI1.03–2.34), and had more prior cardiovascular events (OR = 2.06; 95%CI1.14–3.95). In sensitivity analyses using alternative blood pressure thresholds, suboptimal control remained common, affecting 40% of hypertensive SOTR using a ≤140/90 mmHg threshold. In conclusion, nearly three out of four hypertensive SOTR have suboptimal blood pressure control at 1 year after transplantation with a ≤130/80 mmHg threshold, highlighting a substantial care gap in post-transplant management.

KEYWORDS
blood pressure management, hypertension, solid organ transplantation, suboptimal treatment, uncontrolled hypertension



Introduction

Solid organ transplantation (SOT) is a lifesaving procedure, which not only extends the life-span of recipients with organ failure, but also improves their health-related quality of life [1]. However, even after successful SOT there is still an increased risk for cardiovascular disease (CVD) [2]. CVD is an acknowledged leading cause of morbidity and mortality in SOT recipients [2–4]. Risk for CVD varies between different SOT programs (heart, liver, lung, kidney) [5], but is higher compared to the general population [6–8]. Various factors contribute to CVD, particularly hypertension [2]. In SOT recipients, side effects of immunosuppressive medication, including corticosteroids and calcineurin inhibitors, endothelial dysfunction, and kidney dysfunction, contribute to the occurrence of hypertension [9–11]. Consequently, hypertension is highly prevalent among SOT recipients, affecting 50%–90% of recipients [12–16].

No clear consensus exists regarding blood pressure targets in SOT recipients. Current guidelines recommend systolic blood pressure (SBP) targets ranging from <120 to <140 mmHg and diastolic blood pressure (DBP) targets ranging from <80 to <90 mmHg [17], while most consensus supporting a target of ≤130/80 mmHg [18–22].

In liver transplant recipients, optimal blood pressure control was associated with a 45% reduction in mortality and 38% reduction in cardiovascular events [23]. Additionally, hypertension can contribute to decline of kidney function, which is common among SOT recipients [24].

Globally, approximately half of the general population with hypertension is unaware of their diagnosis, and 80% of those diagnosed have suboptimal control according to the World Health Organization [25]. To the best of our knowledge, this topic has received limited attention in the SOT population. While blood pressure control is a major objective in transplant recipients, evidence on the adequacy of achieved blood pressure control remains scarce. This may in part be explained by the earlier focus on short-term outcomes after transplantation. As survival after SOT continues to improve, long-term outcomes are becoming increasingly important, and cardiovascular risk management deserves greater attention. We therefore aimed to investigate hypertension control in SOT recipients at 1-year after transplantation. Additionally, we determined whether hypertension control differed across SOT programs (heart, liver, lung, kidney) in our center.

Materials and methods

Patient population and study design

Cross-sectional data were used from the ongoing and prospective TransplantLines Biobank and Cohort Study (ClinicalTrials.gov identifier: NCT03272841; METc 2014/077). This study collected data from all SOT recipients and donors (aged ≥18 years) with a written informed consent, starting from June 2015 at the University Medical Centre Groningen (UMCG, Netherlands). TransplantLines adheres with the UMCG Biobank Regulation, WMA Declaration of Helsinki and the Declaration of Istanbul [26, 27].

In the current study, we included adult (aged ≥18 years at inclusion) SOT recipients at 1-year after SOT (liver, lung, heart and kidney recipients). Assessments were performed during the standardized 1-year post-transplant visit, which occurred within a

predefined window of approximately 9–16 months after transplantation. Data between June 2015 and December 2024 were used. If recipients had multiple transplant trajectories included in TransplantLines, data from the first transplant trajectory were used if the first transplant occurred at least 1 year before the second transplant, and the allograft did not fail. We excluded recipients who had a combined SOT. This study was performed in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (Supplementary Table S1).

Covariables

Before and including 2021, clinical data and data on medication use (verified with the patient) were collected during TransplantLines study visits. SBP and DBP, were measured in seated position after 15 min of rest, with four consecutive seated measurements. Waist circumference was measured at least twice. Mean value was used if multiple measurements were available [28]. After 2021, study visits were discontinued, and data were extracted from the electronic patient dossier (EPD), with blood pressure values including both patient-reported and physician-recorded measurements, which ranged from single measurements or averages of repeated measurements. Laboratory values were obtained through standard laboratory measurements. For the calculation of eGFR, the 2009 CKD-EPI formula was used [29]. Metabolic syndrome was defined according to the criteria of the International Diabetes Federation [30]. Instead of fasting glucose, HbA1c was used with a threshold of 53 mmol/mol, as not all patients were able to fast at the time of blood sampling due to long travel times to our transplant center. Cardiovascular events (CVE) were defined as the occurrence of myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular accident (CVA), or transient ischemic attack (TIA). These events were obtained from EPD using ICD-10 codes. A medical history of CVE was included as a composite marker to reflect overall cardiovascular risk burden. Pre-transplant hypertension was defined as documented hypertension before transplantation, based on ICD-10 codes. Diabetes was defined as documented diabetes, based on ICD-10 codes, or use of antidiabetic medication (metformin, sulfonylurea derivatives, SGLT2 inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists, and insulin). Salt intake (g/day) was estimated from 24-h urinary sodium excretion [31]. Lifestyle parameters, including alcohol intake, and smoking status, were derived from self-reported questionnaires.

Outcome measures

The primary outcome was the proportion of SOT recipients with suboptimal hypertension control. As there is no clear consensus about the optimal target values for SBP and DBP after SOT, a target value of ≤130/80 mmHg was applied. This decision was based on local, national and international guidelines, such as the Dutch national guidelines for cardiovascular risk management [32], the guidelines of the various SOT departments at the UMCG, the KDIGO guidelines [20], American guidelines for prevention, detection, and management of high blood pressure in adults [18], and two studies investigating different blood pressure target values [19, 21]. Hypertension was defined as a SBP >130 mmHg, a DBP >80 mmHg or current use of antihypertensive medication. Suboptimal hypertension control was defined as a SBP >130 mmHg or DBP >80 mmHg, regardless of antihypertensive treatment. The following medication were considered as antihypertensives: calcium channel antagonists, beta-blockers, angiotensin-converting enzyme-inhibitors (ACEi), angiotensin receptor blockers (ARB), alpha-blockers, loop diuretics, thiazide diuretics and potassium-sparing diuretics. The secondary outcome was the difference in suboptimal hypertension control between the transplantation programs (heart, liver, lung and kidney).

Statistical analysis

Statistical analyses were performed using SPSS software (version 28.0, IBM Corporation, Armonk, NY) and R version 4.4.1. Normality of distribution was visually assessed using histograms and quartile-quartile plots. Continuous data were presented as means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on data distribution, or in numbers with valid percentages for categorical data. Differences between groups were assessed using independent t-tests or one-way ANOVA for normally distributed variables, with Tukey's HSD or, when variances were unequal, the Games–Howell *post hoc* test applied when applicable. For non-normally distributed variables, the Mann–Whitney U test or Kruskal–Wallis test was used, with Dunn's *post hoc* test (Holm adjustment) applied when applicable. Categorical variables were compared using chi-square or Fisher's exact tests with Bonferroni-corrected pairwise comparisons when applicable. To assess associations between recipient characteristics and blood pressure status, univariable and multivariable multinomial logistic regression analyses were performed. Blood pressure status was categorized as no hypertension (reference group), optimal hypertension control, and suboptimal hypertension control. Multivariable analyses were adjusted for age, sex, and transplantation type. To assess factors associated with antihypertensive treatment among hypertensive SOT recipients, additional univariable and multivariable binary logistic regression analyses were performed comparing treated versus untreated recipients with suboptimal control.

As optimal blood pressure thresholds after SOT are still debated in the literature, sensitivity analyses were performed using target values of ≤135/85 mmHg and ≤140/90 mmHg. Furthermore, because blood pressure measurements differed, and included extractions from EPD and protocolized measurements, a sensitivity analysis restricted to protocolized blood pressure measurements was performed to evaluate the robustness of our findings. To assess potential selection bias due to missing blood pressure data in the liver transplant population, baseline characteristics of included and excluded liver transplant recipients were compared. As CVE was analyzed as a composite outcome, the individual cardiovascular disease components (myocardial infarction, heart failure, peripheral vascular disease, and CVA/TIA) were analyzed separately to assess potential heterogeneity between conditions.

Finally, concordance between prescribed antihypertensive agents and 24-h urinary metabolite detection was assessed in a

random sample of the population for selected antihypertensives. Metabolites of ACEi, ARB, and beta-blockers were evaluated through reversed-phase liquid chromatography coupled to high-resolution quadrupole-time-of-flight mass spectrometry in positive electrospray ionization and with SWATH data-independent acquisition. Recipients were classified as concordant, partially concordant, or non-concordant based on urinary metabolite detection relative to prescribed medication.

Results

Study population

Out of 1169 recipients with available data at 1-year post-transplantation included in the TransplantLines biobank and cohort study, 57 recipients (4.9%) were excluded because of missing data on SBP or DBP. This concerned one heart transplant recipient, 31 liver transplant recipients, 3 lung transplant recipients and 22 kidney transplant recipients. Consequently, 1112 SOT recipients were included in the current study, among which 37 heart, 119 liver, 162 lung and 794 kidney transplant recipients (Supplementary Figure S1). The mean age of this population was 57 ± 13 years, and 433 recipients (39%) were female. Mean SBP was 134 ± 16 mmHg and mean DBP was 78 ± 10 mmHg (Table 1; full version in Supplementary Table S2).

To assess potential selection bias in the liver transplant population, baseline characteristics of included and excluded liver transplant recipients were compared. Differences in baseline characteristics between groups were limited (Supplementary Table S3).

TABLE 1 Characteristics of the SOT recipient population

Characteristics	N	SOT recipients n = 1112
Demographics		
Age, years	1112	57 ± 13
Sex, n (%)	1112	
Male		679 (61)
Female		433 (39)
BMI, kg/m2	1084	26.9 ± 4.4
Metabolic syndrome, n (%)	760	
No		441 (58)
Yes		319 (42)
Transplantation type, n (%)	1112	
Kidney		794 (71)
Liver		119 (11)
Lung		162 (15)
Heart		37 (3)
Blood pressure parameters		
Systolic blood pressure, mmHg	1112	134 ± 16
Diastolic blood pressure, mmHg	1112	78 ± 10
Pulse rate, freq/min	822	74 ± 13
Pulse pressure, mmHg	1112	55 ± 15
Mean arterial pressure, mmHg	1112	97 ± 10
Medical history		
Cardiovascular event, n (%)	1112	281 (25)
Diabetes, n (%)	1112	326 (29)
Pre-transplant hypertension	1112	40 (31)
Medication use		
Number of antihypertensives, n (%)	1112	
0		261 (24)
1		347 (31)
>1		504 (45)

Prevalence of hypertension and suboptimal hypertension control in SOT recipients

Of the SOT recipients, 997 (90%) had hypertension. Of the recipients with hypertension, 851 (85%) used antihypertensives. Within this hypertensive group, 721 (72%) had suboptimal hypertension control and 146 (20%) of them were untreated (Figure 1).

Hypertension status and hypertension control in SOT recipients

SOT recipients with hypertension were more often male, had a higher BMI, had more frequently metabolic syndrome, had more often cardiovascular events in their medical history, had more often pre-transplant hypertension, had higher hematocrit and hemoglobin levels, and had a lower eGFR compared to recipients without hypertension. Recipients with suboptimal control had more frequently diabetes compared to recipients without hypertension. Additionally, recipients with suboptimal control were older, had a higher pulse pressure and had a higher mean arterial pressure (Supplementary Table S4).

In multivariable multinomial logistic regression, using recipients without hypertension as the reference group, several characteristics were independently associated with hypertension status (optimal or suboptimal).

Compared with recipients without hypertension, optimal hypertension control was independently associated with male sex (OR = 1.74; 95%CI1.10–2.76), higher BMI (OR = 1.11; 95% CI1.05–1.18), presence of metabolic syndrome (OR = 8.28; 95% CI3.84–17.84), larger waist circumference (OR = 1.04; 95% CI1.01–1.08), prior cardiovascular events (OR = 2.38; 95% CI1.15–4.92), pre-transplant hypertension (OR = 2.82; 95% CI1.44-5.51) and lower HDL-cholesterol levels (OR = 0.52; 95% CI0.30–0.91) (Supplementary Table S5).

Compared with recipients without hypertension, suboptimal hypertension control was independently associated with older age (OR = 1.03; 95%CI1.01–1.04), male sex (OR = 1.98; 95% CI1.31–3.01), higher BMI (OR = 1.13; 95%CI1.07–1.19), presence of metabolic syndrome (OR = 9.05; 95%CI4.38–18.69), larger waist circumference (OR = 1.04; 95%CI1.01–1.07), prior cardiovascular

FIGURE 1
Distribution of number of antihypertensives across SOT recipients stratified according to the threshold of >130/>80 mmHg.

events (OR = 2.08; 95%CI1.04–4.14), presence of diabetes (OR = 1.99; 95%CI1.18–3.36), pre-transplant hypertension (OR = 2.02; 95%CI1.07-3.84), higher levels of total cholesterol (OR = 1.23; 95% CI1.01–1.51), higher levels of triglycerides (OR = 1.33; 95% CI1.04–1.69), higher levels of creatinine (OR = 2.07; 95% CI1.05–4.08), and a lower eGFR (OR = 0.99; 95%CI0.97–1.00) (Supplementary Table S5).

Treatment status of suboptimally controlled hypertension in SOT recipients

Suboptimal control was observed in 721 (72%) of recipients with hypertension, of whom 146 (20%) were not receiving antihypertensive treatment. These participants were younger, more often female, and had a lower BMI. They also had a higher pulse rate, lower pulse pressure, higher mean arterial pressure, lower salt intake, a lower prevalence of cardiovascular events, and a lower prevalence of pre-transplant hypertension compared with those who received treatment. Additionally, they used less often prednis(ol)on. In terms of metabolic and renal parameters, they showed lower hematocrit levels, lower hemoglobin levels, higher LDL-cholesterol values and higher eGFR values (Supplementary Table S6).

In multivariable logistic regression analyses several factors were independently associated with treatment: a higher age (OR = 1.03; 95%CI1.01–1.05), male sex (OR = 1.55; 95%CI1.03–2.34), higher salt intake (OR = 1.07; 95%CI1.00–1.14), medical history of cardiovascular events (OR = 2.06; 95%CI1.14–3.95), higher levels of glucose (OR = 1.16; 95%CI1.04–1.31), and lower eGFR values (OR = 0.99; 95%CI0.97–1.00) (Supplementary Table S7).

Differences between the solid organ programs

Comparing the different SOT transplantation programs, hypertension prevalence was different between the groups ($p < 0.001$), with hypertension present in 92% of heart, 69% of liver, 80% of lung and 95% of kidney transplant recipients. Suboptimal hypertension control was observed in 74% heart, 84% liver, 73% lung and 71% kidney transplant recipients, with no significant difference between groups ($p = 0.09$). However, the proportion of untreated recipients within the suboptimal hypertension control group varied significantly between organ groups ($p < 0.001$): 24% of heart, 54% of liver, 47% of lung, and 11% of kidney transplant recipients, with suboptimal hypertension control, remained untreated. Additionally, 32% of heart, 13% of liver, 12% of lung and 59% of kidney transplant recipients with suboptimal treatment, received multiple antihypertensive agents (Figure 2).

Kidney transplant recipients were more likely to have both optimally and suboptimally controlled hypertension compared with liver and lung transplant recipients (Supplementary Table S5). No significant differences were observed between kidney and heart transplant recipients.

Treatment status of suboptimally controlled hypertension across organ programs

Kidney transplant recipients without treatment were primarily younger, more frequently women, had less often diabetes and had fewer cardiovascular events in their medical history (Supplementary

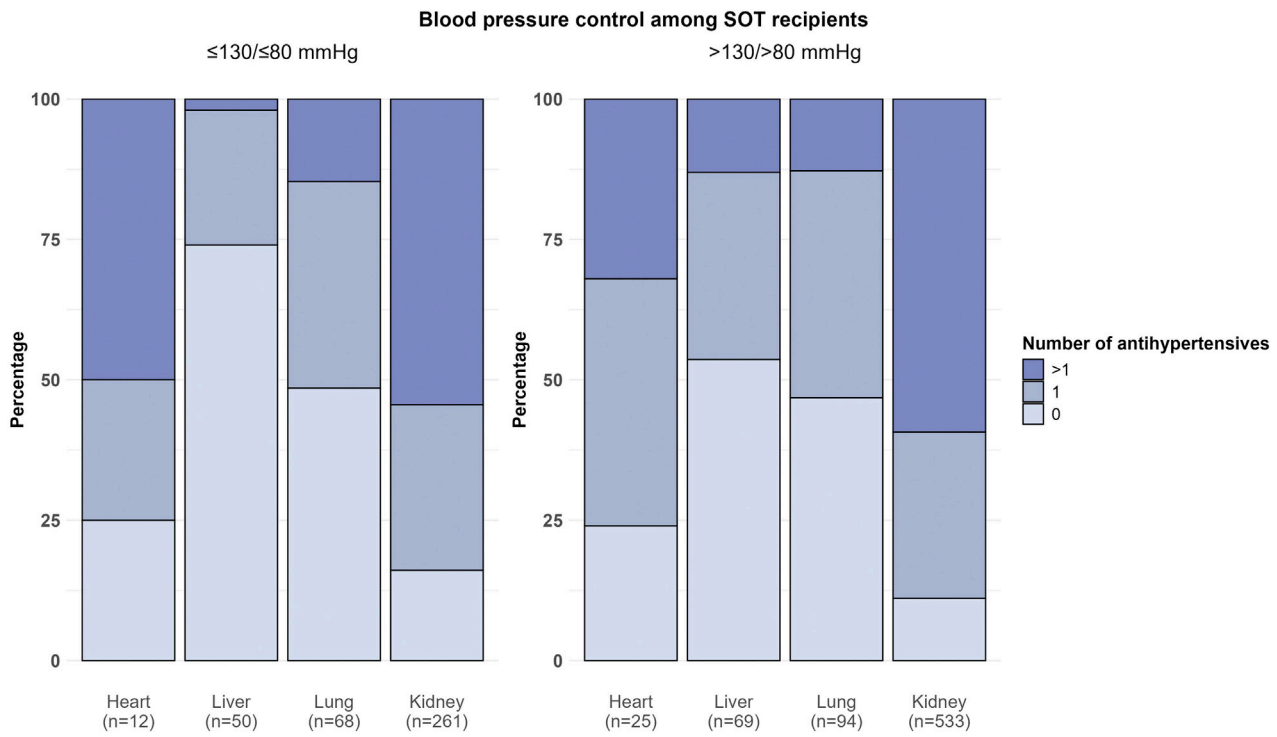


FIGURE 2
Distribution of number of antihypertensives across heart, liver, lung and kidney transplant recipients stratified according to the threshold of >130/>80 mmHg.

Table S8). Liver transplant recipients without treatment were characterized by a lower frequency of metabolic syndrome, lower frequency of pre-transplant hypertension and lower salt intake (Supplementary Table S9). Untreated lung transplant recipients were younger compared to those treated (Supplementary Table S10). No significant differences were found in the heart transplant subgroup (Supplementary Table S11).

Kidney transplant recipients were more likely to receive antihypertensive treatment compared to liver and lung transplant recipients (Supplementary Table S7). Heart transplant recipients did not differ significantly from kidney transplant recipients.

Sensitivity analyses

Different blood pressure cut-off values (≤135/85 mmHg and ≤140/90 mmHg) were applied in sensitivity analyses. The proportion of recipients reaching these target values increased compared to the primary threshold of ≤130/80 mmHg. Using a target cut-off of ≤135/85 mmHg, hypertension occurred in 957 (86%) of SOT recipients and suboptimal control was present in 524 (55%) SOT recipients with hypertension (Supplementary Figure S2). Across transplant groups, the proportion of SOT recipients with suboptimal hypertension control ranged from 52% to 76% (Supplementary Figure S3).

Using a target cut-off of ≤140/90 mmHg, hypertension occurred in 921 (83%) of SOT recipients and suboptimal control was present in 370 (40%) SOT recipients with hypertension (Figure 3). Across transplant groups, the proportion of SOT recipients with suboptimal hypertension control ranged from 44% to 62% (Supplementary Figure S4).

To address potential heterogeneity in blood pressure measurements, an additional sensitivity analysis was performed restricted to recipients with protocolized study visit-based blood pressure measurements (Supplementary Table S12). In the primary analysis, suboptimal hypertension control was present in 721 of 997 hypertensive SOT recipients (72%). Findings remained consistent when restricting the analysis to recipients assessed with protocolized study visit-based measurements (298/386, 77%).

Because CVE was analyzed as a composite outcome, separate sensitivity analyses were performed for the individual cardiovascular disease components (myocardial infarction, heart failure, peripheral vascular disease, and CVA/TIA) to assess potential heterogeneity. These analyses showed broadly comparable directions of association to those observed for the composite CVE outcome. However, confidence intervals were wider and statistical significance was less consistent across individual cardiovascular conditions (Supplementary Tables S13, 14).

Antihypertensive medication adherence

In a randomly selected subgroup of 156 recipients, metabolites of selected antihypertensive agents (ACEi, ARB, and beta-blockers) were analyzed in 24-h urine samples. Of these, 60 recipients used no antihypertensive medication according to medication lists, consistent with urinary metabolite measurements. Of the 96 recipients prescribed one or more ACEi, ARB, or beta-blockers, 88 (92%) showed concordance between prescribed medication and urinary metabolite detection, whereas 4 (4%) showed partial concordance and 4 (4%) showed no concordance (Supplementary Table S15).

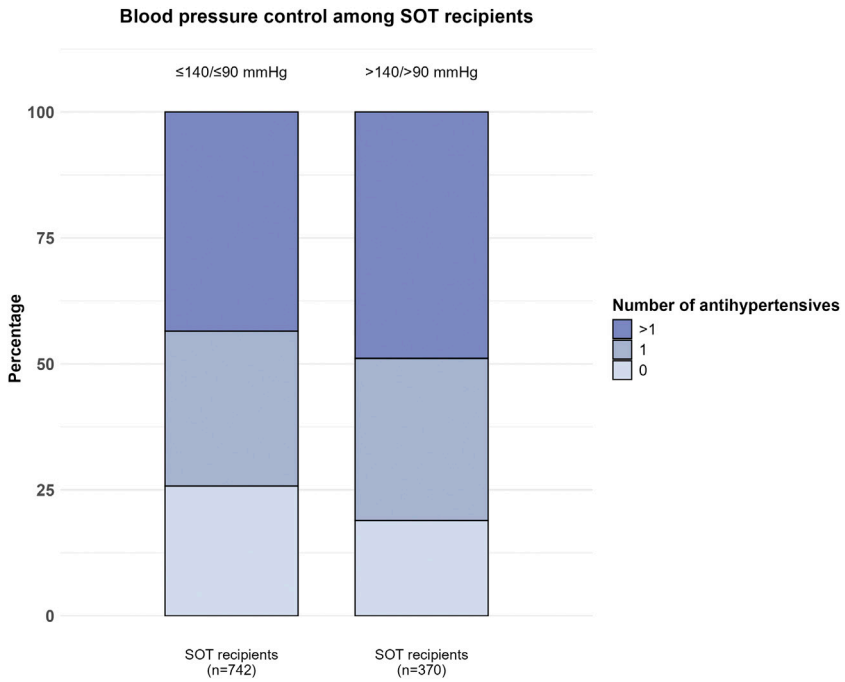


FIGURE 3
Distribution of number of antihypertensives across SOT recipients stratified according to the threshold of >140/>90 mmHg.

Discussion

In this large cross-sectional study among SOT recipients, hypertension was highly prevalent. Among SOT recipients, 997 (90%) had hypertension, and of them 721 (72%) had suboptimal hypertension control. Importantly, findings remained consistent in a sensitivity analysis restricted to protocolized blood pressure measurements. In addition, the observed burden of suboptimal hypertension control depended on the blood pressure threshold applied. While 72% of hypertensive recipients had suboptimal control using the primary threshold of ≤130/80 mmHg, suboptimal control remained common even when applying less stringent thresholds of ≤135/85 mmHg and ≤140/90 mmHg (55% and 40%, respectively) in sensitivity analyses. These findings suggest that suboptimal control of hypertension in SOT recipients remains clinically relevant irrespective of the threshold used. Similar prevalence rates have been reported in another transplant population, however the proportion of suboptimally control hypertension in our cohort was higher [13, 33]. Other studies in transplant populations about hypertension control remain limited. In a population with chronic kidney disease a high prevalence of uncontrolled hypertension has also been described [34]. Maintaining adequate blood pressure control in the SOT population is of significant importance, given the high burden of multimorbidity and elevated cardiovascular risk.

In this study was seen that recipients without hypertension had a lower risk profile (younger age, better profile of cardiovascular parameters, higher eGFR, less frequently pre-transplant hypertension and less frequently metabolic syndrome, cardiovascular events or diabetes in their medical history), as expected. Recipients with suboptimal control but a comparable low-risk profile were more often left untreated, likely because their profile was similar to that of recipients without hypertension. Recipients with a more typical high-risk profile (more frequent metabolic syndrome, and a history of cardiovascular disease) were more likely to be treated in the suboptimally controlled group, reflecting practices seen in the general population. Mildly elevated blood pressure in healthy individuals is often managed initially with lifestyle interventions, reserving pharmacological treatment for those at higher cardiovascular risk [32]. However, given the elevated cardiovascular risk among transplant recipients, pharmacological treatment is crucial even in seemingly low-risk patients. Recipients who remain untreated, or who are on monotherapy despite suboptimal control, should be considered for treatment intensification. Age and prior cardiovascular events were associated with both suboptimal hypertension control and with receiving antihypertensive agents. This was expected, as hypertension becomes more prevalent and resistant with older age and cardiovascular history [35]. These risk factors are likely closely monitored by physicians, explaining their association with treatment in the suboptimally controlled group. Immunosuppressive therapy, particularly calcineurin inhibitors and corticosteroids, has been recognized as a contributor to post-transplant hypertension [36]. However, no independent association between immunosuppressive therapy and hypertension status or antihypertensive treatment was observed in our analyses. This may partly reflect limited contrast in exposure within our cohort, as all recipients were assessed 1 year after transplantation, used immunosuppressive therapy, and hypertension was highly prevalent.

Furthermore, salt intake was high in this cohort, suggesting that, in addition to pharmacological treatment given the high cardiovascular risk in transplant recipients, complementary lifestyle interventions may help optimize blood pressure control.

Stratification by transplant type showed that hypertension was most prevalent among heart and kidney recipients. Suboptimal control was similar across groups, but treatment patterns differed. Most kidney and heart recipients received antihypertensive therapy, often with multiple agents, while lung and liver recipients were less frequently treated, with many either untreated or managed with monotherapy despite being above target. Heart and kidney are primary target organs of hypertension and have a more direct role in blood pressure regulation [37], making strict treatment crucial for graft preservation. This can explain the higher treatment rates in heart and kidney recipients in comparison to liver and lung recipients. Additionally, mean survival differs between organ recipient groups making cardiovascular control particularly important for those with longer expected survival, as cardiovascular complications become more relevant over the long term. Notably, mean survival is lowest among lung transplant recipients [38]. Nevertheless, effective blood pressure control remains essential to reduce long-term morbidity and mortality. Compared to lung and liver recipients, many kidney and heart recipients remained hypertensive despite multi-drug therapy. This reflects the complexity of hypertension control in SOT recipients, influenced by (interactions with) immunosuppressive drugs, renal vascular disease, and possibly resistant hypertension [39, 40]. Non-adherence could also contribute, but we lacked comprehensive adherence data. In heart transplant recipients specifically, frequent follow-up and invasive procedures (e.g., routine biopsies according to local protocols) in the first year may delay blood pressure optimization [41, 42]. Better control may be achieved later, although definitive conclusions could not be drawn given the exploratory nature of the analyses in this relatively small heart-transplant subgroup. Nevertheless, heart transplant recipients were included because this study evaluated different solid organ transplant populations, of which heart transplantation represents one subgroup.

Strengths of this study include its large sample size and the inclusion of four distinct SOT groups, enabling broad comparisons across transplant populations. Limitations include the single-center and cross-sectional design, which precludes causal inference, and the inability to assess blood pressure trends over time. Medication changes due to side effects or lack of efficacy were not recorded. Another limitation of this study is the absence of systematic medication adherence data. Non-adherence is a recognized contributor to uncontrolled hypertension and may partly explain persistent elevated blood pressure [43], particularly among recipients receiving multiple antihypertensive agents. However, in a randomly selected subgroup of recipients, concordance between prescribed medication and urinary metabolite detection was high (>90%). Nevertheless, these measurements were analyzed in a subset of recipients and did not include all antihypertensive drug classes. Therefore, non-adherence cannot be excluded as a contributor to suboptimal blood pressure control. Additionally, phenomena such as masked hypertension and white coat hypertension may have led to under- or overestimation of blood pressure control rates [44]. Specifically, masked hypertension may have resulted in underestimation of the prevalence of hypertension and suboptimal blood pressure control, whereas white coat hypertension may have contributed to overestimation. This limitation is particularly relevant because most blood pressure measurements in the present study were based on office blood pressure assessments rather than 24-h ambulatory blood pressure monitoring (ABPM), which can also account for nocturnal hypertension. In kidney transplant recipients, approximately 32% have been reported to experience masked hypertension and 6% white coat hypertension, highlighting the potential for misclassification when relying solely on office blood pressure measurements [44]. Furthermore, blood pressure measurements were unavailable for a disproportionate number of liver transplant recipients. Although baseline characteristics between included and excluded liver transplant recipients were largely comparable, excluded recipients had a higher prevalence of prior cardiovascular events, and the possibility of selection bias or non-random missingness cannot be excluded. A minor limitation is that, among participants classified as using a single antihypertensive medication, some may have been prescribed the drug for reasons other than hypertension. While this affects only a small proportion of the cohort, it introduces some uncertainty in the classification of antihypertensive use for these individuals. This could also be the case for the definition of diabetes, as this was defined based on ICD-10 codes or the use of antidiabetic medication. A limited number of antidiabetic medication may also be prescribed for indications other than diabetes. Finally, as the heart-transplant program represents a relative small subgroup, analyses in heart transplant recipients should be considered exploratory.

In conclusion, hypertension and suboptimal hypertension control remain highly prevalent among SOT recipients. Although most SOT recipients with suboptimal control were treated, target blood pressure was often not reached, even with multi-drug regimens. Given the elevated cardiovascular risk in this population, these findings highlight the importance of careful blood pressure monitoring and individualized evaluation of hypertension control. It is essential that recipients with suboptimal hypertension control receive appropriate therapy and that treatment is intensified for those suboptimally controlled. Additionally, lifestyle interventions such as dietary sodium restrictions could be considered. Finally, recipients on multiple antihypertensive agents may benefit from further assessment of factors potentially contributing to suboptimal blood pressure control, including therapy-resistant hypertension or non-adherence. Improving hypertension control in SOT recipients may represent an important opportunity to reduce cardiovascular risk and mortality.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Due to patient confidentiality and privacy restrictions, individual participant data from the TransplantLines Biobank and Cohort Study cannot be made publicly available, as public data sharing was not included in the informed consent forms. However, the data may be made available to qualified researchers upon reasonable request and approval by the TransplantLines Scientific Committee. Requests to access these datasets should be directed to datarequest.transplantlines@umcg.nl.

Ethics statement

The studies involving humans were approved by the Institutional Review Board (METc 2014/077) (METc UMCG), adheres to the UMCG Biobank Regulation, and is in accordance with the WMA Declaration of Helsinki and the Declaration of

Istanbul. 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

AP, HB, SB, and VM conceptualised the study and contributed to methodology and formal analysis. AP, TK, DK, ME, JS, SB, CS, FK, CG, EV, KD, MB, HB, SB, and VM contributed to investigation. AP contributed to visualisation and drafted the original manuscript. HB, SB, and VM provided supervision. 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.2026.16565/full#supplementary-material

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Undersized lung grafts in chronic obstructive pulmonary disease transplant recipients: risk factor or acceptable compromise?

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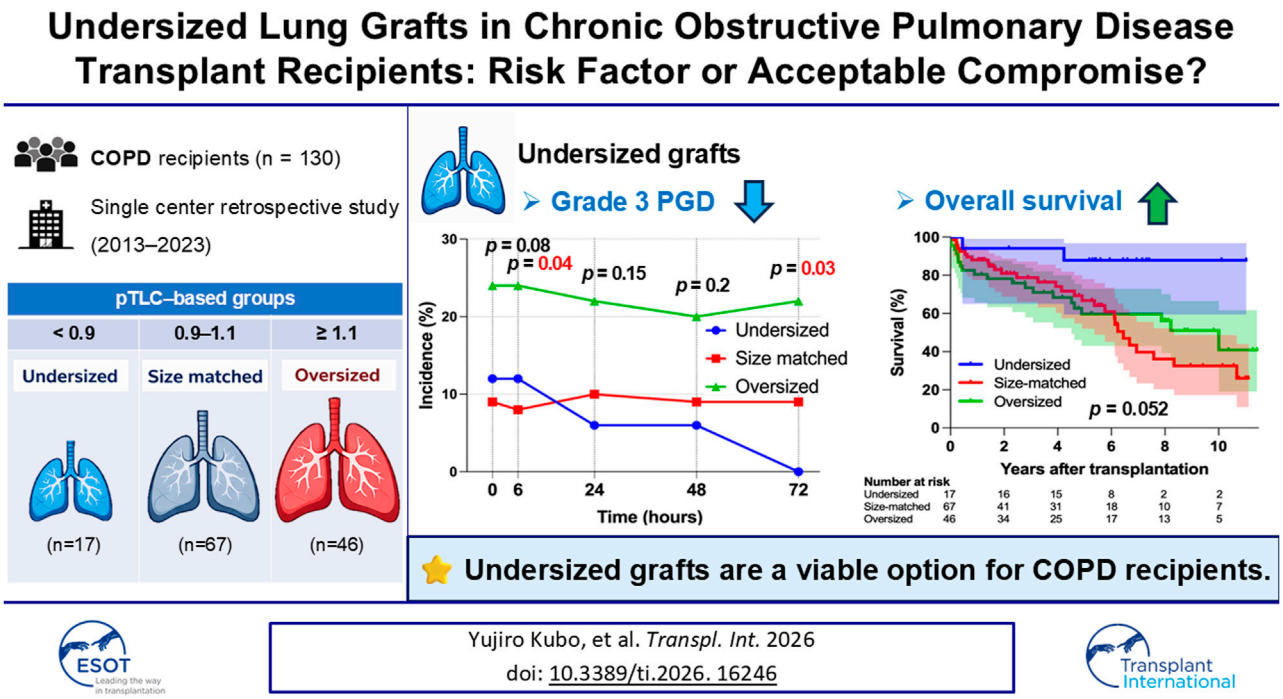
Size matching is an important concern during lung allocation for lung transplantation (LTx). Although some mismatch is accepted—often favoring larger grafts for patients with chronic obstructive pulmonary disease (COPD)—the optimal strategy remains unclear. This study evaluated the impact of graft size mismatch on postoperative outcomes in COPD. We retrospectively reviewed 130 of 491 patients who underwent LTx at a single center between January 2013 and December 2023. Patients were classified into three groups based on donor-to-recipient predicted total lung capacity ratio: undersized (<0.9), size-matched (0.9–1.1), and oversized (≥1.1). Donor and recipient characteristics were collected. Primary graft dysfunction (PGD) was the primary endpoint; overall survival was secondary. Of the 130 patients, 17 (13%) received undersized grafts, 67 (52%) size-matched grafts, and 46 (35%) oversized grafts. The undersized group had a lower incidence of PGD at 48 and 72 h than other groups ($p < 0.01$ and $p = 0.02$). Grade 3 PGD at 72 h was less frequent among groups ($p = 0.03$). Overall survival was higher in the undersized group ($p = 0.018$ and $p = 0.045$). Oversized grafts may not be optimal for LTx in COPD. Undersized grafts appear to be a viable strategy.

KEYWORDS
chronic obstructive lung disease, overall survival, predicted total lung capacity, primary graft dysfunction, size matching

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive and irreversible respiratory disorder characterized by persistent airflow limitation, often culminating in respiratory failure. Lung transplantation (LTx) serves as a definitive therapy for patients with end-stage COPD. Among the multiple factors influencing post-transplant outcomes, donor-recipient lung size matching has been recognized as an important consideration.

While size-matching strategies have traditionally aimed to minimize graft-recipient mismatch, the clinical impact of oversizing or undersizing remains a matter of ongoing debate. Some studies suggest that oversized lungs may offer functional advantages in COPD patients [1–3], whereas excessive oversizing may increase the risk of complications such as



GRAPHICAL ABSTRACT
Graphical abstract of the study. In 130 COPD recipients undergoing bilateral lung transplantation, recipients were divided into the following pTLC-based groups: undersized (<0.9, n = 17), size-matched (0.9–1.1, n = 67), and oversized (≥1.1, n = 46). The undersized group showed lower incidences of grade 3 PGD compared with the other groups. Overall survival was significantly higher in the undersized group compared with the size-matched and oversized groups (p = 0.018 and p = 0.045, respectively). COPD, chronic obstructive pulmonary disease; PGD, primary graft dysfunction; pTLC, predicted total lung capacity.

delayed chest closure, impaired ventilation, and postoperative infections [1, 4]. Nonetheless, the evidence remains inconclusive, and real-world data regarding the prognostic significance of size mismatch—particularly in the context of COPD—are still limited.

This study aimed to evaluate the impact of donor lung size mismatch on perioperative and long-term outcomes in patients with COPD who underwent bilateral LTx at a single center.

Materials and methods

Patient selection

This retrospective study was conducted at [Author information withheld for anonymized peer review]. We reviewed data from 491 lung transplants performed between January 2013 and December 2023 (Figure 1). After exclusion of non-COPD cases, unilateral transplants, *ex vivo* lung perfusion (EVLP), re-transplantation, lobar transplants, pediatric recipients, cardiopulmonary transplants, and cases with incomplete data, a total of 130 COPD patients were included in the analysis. Patients were divided by predicted total lung capacity (pTLC) donor-to-recipient ratio into undersized (<0.9), size-matched (0.9–1.1), and oversized (≥1.1) groups, including 17 undersized, 67 size-matched, and 46 oversized patients. pTLC was calculated using equations established by the European Respiratory Society in 1995 [5]. For men, pTLC (L) = (7.99 × height [m] − 7.08); for women, pTLC (L) = (6.60 × height [m] − 5.79). The pTLC ratio thresholds were selected based on previous reports and our institutional experience, reflecting clinically relevant differences in outcomes across these ranges [6–8]. This retrospective study was approved by the Institutional Review Board of [Author information withheld for anonymized peer review] (approval number: PI 159/25, 7 July 2025). The requirement for informed consent was waived due to the retrospective nature of the study.

Organ allocation policy and recipient selection

In Spain, the allocation of lungs is coordinated at the national level by the National Transplant Organization (ONT). Donated lungs are offered to candidate hospitals in order, considering the distance from the donor location. In selecting recipients, our institute considers criteria such as

Abbreviations: BMI, body mass index; BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; ECLS, intraoperative extracorporeal life support; ECMO, extracorporeal membrane oxygenation; EVLP, *ex vivo* lung perfusión; FEV_1, forced expiratory volume in 1 s; FiO_2, fraction of inspired oxygen; HLA, anti-human leukocyte antigen; ICU, intensive care unit; LAS, lung allocation score; LTx, lung transplantation; PaO_2, arterial partial pressure of oxygen; pTLC, predicted total lung capacity; PGD, primary graft dysfunction; RAS, restrictive allograft syndrome; VA, veno-arterial; V/Q, ventilation-perfusion; VV, veno-venous.

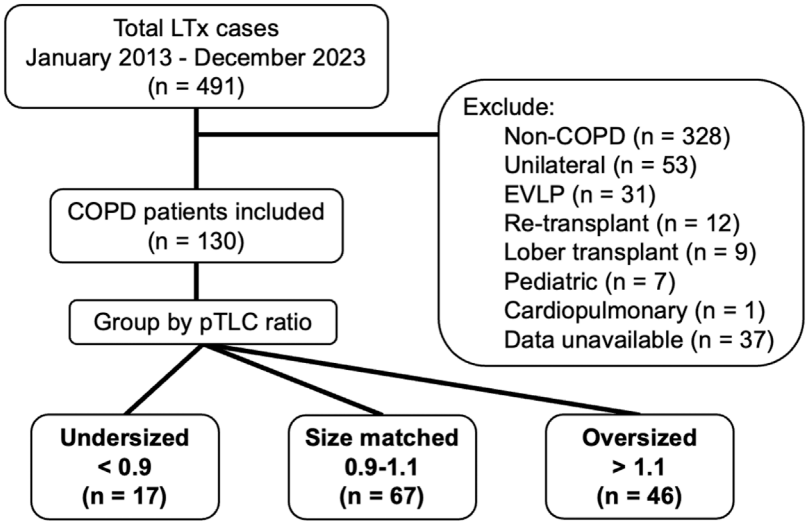


FIGURE 1
Flowchart of patient selection. Among 491 lung transplants performed between January 2013 and December 2023, 130 patients with chronic obstructive pulmonary disease (COPD) who received bilateral lung transplantation were included. Exclusions comprised non-COPD cases, unilateral or lobar transplants, re-transplants, pediatric or cardiopulmonary transplants, cases with incomplete data, and *ex vivo* lung perfusion (EVLP). Groups were classified by predicted total lung capacity (pTLC) ratio: undersized (<0.9), size-matched (0.9–1.1), and oversized (≥1.1).

urgency, blood group compatibility, clinical factors (including age, infection status and hemodynamics), and size matching between donor and recipient. Size mismatch was not intentionally selected based on recipient characteristics, reflecting real-world allocation practices.

Surgical technique, perioperative management, and postoperative follow-up

Bilateral lung transplantation was performed utilizing the sequential technique. Each native lung was removed one at a time via the clamshell or bilateral thoracotomy, and donor lungs were transplanted sequentially. Anastomoses of the bronchi, pulmonary arteries, and left atrium were performed with conventional methods. Extracorporeal life support (ECLS) was instituted when clinically indicated, including in cases of severe pulmonary hypertension, hemodynamic instability, hypoxemia, or hypercapnia. For oversized grafts, chest closure was performed cautiously to avoid graft compression, with consideration of delayed chest closure or graft size reduction when necessary. Postoperative ventilatory management was based on a lung-protective strategy, including low tidal volume ventilation and appropriate positive end-expiratory pressure, with early extubation whenever feasible. The immunosuppressive therapy includes basiliximab (20 mg) on Days 1 and 4 post-operatively, and a life-time triple immunosuppression regimen based on tacrolimus, mycophenolate mofetil and prednisone. Prophylactic antibiotic therapy is adjusted based on the bacterial species isolated from specimens taken from the donor and recipient at the time of surgery. Empirical administration of broad-spectrum antibiotics should be terminated after 7–10 days. For prophylactic antifungal therapy, liposomal amphotericin B (6 mL) is administered via nebulizer every 48 h until discharge, and once weekly thereafter. Follow-up included regular clinical visits, laboratory testing with monitoring of immunosuppressant levels, and spirometry. Visit frequency decreased progressively over time, from weekly after discharge to quarterly in the long term.

Study design

Demographic data collected for recipients included age, sex, height, body mass index (BMI), lung allocation score (LAS), secondary pulmonary hypertension, smoking history, cytomegalovirus (CMV) infection, previous thoracic surgery, arterial hypertension, diabetes mellitus, dyslipidemia, gastroesophageal, reflux disease, coronary artery disease, anti-human leukocyte antigen (HLA) antibodies, forced expiratory volume in 1 s (FEV_1), pretransplant medical condition—such as extracorporeal membrane oxygenation (ECMO), invasive mechanical ventilation, or non-invasive mechanical ventilation—intensive care unit stay prior to LTx, and pTLC.

For each recipient, donor demographic characteristics were also collected: age, sex, sex mismatch, height, BMI, type of donor, cause of death, duration of mechanical ventilation, arterial partial pressure of oxygen over fraction of inspired oxygen (PaO_2/FiO_2), smoking history, and pTLC.

Perioperative and postoperative outcomes included ischemic times for each lung, use of extracorporeal life support (ECLS), primary graft dysfunction (PGD) grading at 0, 6, 24, 48, and 72 h post-transplantation, rethoracotomy, postoperative ECMO, tracheostomy, duration of mechanical ventilation, intensive care unit (ICU) and hospital stay, and in-hospital mortality. Long-term outcomes included development of chronic lung allograft dysfunction (CLAD), time to CLAD onset, and survival at 30 days, 1 year, 3 years, and 5 years. PGD was assessed according to the International

TABLE 1 Recipient characteristics.

Variables	Undersized (n = 17)	Size matched (n = 67)	Oversized (n = 46)	*p* value
Age (years)	61 (51–69)	59 (40–69)	59 (27–70)	0.72
Sex				
Male	16 (94)	46 (69)	16 (35)	**<0.001**
Female	1 (6)	21 (31)	30 (65)	
Height (mm)	169 (158–185)	170 (156–183)	158 (147–184)	**<0.001**
BMI (kg/m^2)	24 (18–28)	25 (17–30)	23 (18–31)	0.82
Lung allocation score	33 (30–50)	33 (28–66)	33 (26–55)	0.61
Pretransplant SPH	15 (88)	41 (61)	37 (80)	**0.026**
Smoking history	16 (94)	56 (83)	38 (83)	0.66
CMV infection	16 (94)	57 (88)	44 (96)	0.38
Prev. thoracic surgery	0 (0)	5 (8)	1 (2)	0.41
Arterial hypertension	8 (47)	19 (31)	11 (26)	0.27
Diabetes mellitus	1 (6)	6 (9)	3 (7)	0.90
Dyslipidemia	6 (35)	13 (21)	13 (31)	0.34
GERD	1 (6)	2 (3)	2 (5)	0.84
CAD	1 (6)	7 (11)	4 (10)	1
Anti-HLA antibodies	2 (12)	3 (5)	1 (2)	0.22
FEV_1 (%)	27 (14–78)	25 (14–75)	28 (15–86)	0.66
Bridge to transplant				0.26
ECMO	0 (0)	0 (0)	0 (0)	
IMV	1 (6)	1 (2)	0 (0)	
NIMV	0 (0)	2 (3)	0 (0)	
ICU before LTx	1 (6)	1 (2)	0 (0)	0.37
pTLC (L)	6.42 (5.36–7.70)	6.50 (4.51–7.54)	4.70 (3.91–7.22)	**<0.001**
pTLC ratio, median (IQR)	0.84 (0.82–0.89)	1.02 (0.99–1.07)	1.27 (1.16–1.36)	**<0.001**

Data are presented as median (range) or n (%).
Bold values represent statistical significance ($p < 0.05$).
BMI, body mass index; CAD: coronary artery disease; CMV, cytomegalovirus; ECMO, extracorporeal membrane oxygenation; FEV1, forced expiratory volume in 1 s; GERD, gastroesophageal reflux disease; HLA, anti-human leukocyte antigen; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; LTx, lung transplantation; NIMV, non-invasive mechanical ventilation; Prev. thoracic surgery, previous thoracic surgery; SPH, secondary pulmonary hypertension; pTLC, predicted total lung capacity.

Society for Heart and Lung Transplantation (ISHLT) criteria (2005 consensus definition, revised 2017) [9, 10].

The incidence of PGD was analyzed as the primary outcome, and overall survival as the secondary outcome.

Statistical analysis

All statistical analyses were performed using GraphPad Prism 10 Software version 10.4.2 (GraphPad Software, Inc., San Diego, CA) and EZR version 1.68 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 4.4.2 (The R Foundation for Statistical Computing, Vienna, Austria) [11]. Statistical significance was evaluated using the Student's t-test or the Mann–Whitney U-test for comparisons between two groups of continuous variables, depending on the normality of data distribution; one-way ANOVA followed by Tukey's *post hoc* test or the Kruskal–Wallis test for comparisons among multiple groups of continuous variables; and Fisher's exact test or the chi-squared test for categorical variables, depending on the size of the groups. Overall survival was defined as the period from transplantation to death from any cause, with patients who were still alive at the last follow-up considered censored. Kaplan–Meier estimates were used to generate survival curves, and differences between groups were assessed using the log-rank test. Multivariable analysis was performed using a Cox proportional hazards regression model, including variables considered clinically relevant. Statistical significance was defined as $p < 0.05$.

TABLE 2 Donor characteristics.

Variables	Undersized (n = 17)	Size matched (n = 67)	Oversized (n = 46)	p value
Age (years)	57 (18–76)	54 (16–78)	57 (20–80)	0.46
Sex				
Male	1 (6)	34 (51)	33 (72)	**<0.001**
Female	16 (94)	33 (49)	13 (28)	
Sex mismatch	5 (29)	8 (12)	17 (37)	**<0.01**
Female-to-male	5 (29)	6 (9)	0 (0)	**0.001**
Male-to-female	0 (0)	2 (3)	17 (37)	**<0.001**
Height (mm)	170 (155–180)	175 (158–190)	175 (147–195)	0.13
BMI (kg/m^2)	26 (21–33)	26 (17–37)	25 (16–34)	0.72
Type of donor				
DBD	15 (88)	48 (72)	35 (76)	0.40
DCD	2 (12)	19 (28)	11 (24)	
Cause of death				0.57
CVA	12 (71)	42 (63)	33 (72)	
Trauma	4 (24)	11 (16)	5 (11)	
Anoxia	1 (6)	7 (10)	2 (4)	
Duration of MV (days)	2 (1–15)	2 (1–19)	2 (0–28)	0.52
PaO2/FiO2	504 (334–608)	445 (260–719)	432 (312–700)	0.40
Smoking history[a]	7 (41)	21 (34)	17 (39)	0.79
pTLC (L)	5.43 (4.44–6.09)	6.42 (4.64–8.10)	6.54 (4.67–8.50)	**0.001**
Graft size reduction	0 (0)	3 (4)	1 (2)	1

Data are presented as median (range) or n (%).
Bold values represent statistical significance ($p < 0.05$).
BMI, body mass index; CVA, cerebrovascular accident; DBD, donation after brain death; DCD, donation after circulatory death; MV, mechanical ventilation; PaO2/FiO2, arterial partial pressure of oxygen over fraction of inspired oxygen; pTLC, predicted total lung capacity.
[a]Seven cases with missing data were excluded.

Results

Recipient characteristics

Recipient characteristics are shown in Table 1. The median pTLC ratios were 0.84 (IQR 0.82–0.89) in the undersized group, 1.02 (IQR 0.99–1.07) in the size-matched group, and 1.27 (IQR 1.16–1.36) in the oversized group. The oversized group had a higher proportion of female recipients (only 35% male; $p < 0.001$) and was significantly shorter (median height: 158 cm) with lower pTLC (4.70 L), contributing to graft oversizing. Secondary pulmonary hypertension was most frequent in the undersized group ($p = 0.026$). Other baseline factors were comparable across groups.

Donor characteristics

Donor data are summarized in Table 2. Male donors were more common in the oversized group (72%; $p < 0.001$), corresponding to higher male-to-female mismatches and higher donor pTLC (median: 6.54 L). Sex mismatch patterns varied significantly ($p \leq 0.001$). No significant differences were found in other donor variables.

Perioperative and postoperative outcomes

The incidence of PGD, the primary outcome of this study, is shown in Figure 2; Table 3. As illustrated in Figure 2A, both the undersized and oversized groups showed significantly higher PGD rates than the size-matched group at 6 and 24 h post-transplantation ($p = 0.04$ and $p = 0.03$, respectively). At later time points, only the oversized group remained significantly higher ($p = 0.006$ at 48 h; $p = 0.017$ at 72 h). Figure 2B presents grade 3 PGD incidence. Although early-phase differences were not significant ($p = 0.08$ at 0 h; $p = 0.15$ at 24 h; $p = 0.2$ at 48 h), the oversized group consistently showed higher rates. At 72 h, the undersized group had significantly lower incidence compared across the three groups ($p = 0.03$).

Other perioperative and postoperative outcomes are summarized in Table 3. The first and second graft ischemic times were significantly longer in the size-matched group compared to the other groups ($p = 0.008$ and $p = 0.009$, respectively). In contrast, no

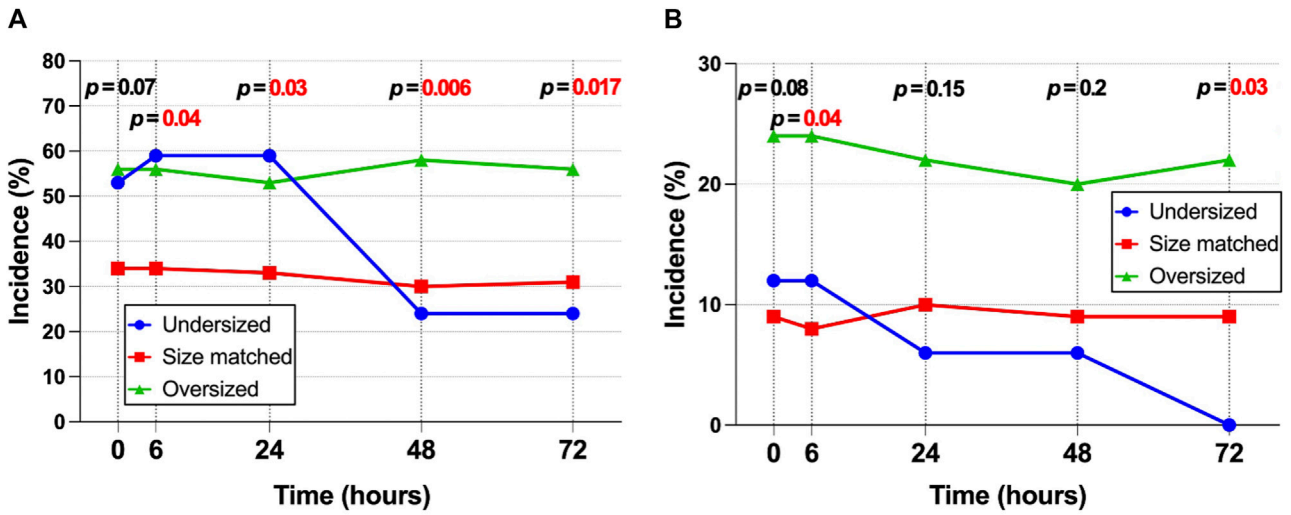


FIGURE 2
Incidence and temporal distribution of primary graft dysfunction (PGD) following lung transplantation. **(A)** Distribution of PGD grades (0–3) over time. **(B)** Incidence of Grade 3 PGD at each postoperative time point.

significant differences were observed regarding intraoperative ECLS, postoperative ECMO, tracheostomy, rethoracotomy, ventilation duration, ICU stay, or hospital stay. Mid-to long-term outcomes—including in-hospital mortality, CLAD incidence, and time to CLAD onset—were also comparable across groups.

Survival analysis

Overall survival curves stratified by donor-to-recipient lung size group are shown in Figure 3. The median follow-up period was 6.23 years, estimated utilizing the reverse Kaplan-Meier method. Although the three-group comparison showed no statistically significant difference (p = 0.052), the undersized group demonstrated a favorable survival trend. Notably, pairwise comparisons revealed significantly better survival in the undersized group compared to both the size-matched (p = 0.018) and oversized groups (p = 0.045).

Furthermore, although the sample size was small, we performed a multivariate Cox regression analysis based on the available data variables (Table 4). The significance of the undersized group was maintained in the multivariate analysis as well.

Discussion

This retrospective study investigated the impact of donor-to-recipient pTLC mismatch on clinical outcomes following bilateral lung transplantation for COPD. Notably, our findings revealed a significantly higher incidence of early PGD in both undersized and oversized graft groups compared to the size-matched group. Despite this, the undersized group demonstrated favorable long-term survival, with significantly better outcomes in pairwise comparisons against both the size-matched and oversized groups.

Previous study in patients with pulmonary fibrosis have reported that oversized grafts may be associated with worse early outcomes and impaired long-term survival [12]. However, the physiological implications of size mismatch likely differ between fibrotic and emphysematous lungs, due to differences in thoracic cavity compliance and native lung volume [2, 13]. Our findings suggest that in the context of COPD, modest undersizing may be considered a viable option.

The association between oversized grafts and increased PGD incidence aligns with prior studies suggesting that excessive lung size may contribute to ventilation-perfusion (V/Q) mismatch and impaired graft function [1, 4, 6, 7, 14]. Although oversized grafts may anatomically fit within the hyperinflated thoracic cavities of COPD recipients, the recipient's limited cardiac output may be insufficient to fully perfuse the graft, potentially leading to perfusion mismatch and hypoxia-induced injury [1, 6]. Moreover, the mechanical compression of oversized grafts may hinder microcirculatory flow, exacerbating early graft injury [14].

Conversely, the undersized group exhibited a more favorable PGD profile at later postoperative time points and significantly superior overall survival. One possible explanation is that following pneumonectomy of hyperinflated native lungs, the thoracic cavity undergoes partial remodeling [13, 15]. Moderately undersized grafts may better accommodate this remodeled space without causing compression, thereby facilitating optimal expansion and improving V/Q matching [1, 14]. This may lead to reduced ischemia-reperfusion injury and support better long-term outcomes.

In our cohort, although secondary pulmonary hypertension was more common in the undersized group, the incidence of PGD at 48 and 72 h was significantly lower in this group, which may appear to be paradoxical. This can be explained by the fact that in transplant patients with COPD, replacing an autologous lung severely damaged by emphysema with a structurally normal donor lung may increase the functional pulmonary vascular bed and reduce reperfusion-related injury [16], even when a smaller graft is used. Another reason is that PGD is a multifactorial condition involving ischemia-reperfusion injury, inflammatory responses, and donor-recipient-related factors [17], and size mismatch is only one of these factors.

TABLE 3 Perioperative and postoperative outcomes.

Variables	Undersized (n = 17)	Size matched (n = 67)	Oversized (n = 46)	*p* value
Ischemic time				
First lung	300 (190–967)	390 (180–1035)	315 (150–819)	**0.008**
Second lung	400 (280–590)	490 (270–1120)	440 (240–933)	**0.009**
Intraoperative ECLS	7 (41)	36 (54)	22 (49)	0.42
ECMO	6 (35)	30 (45)	14 (30)	
CPB	1 (6)	6 (9)	8 (17)	
PGD				
0 h	9 (53)	23 (34)	25 (56)	0.07
6 h	10 (59)	23 (34)	25 (56)	**0.04**
24 h	10 (59)	22 (33)	24 (53)	**0.03**
48 h	4 (24)	20 (30)	26 (58)	**0.006**
72 h	4 (24)	21 (31)	25 (56)	**0.017**
PGD grade 3				
0 h	2 (12)	6 (9)	11 (24)	0.079
6 h	2 (12)	5 (8)	11 (24)	**0.04**
24 h	1 (6)	7 (10)	10 (22)	0.15
48 h	1 (6)	6 (9)	9 (20)	0.2
72 h	0 (0)	6 (9)	10 (22)	**0.03**
Rethoracotomy	1 (6)	8 (12)	6 (13)	0.86
Postoperative ECMO	2 (12)	6 (9)	5 (11)	0.85
VA ECMO	0 (0)	0 (0)	2 (4)	0.24
VV ECMO	2 (12)	6 (9)	3 (7)	0.68
Delayed chest closure	0 (0)	0 (0)	1 (2)	0.49
Acute rejection	9 (53)	33 (49)	25 (56)	0.91
Tracheostomy	3 (18)	16 (24)	11 (24)	0.92
Airway complication	11 (24)	22 (33)	4 (24)	0.56
Mechanical ventilation (days)	2 (1–40)	1 (1–50)	2 (1–159)	0.19
ICU stay (days)[a]	6 (4–42)	7 (2–54)	8 (2–43)	0.98
Hospital stay (days)[a]	51 (27–102)	44 (26–176)	38 (9–110)	0.69
In-hospital mortality	1 (6)	4 (6)	7 (15)	0.22
CLAD	4 (24)[b]	17 (25)	7 (15)	0.43
BOS	2 (12)	15 (22)	7 (15)	1
RAS	0 (0)	2 (3)	0 (0)	
Time to CLAD onset (years)	3.9 (0.84–7.2)	2.5 (0.29–6.9)[c]	2.6 (0.86–7.2)	0.41
30-Day survival[d]	17 (100)	67 (100)	44 (96)	0.23
1-Year survival[d]	16 (94)	59 (88)	37 (80)	0.32
3-Year survival[d]	15 (94)	34 (72)	30 (71)	0.18

(*Continued*)

TABLE 3 Continued

Variables	Undersized (n = 17)	Size matched (n = 67)	Oversized (n = 46)	*p* value
5-Year survival[d]	14 (88)	27 (60)	20 (54)	0.05

Data are presented as median (range) or n (%).
Bold values represent statistical significance ($p < 0.05$).
BOS, bronchiolitis obliterans syndrome;CPB, cardiopulmonary bypass; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; PGD, primary graft dysfunction; RAS, restrictive allograft syndrome; VA, veno-arterial; VV, veno-venous.
[a]Among patients who survived to discharge.
[b]Two cases with missing data were excluded.
[c]One case with missing data was excluded.
[d]Cases with insufficient follow-up duration were excluded.

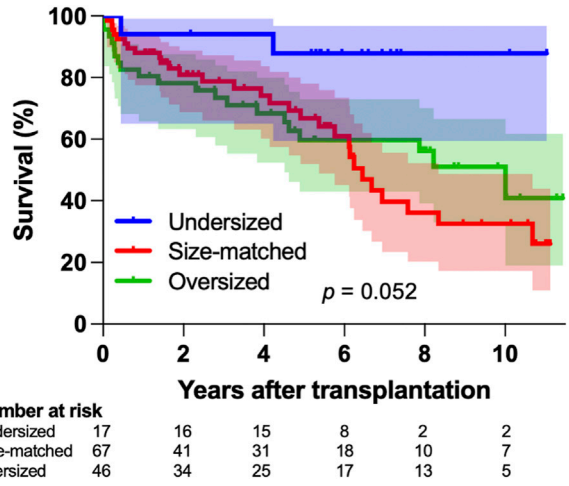


FIGURE 3
Kaplan–Meier survival curves according to donor-to-recipient lung size group. The colored area indicates the 95% confidence interval.

On the other hand, CLAD is a major determinant of long-term outcomes after lung transplantation and is associated with repeated epithelial injury driven by factors such as acute rejection and infection [18]. These insults promote chronic inflammation, impaired repair, and progressive fibrotic remodeling of the allograft [19]. Although these mechanisms are widely recognised, the onset of CLAD is multifactorial and is influenced by immunological, genetic and environmental factors [20, 21]. Based on this background, while there was no significant difference in the incidence of CLAD between the size-matched groups in this study, multiple factors may have interacted during the development process, potentially contributing to the observed differences in long-term prognosis.

This study has several limitations. First, it was a single-center retrospective analysis, and the sample size—particularly in the undersized group—was relatively small. Due to the fact that only two patients had a pTLC ratio <0.8, we set the cutoff value for undersizing at 0.9. As a result, this study includes very few cases of extreme undersizing, which may have limited our ability to detect its potential physiological consequences. Second, missing data on certain perioperative parameters, such as transfusion volume, precluded comprehensive analysis of all relevant variables. Third, while we attempted to account for baseline differences, unmeasured confounding factors (e.g., renal function, cardiac performance, infection, or malignancy) may have influenced long-term survival. Finally, although some oversized grafts underwent wedge resection, its potential impact on clinical outcomes could not be separately assessed in this study. Graft reduction may be one

TABLE 4 Multivariable Cox regression analysis for overall survival.

Variable	Hazard ratio	95% CI	*p* value
Group			
Oversized	0.83	0.45–1.55	0.57
Undersized	0.14	0.03–0.64	**0.01**
Donor age	1.02	1.00–1.05	0.08
DCD donor	0.62	0.29–1.33	0.22
Urgent case	2.26	0.50–10.35	0.29
Sex mismatch	1.32	0.66–2.62	0.43
Recipient sex	1.09	0.53–2.28	0.81
Donor smoking history	1.46	0.38–5.58	0.58

Undersized grafts were independently associated with improved overall survival, whereas oversized grafts were not significantly associated with survival.
Bold values represent statistical significance ($p < 0.05$).
CI, confidence interval; DCD, donation after circulatory death.

reason for the poor prognosis of oversized grafts, which is consistent with the previous study [22].

In summary, our data suggest that in bilateral lung transplantation for COPD, modest undersizing may be associated with lower PGD incidence and improved long-term survival, whereas oversized grafts may predispose recipients to early graft dysfunction. Further multicenter studies with larger cohorts are warranted to validate these findings and refine donor-recipient size matching strategies.

In conclusion, undersized grafts could be considered a viable option in COPD patients undergoing bilateral lung transplantation. These results may carry implications for optimizing graft size selection in clinical settings.

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 Institutional Review Board of Puerta de Hierro University Hospital. 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 of the retrospective nature of the study.

Author contributions

Corresponding author (DG-d-A) and YK were responsible for the study design. YK performed the statistical analysis. All the authors contributed to the critical appraisal and writing of the manuscript and approved the final submission.

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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.

Generative AI statement

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

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Acceptance of deceased donor livers in the United Kingdom – development of a liver "donor utilisation index"

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Published Donor Risk Indices are often used to estimate the risk associated with transplanting a donor liver. Such indices have been constructed by considering only livers that are transplanted and estimating the risk of graft loss or patient death. Until now, there has been no index available that reflects the chance of an offered organ not being transplanted in the United Kingdom (UK). This paper presents a UK Donor Utilisation Index (UKDUI) which quantifies the impact of donor factors upon liver non-use. By comparing our developed UKDUI with a commonly used UK Donor Risk Index, we are able to see that there are differences between the factors that influence liver non-use and the factors that influence liver post-transplant outcomes. Importantly, this UKDUI can be used in future studies to characterise and identify offered livers that are either more or less likely to be transplanted. For example, the UKDUI can be used for study inclusion criteria or for risk adjustment/stratification.

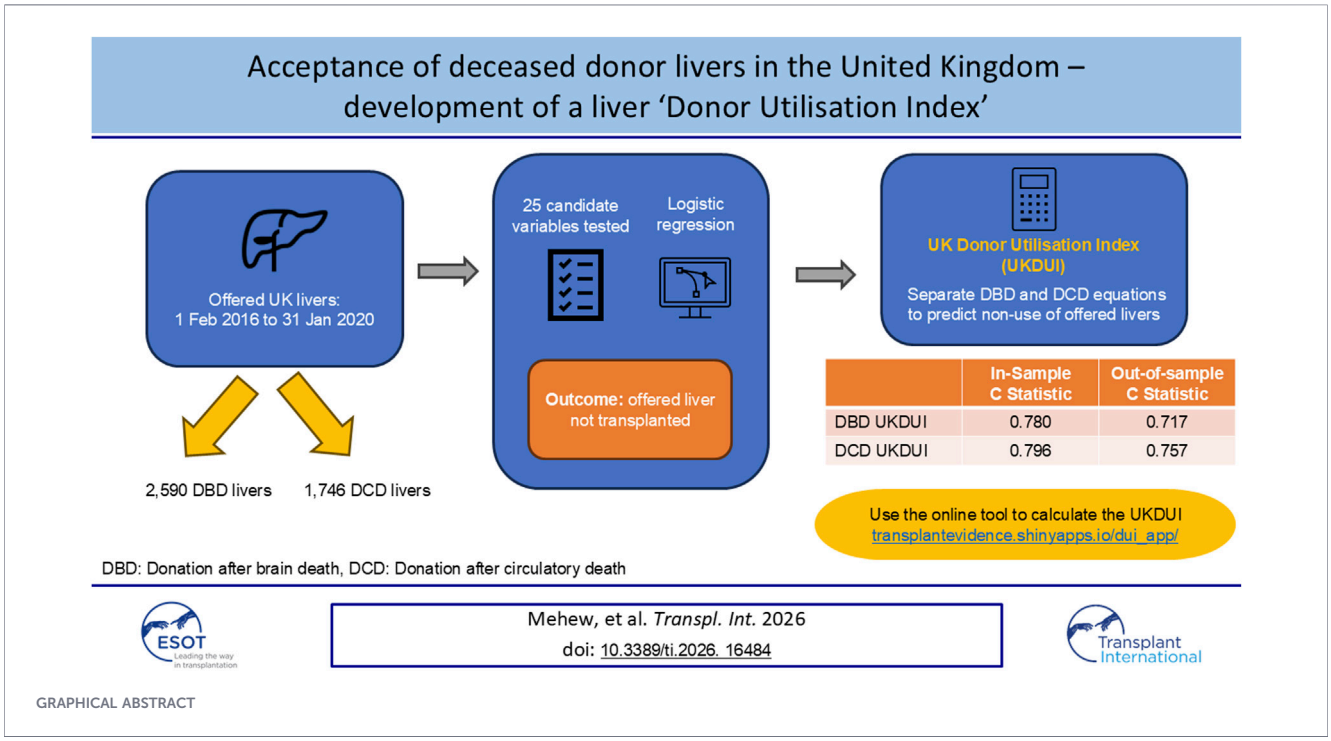
KEYWORDS
donation after brain death, donation after circulatory death, liver transplantation, organ donation, organ utilisation

Introduction

The dominant challenge in current-day clinical organ transplantation is the shortage of deceased donor organs. Although the number of UK deceased organ donors increased from 1,282 in the 2014/15 financial year to 1,510 in 2023/24 [1], there remains a major discrepancy between demand and supply. For instance, on 1 April 2023, there were 815 patients on the UK liver transplant list and a further 1,148 added over the course of the next 12 months; only 45% (884) were transplanted within the same 12-month period [1]. Waiting lists are even longer in other parts of the world: in the USA, the equivalent figure was 39% (9,516) for the 10,538 patients on the USA liver transplant list on 1 January 2023 and the further 13,954 patients added over the next 12 months [2].

As part of an effort to reduce the waiting time for patients in need of transplants, donor livers being offered for transplant are progressively more marginal, in terms of hypoxic injury, obesity, cardiovascular disease and age. Because of this, only 57% (854/1510) of deceased donors (where at least one organ was retrieved) in the UK resulted in a UK liver transplant in 2023/24 [1].

Until now, the degree of marginality, or risk, of offered livers in the UK has commonly been characterised using the UK Donor Liver Index (UKDLI) [3] or the US Donor Risk Index (USDRI) [4]. Such indices are useful in estimating the risk associated with



transplanting such organs as these were derived from statistical models for graft survival and graft failure, respectively. However, the factors considered by these indices are therefore associated with the outcome of transplanted organs and, therefore, by definition, declined or retrieved not transplanted livers would not have been included in the model development.

It is valuable to be able to measure trends in organ utilisation over time. In order to do this accurately, changes in the degree of marginality need to be accounted for. Using the UKDLI or USDRI to characterise marginality of offered organs is not appropriate because these only apply to transplanted organs; the risk profile of offered organs is inherently different to that of transplanted organs. This study therefore focuses on non-utilisation of all livers offered for transplant following donor family consent. We aimed to assess the factors associated with liver non-utilisation (i.e., livers not transplanted) in the UK and subsequently to produce a UK liver Donor Utilisation Index (UKDUI) which can be used formally to characterise perceived marginality at the time of offer, as the risk of non-use for offered livers. If an organ has not been transplanted, the outcome had it been transplanted (i.e., the true level of marginality) will always be unknown but surgeons have chosen not to transplant it based on the perception that it would not lead to successful transplant outcomes, i.e., perceived marginality. The ability to quantify the risk of non-utilisation will be valuable in clinical studies in which utilisation is a key endpoint.

Abbreviations: DBD, Donation after brain death; DCD, Donation after circulatory death; NHSBT, National Health Service Blood and Transplant; NLOS, National Liver Offering Scheme; UK, United Kingdom; UKDLI, United Kingdom Donor Liver Index; UKDUI, United Kingdom liver Donor Utilisation IndexUS or USA: United States of America; USDRI, United States of America Donor Risk Index; USDSRI, United States of America liver Discard Risk Index.

Materials and methods

UK liver offering scheme

In the UK, there is a separate liver offering process for DBD donors and DCD donors. On 20 March 2018, NHS Blood and Transplant (NHSBT) introduced a new named-patient National Liver Offering Scheme (NLOS) for DBD donors. The new DBD scheme uses a Transplant Benefit Score [5] for patients on the elective waiting list which helps to place the organ with the patient most likely to benefit from it. Table 1 outlines the key components of the UK liver offering scheme for adult DBD and DCD donors, including these changes.

Study population

Data from UK adult (aged ≥16 years) deceased donors where the liver was offered through the UK liver offering scheme between 1 February 2016 and 31 January 2020 were obtained from the UK Transplant Registry (UKTR) held by NHSBT. No restrictions were applied to the offer type; super-urgent, elective patient, hepatoblastoma, multi-organ, split liver, fast-track offers were all included. Donation after circulatory death (DCD) donors where the reason for non-use was recorded as 'prolonged time to asystole' were excluded from analysis as organ donation is not considered viable in these cases. Donors where all liver offers were withdrawn were also excluded.

Donors where the liver was transplanted outside of the UK were also excluded as we intended to assess non-utilisation of livers offered through the UK liver offering scheme. Donors where the liver was transplanted by the Dublin transplant centre were included in the analysis because "super-urgent" (Table 1) patients registered at Dublin are formally part of the national liver offering scheme.

TABLE 1 Description of the UK liver offering scheme.

DCD donors	DBD donors	
	Pre-20 March 2018	From 20 March 2018
1. Zonal centre offer (donor hospitals are assigned to one zonal transplant centre). Centre chooses the patient to transplant 2. Regional centre offers (each zonal centre has a set of linked centres, described as regional centres). Centre chooses the patient to transplant 3. Fast-track offers. Centre chooses the patient to transplant	1. Super-urgent patients (those who will not live long without a transplant) ordered by waiting time 2. Hepatoblastoma patients ordered by waiting time 3. Intestinal patients ordered by waiting time 4. Liver and cardiothoracic patients ordered by waiting time 5. Split liver – if donor meets the split liver criteria, a separate set of rules are followed 4. Zonal centre offer for elective patients (donor hospitals are assigned to one zonal transplant centre). Centre chooses the patient to transplant 5. Centre-based offers for elective patients. The order of the centres follows a rota. Centre chooses the patient to transplant 6. Fast-track offers. Centre chooses the patient to transplant	1. Super-urgent patients (those who will not live long without a transplant) ordered by waiting time 2. Hepatoblastoma patients ordered by waiting time 3. Intestinal patients ordered by waiting time 4. Liver and cardiothoracic patients ordered by waiting time 5. Split liver – if donor meets the split liver criteria, a separate set of rules are followed 6. Elective liver patients via either the transplant benefit score or time on the list 7. Fast-track offers. Centre chooses the patient to transplant

Further information is available at https://www.odt.nhs.uk/odt-structures-and-standards/odt-hub-programme/national-liver-offering-scheme/ and https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/37390/pol196.pdf.

TABLE 2 Number of donors used in model development and validation stages.

No. DBD donors			No. DCD donors		
Total	Model development	Model validation	Total	Model development	Model validation
3,657	2,590	1,067	2,504	1,746	758

However, all other donors where the liver was transplanted in Ireland were excluded. HIV positive donors were excluded because liver utilisation for this cohort of donors is rare (no HIV donor livers (0/9) were transplanted in our cohort); the effect of HIV status upon non-utilisation would far outweigh the effect of any other donor factor if this was included in the model. Hepatitis B status was determined using Hepatitis B core antibody. Hepatitis C status was determined using both antibody and Blood Borne Virus Nucleic Acid Test (BBVNAT) testing.

Donation after brain death (DBD) donors and DCD donors were considered separately in two distinct cohorts, as the features leading to acceptance and utilisation were believed to be different. A random selection of donors representing approximately 70% of each cohort were selected for model development and 30% for model validation (Table 2).

Statistical analysis

Non-utilisation was defined as no liver transplant resulting from a donor where the liver (whole or split) was offered for transplantation. Although the donor cohort included livers that met the UK criteria for splitting, we counted each donor only once irrespective of whether the liver was actually split. Twenty-five candidate variables collected in the UKTR were considered: 8 continuous and 17 binary/categorical (Table 3). Only variables that were known at time of offer were considered so that data missingness was not dependent upon the outcome of the offered organ; factors that were dependent on organ retrieval (e.g., steatosis) therefore could not be included. Two multivariable logistic regression models were developed to test and quantify the association of such variables with liver 'non-utilisation'; one for DBD donors and one for DCD donors. A stepwise variable selection method was used where candidate explanatory variables were retained in the model if these reduced the model deviance significantly ($p < 0.1$) according to the likelihood ratio test. All explanatory variables retained in the final model were therefore statistically significant at the 10% level in the presence of other factors.

Missing values for any of the 25 candidate variables (Supplementary Material 2) were imputed by Multiple Imputation using the fully conditional specification method. Further details on the missing data imputation methodology are outlined in Supplementary Material 2.

All eight continuous variables were tested once as a linear variable (e.g., difference in odds of "non-utilisation," between age 25 and 26 is the same as between age 65 and 66) and once as a non-linear variable (e.g., difference in odds of 'non-utilisation', between age 25 and 26 is not the same as between age 65 and 66). Natural cubic splines were used to explore non-linearity, enabling cubic expressions between "knots" at the 5%, 35%, 65% and 95% percentile

TABLE 3 Donor factors associated with the probability of non-utilisation with corresponding p values and odds ratios.

Factor	Categorisation	DBD model			DCD model		
		P-value	Odds ratio (for non-utilisation) Higher values = less likely to be transplanted	95% CI	P-value	Odds ratio (for non-utilisation) Higher values = less likely to be transplanted	95% CI
Body Mass index (BMI)	Non-linear spline (DBD) Linear[1] (DCD)	$p < 0.0001$	Figure 1	-	$p < 0.0001$	Figure 3	-
Alanine transaminase, ALT (iu/L)	Non-linear spline	$p < 0.0001$	Figure 2	-	0.01	1.001	(1.0–1.001)
Hepatitis C status	Negative	$p < 0.0001$	1	-	$p < 0.0001$	1	-
	Positive		25.16	(12.15–52.10)		26.34	(3.39–204.96)
History of alcohol abuse	None/rarely/light	$p < 0.0001$	1	-	$p < 0.0001$	1	-
	Moderate		1.37	(1.02–1.85)		1.29	(0.91–1.81)
	Heavy/Very heavy		3.08	(2.31–4.10)		2.82	(1.95–4.08)
	Stopped		0.72	(0.27–1.88)		0.72	(0.30–1.71)
Bilirubin (μmol/L)	Linear[1]	$p < 0.0001$	1.04	(1.03–1.06)	0.12		
Age (years)	Linear[1] (DBD) Non-linear spline (DCD)	$p < 0.0001$	1.03	(1.02–1.04)	$p < 0.0001$	Figure 4	-
Alkaline phosphate (iu/L)	Linear[1]	$p < 0.0001$	1.005	(1.003–1.007)	0.0004	1.005	(1.002–1.008)
History of diabetes mellitus	No	$p < 0.0001$	1	-	0.07	1	-
	Yes		2.14	(1.53–2.98)		1.51	(0.95–2.41)
Blood group	O	$p < 0.0001$	1	-	0.0003	1	-
	A		1.28	(1.02–1.62)		1.26	(0.98–1.61)
	B		1.27	(0.88–1.85)		1.33	(0.84–2.10)
	AB		3.96	(2.25–6.96)		4.55	(2.07–9.99)
Cause of death	Trauma	0.001	1	-	0.0002	1	-
	Cerebrovascular accident (CVA)		1.51	(0.73–3.10)		1.16	(0.61–2.22)
	Anoxia		0.95	(0.45–2.02)		2.16	(1.09–4.28)
	Other		2.11	(0.97–4.58)		2.69	(1.31–5.54)

(*Continued*)

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TABLE 3 Continued

Factor	Categorisation	DBD model P-value	DBD model Odds ratio (for non-utilisation) Higher values = less likely to be transplanted	DBD model 95% CI	DCD model P-value	DCD model Odds ratio (for non-utilisation) Higher values = less likely to be transplanted	DCD model 95% CI
Hepatitis B status	Negative	0.006	1	-	0.60		
	Positive		2.23	(1.28–3.88)			
History of a past tumour	No	0.02	1	-	0.04	1	-
	Yes		1.61	(1.07–2.44)		1.75	(1.00–3.05)
National liver offering scheme (NLOS) status	Liver offered before 20 March 2018	0.05	1	-	0.05	1	-
	Liver offered on or after 20 March 2018		1.24	(1.00–1.53)		1.27	(1.00–1.61)
History of cardiac or respiratory arrest	No	0.10			0.02	1	-
	Yes					0.66	(0.45–0.96)
Noradrenaline administered	No	0.12			0.33		
	Yes						
History of drug abuse	No	0.12			0.35		
	Yes						
History of cardiac disease	No	0.14			0.12		
	Yes						
History of hypertension	No	0.24			0.002	1	-
	Yes					1.56	(1.17–2.06)
Sodium (mmol/L)	Linear[1]	0.41			0.08	1.02	(1.00–1.04)
ITU stay prior to death (hours)	Linear[1] (DBD) Non-linear spline (DCD)	0.44			0.0001	Figure 5	-
History of smoking	No	0.51			0.02	1	-
	Yes					1.35	(1.05–1.75)
Creatinine (µmol/)	Linear[1]	0.67			0.02	1.002	(1.0–1.004)

(*Continued*)

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TABLE 3 Continued

Factor	Categorisation	DBD model			DCD model		
		P-value	Odds ratio (for non-utilisation) Higher values = less likely to be transplanted	95% CI	P-value	Odds ratio (for non-utilisation) Higher values = less likely to be transplanted	95% CI
Sex	Male	0.85			0.02	1.37	(1.06–1.78)
	Female					1	-
Ethnicity	White	0.89			0.32		
	Asian						
	Black						
	Other						
Cytomegalovirus status (CMV)	Negative	0.91			0.36		
	Positive						
C statistic		0.780			0.796		

Factors found to be non-significant and hence not included in the final models are shaded in grey.
[1]Also tested as a non-linear term but found not to be significant.
CI, Confidence Interval.

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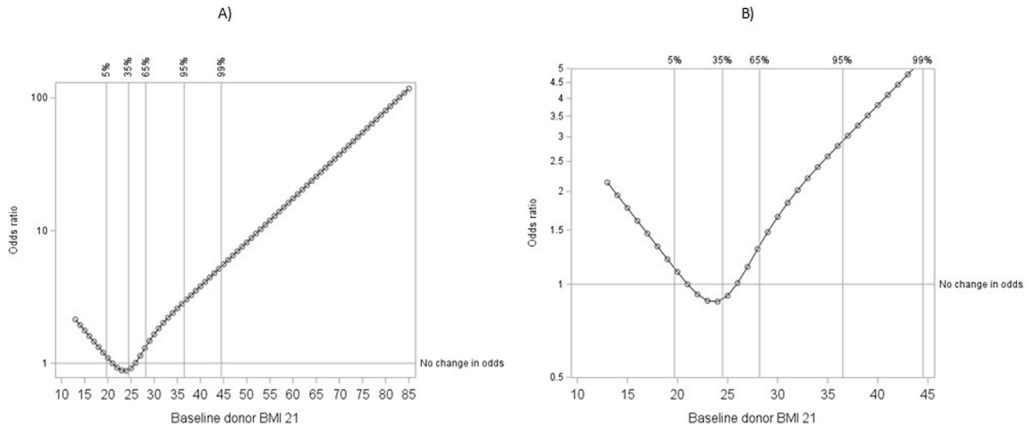

FIGURE 1
Odds ratios for Body Mass Index (BMI) relative to a BMI = 21 donor (Donation after Brain Death (DBD) model). **(A)** Full range of observed BMI values. **(B)** BMI values up to 45 (99% of observed data).

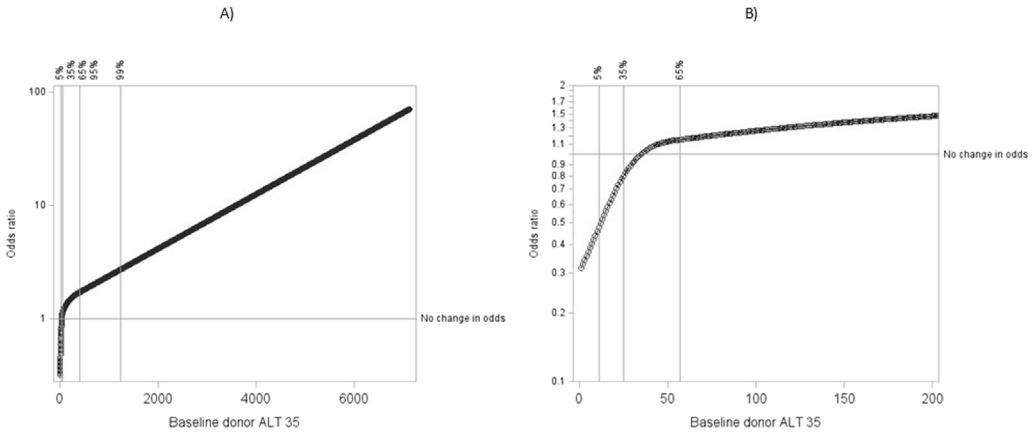

FIGURE 2
Odds ratios for Alanine transaminase (ALT) relative to an ALT = 35 donor (Donation after Brain Death (DBD) model). **(A)** Full range of observed ALT values. **(B)** ALT values up to 200 (89% of observed data).

values. A model containing the spline terms was considered more appropriate than a model containing just the linear term if it reduced the model deviance significantly ($p < 0.1$) according to the likelihood ratio test. Interaction terms were not considered in the interest of parsimony and to reduce the risk of over-fitting.

Separate DBD and DCD liver Donor Utilisation Index (UKDUI) equations were derived from the linear predictor of the resulting two models. As the models were developed from logistic regression, the UKDUI value was equivalent to the 'probability of non-utilisation' whereby only values between 0 and 1 were possible, with higher values representing donors perceived to be more marginal and hence higher risk of non-utilisation. Providing the calibration (or predictive ability) of the DBD model was comparable with that of the DCD model, UKDUI values from the DBD model could be compared with UKDUI values from the DCD model.

Rigorous model checking and validation was performed for both the DBD and DCD models. The methodology used is outlined in Supplementary Material 1.

All analyses were performed using SAS version 9.4 (SAS Institute Inc., NC, USA).

Using the UKDUI

To illustrate how the UKDUI equation can be used, the UKDUI was calculated for a range of hypothetical donors with differing characteristics. The UKDLI was also calculated for these donors for reference. To understand how the UKDUI compares with the UKDLI, the UKDUI and UKDLI was calculated for each donor in the validation cohort and plotted as a scatter plot. Where there were missing data in the validation cohort for any of the UKDUI or UKDLI factors, the most common values identified from the model development cohort were used. To understand how the UKDUI and UKDLI compares in terms of ability to distinguish between livers that are transplanted and those that are not transplanted, a boxplot was created for donors in the validation dataset separately for livers that were transplanted and for livers that were not transplanted. This

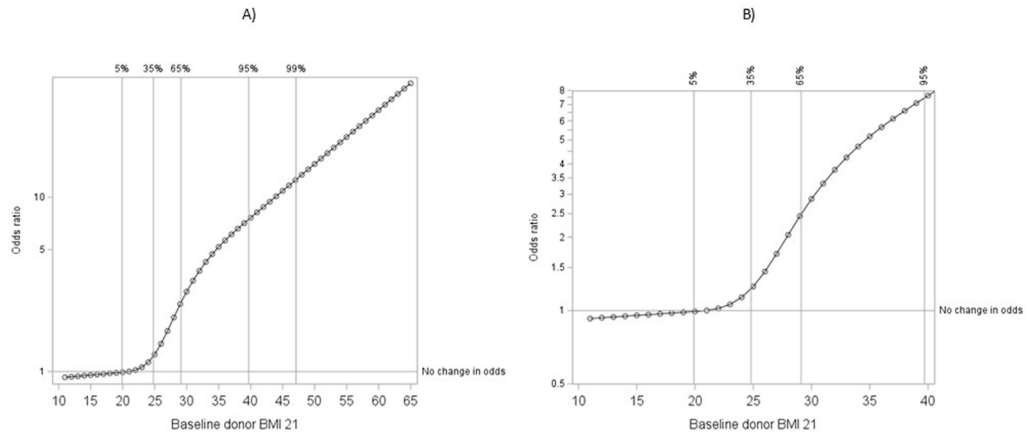

FIGURE 3
Odds ratios for Body Mass Index (BMI) relative to a BMI = 21 donor (Donation after Circulatory Death (DCD) model). **(A)** Full range of observed BMI values. **(B)** BMI values up to 40 (95% of observed data).

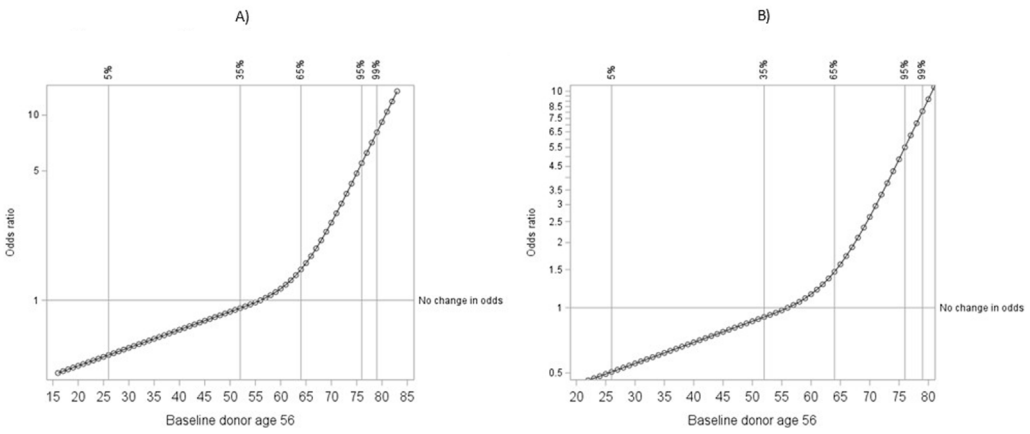

FIGURE 4
Odds ratios for age relative to an age = 56 donor (Donation after Circulatory Death (DCD) model). **(A)** Full range of observed age values. **(B)** Ages 20–80 only (97.5% of observed data).

boxplot was performed once for UKDLI values and once for UKDUI values, for DBD and DCD donors separately.

Results

Model development

Of the 2,590 DBD donors whose livers were offered in the development dataset, 2,015 (78%) were transplanted. This figure was lower for DCD donors with 538 out of 1,746 (31%) being transplanted. The factors found to be significantly associated with non-utilisation and associated odds ratios are shown in Table 3 for DBD and DCD donors separately. The p values for those factors not found to be significant, and hence not included in the final models, are also shown in Table 3 shaded in grey. Note that the effects of donor Body Mass Index (BMI) and alanine transaminase (ALT) upon liver non-use were found to be non-linear for DBD donors, as were the effects of BMI, age and ITU stay for DCD donors. The odds ratios for these factors are illustrated by Figures 1–5 respectively. Figure 1 shows that livers from DBD donors with a BMI around 25 were most likely to be transplanted, but the odds of non-utilisation increased 1) as BMI increased higher than 25 and 2) as BMI decreased lower than 25. This counter-intuitive effect for lower (<25) BMI donors was felt to be due to confounding factors not incorporated by the model; low BMI in donors may be associated with other medical factors. For DCD donors, Figure 3 shows that there was little effect of BMI upon non-utilisation unless the donor had a BMI greater than approximately 23 after which point the odds of non-utilisation increased as BMI increased. Figure 2 shows that higher values of ALT lead to higher odds of non-utilisation for DBD donors. The change in odds is more drastic for low ALT values; the difference between ALT values of 14 and 15 in terms of odds is greater than for ALT values of 49 and 50.

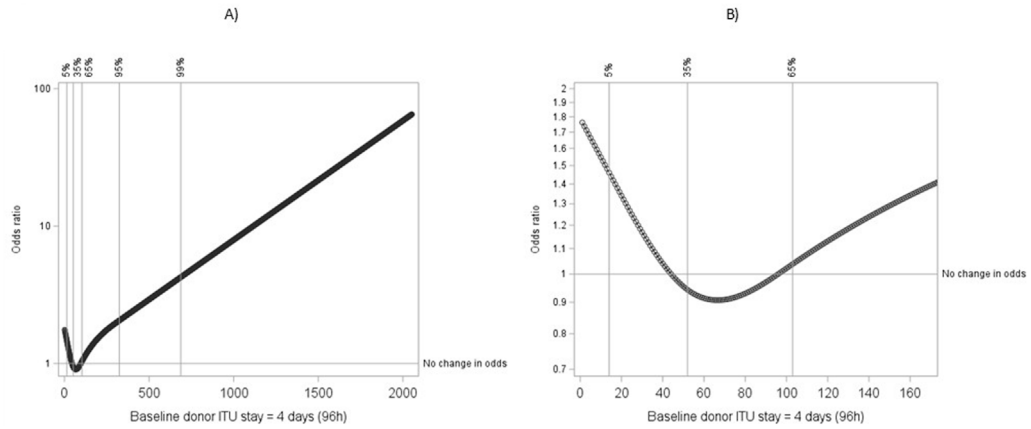

FIGURE 5
Odds ratios for Intensive Therapy Unit (ITU) Stay relative to an ITU Stay = 96 h donor (Donation after Circulatory Death (DCD) model). **(A)** Full range of observed ITU stay values. **(B)** ITU stay values up to 168 hrs (7 days) (83% of observed data).

Figure 4 shows that for DCD donors, the odds of non-utilisation increase as donor age increases. This effect is amplified for donors over the age of 60; the difference between age 65 and 66 in terms of odds is greater than the difference between age 40 and 41. Figure 5 shows that livers from DCD donors with an ITU stay between approximately 60–80 h were most likely to be transplanted, but the odds of non-utilisation increased 1) as ITU stay increased higher than 80 h and 2) lower than 60 h. This counter-intuitive effect for shorter ITU stays (<60 h) was felt to be due to confounding factors not incorporated by the model; shorter ITU stays may be associated with less stable donors.

The resulting UKDUI equations derived from the logistic regression models presented in Table 3 are shown in Equation 1 (for DBD donors) and Equation 2 (for DCD donors). Note that if the equations are to be used with prospectively collected data, or for livers offered on or after 20 March 2018, the 'post NLOS' term can be added on to the intercept term (−4.3888 + 0.2157 for DBD donors and −5.4499 + 0.2354 for DCD donors) and held fixed. Details of the UKDUI spline terms can be found in Supplementary Material 3 (DBD) and Supplementary Material 4 (DCD).

The model checking and model validation performed suggested both the DBD and DCD models were an adequate representation of liver non-utilisation (Supplementary Material 5). In particular, the in-sample C statistic (which represented the model's ability to discriminate between utilised and non-utilised livers within the development dataset) was 0.780 for the DBD model and 0.796 for the DCD model. Furthermore, the out-of-sample C statistic (evaluating discrimination within the validation dataset) was 0.717 for the DBD model and 0.757 for the DCD model.

Using the UKDUI

For those wishing to use the UKDUI to estimate the probability of non-utilisation for a particular donor, there is an online UKDUI calculator [6].

Table 4 illustrates the UKDUI values for various hypothetical donors. For comparison, UKDLI values are also shown for these donors. Note that UKDUI values can range from 0 to 1 but no such restriction applies to the UKDLI (values are usually between 1 and 4 although can sometimes be higher). Where missing data occurred for the donor factors included in the UKDUI or UKDLI equations, the values in Supplementary Material 6 were imputed. A description of each hypothetical donor is provided in Supplementary Material 10 along with an explanation for the similarities and disparities between calculated UKDUI and UKDLI values.

Figure 6 illustrates the correlation between UKDUI and UKDLI values for all donors in the validation cohort. For DBD donors (Figure 6A), there appears to be some positive correlation for donor livers with UKDUI values between 0 and 0.2 suggesting that the UKDUI and UKDLI are generally in agreement for livers that are likely to be transplanted. However, there are large discrepancies between the UKDUI values and UKDLI values for livers less likely to be transplanted; the UKDUI may predict a very high chance of non-use while the UKDLI may be relatively low. For DCD donors (Figure 6B), there is some positive correlation across all values of the UKDUI however there are still large discrepancies.

Figures 7A,C shows that for DBD donors, the UKDUI can distinguish between livers that were transplanted from those that were not transplanted much better than the UKDLI. The same applies to DCD donor livers (Figures 7B,D).

Discussion

Our analysis has highlighted the substantial difference in utilisation between offered UK DBD donor livers and offered UK DCD donor livers. The distribution of UKDUI values for DBD donors in the validation cohort (Supplementary Material 7A) shows that the large majority (971/1,067, 91%) of donors fell in the lower half of possible UKDUI values (UKDUI<0.5) representing lower risk of non-use whereas for DCD donors the large majority (586/758, 77%) of donors in the validation cohort (Supplementary Material 7B) fell in the upper half of possible UKDUI values (UKDUI>=0.5), reflecting the higher risk of non-use.

The strengths and weaknesses of our UKDUI are summarised in Table 5 and discussed below in further detail.

TABLE 4 UKDUI values for various hypothetical donors (differences from Donor A highlighted in bold).

Donor	A	B	C	D	E	F	G
UKDUI	**0.03**	**0.16**	**0.98**	**0.99**	**0.12**	**0.46**	**0.83**
UKDLI	0.90	1.69	1.75	3.31	1.39	0.90	1.69
Donor type	DBD	**DCD**	DBD	**DCD**	**DCD**	DBD	**DCD**
Hepatitis B status	Negative	Negative	**Positive**	**Positive**	Negative	Negative	Negative
Hepatitis C status	Negative	Negative	Negative	Negative	Negative	**Positive**	**Positive**
History of diabetes mellitus	No	No	**Yes**	**Yes**	No	No	No
National liver offering scheme status	Post 20 March 2018	Post 20 March 2018	Post 20 March 2018	Post 20 March 2018	Post 20 March 2018	Post 20 March 2018	Post 20 March 2018
History of a past tumour	No	No	No	No	No	No	No
Age (years)	20	20	**68**	**68**	20	20	20
Bilirubin (μmol/L)	9	9	**17**	**17**	9	9	9
Alkaline phosphate (iu/L)	75	75	**159**	**159**	75	75	75
Cause of death	Trauma	Trauma	**CVA**	**CVA**	Trauma	Trauma	Trauma
Blood group	O	O	**B**	**B**	O	O	O
History of alcohol abuse	None/rarely/ light	None/rarely/ light	**Heavy/very heavy**	**Heavy/very heavy**	None/rarely/ light	None/rarely/ light	None/rarely/ light
Body Mass index (BMI)	18.5	18.5	**45**	**45**	18.5	18.5	18.5
Alanine transaminase, ALT (iu/L)	35	35	**150**	**150**	35	35	35
History of smoking	No	No	**Yes**	**Yes**	No	No	No
Sex	Male	Male	Male	Male	**Female**	Male	Male
History of hypertension	No	No	No	No	No	No	No
History of cardiac or respiratory arrest	No	No	No	No	No	No	No
Creatinine (μmol/)	75	75	**150**	**150**	75	75	75
Sodium (mmol/L)	141	141	**150**	**150**	141	141	141
ITU stay prior to death (hours)	18	18	**50**	**50**	18	18	18
Height (cm) [required for UKDLI]	160	160	160	160	160	160	160

CVA: Cerebrovascular accident.

The developed DBD model consisted of 13 factors found to be significantly associated with liver non-use while the DCD model had 19 factors. Despite the substantial difference between the two donor types, there were still 11 factors that were found to be significantly associated with liver non-use irrespective of donor type. Hepatitis C status was by far the most influential factor for both models as few Hepatitis C donor livers were transplanted (11/62 DBD and 1/32 DCD). However, it is acknowledged that the UK landscape has since changed such that livers from these donors are now considered for transplantation more often following the British Viral Hepatitis Group position statement [7]. As a result, the UKDUI will likely overestimate the probability of non-utilisation for Hepatitis C positive donors when considering more recent cohorts. As the effect of all other factors are considered to be independent of each other, this would have minimal impact on the applicability of the rest of the UKDUI.

Blood group AB and heavy/very heavy alcohol use was also found to be significantly associated with non-use for both DBD and DCD donors. The effect of blood group upon non-utilisation may be a result of the pool of available recipients on the list. For example, only 2% of patients on the active liver transplant list on 31 March 2024 were blood group AB [1]. The effect of sex may also be a result of other donor factors that are not easily defined/captured but are more dominant in either males or females.

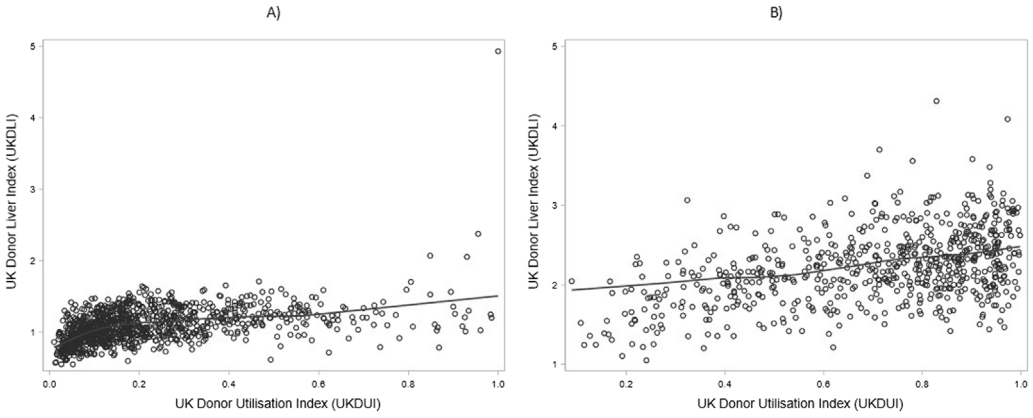

FIGURE 6
Distribution of United Kingdom liver Donor Utilisation Index (UKDUI) values in the validation dataset plotted against the corresponding United Kingdom Donor Liver Index (UKDLI) values for each **(A)** Donation after Brain Death (DBD) donor and **(B)** Donation after Circulatory Death (DCD) donor. Note that two extreme UKDLI values (UKDLI: 9.07, UKDUI: 0.84), (UKDLI:29.1, UKDUI: 0.25) have been removed from the DCD plot in order to visualise the trends more easily. Line represents a loess smoother with smoothing parameter set to 0.5.

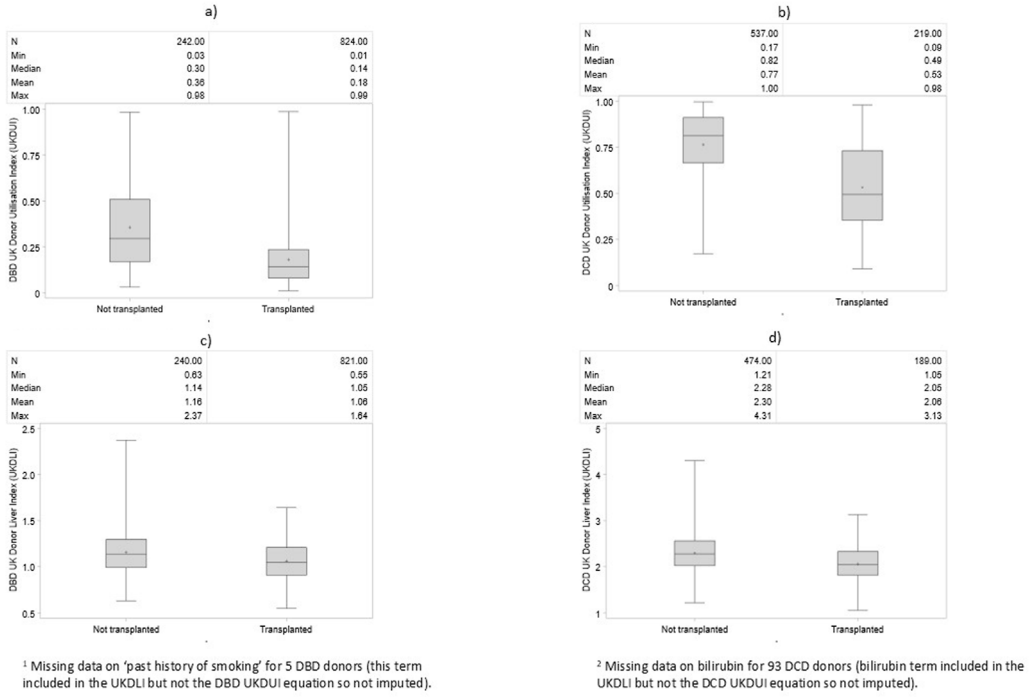

FIGURE 7
Distribution of United Kingdom liver Utilisation Index (UKDUI) values for DBD donors **(A)** and DCD donors **(B)**, and United Kingdom Donor Liver Index (UKDLI) values for DBD donors **(C)** and DCD donors **(D)**. Values are calculated from the validation dataset and split by whether the liver was transplanted or not. Note that one extreme Donation after Brain Death (DBD) UKDLI value (UKDLI: 4.93, UKDUI:1.00, liver not transplanted) and two extreme Donation after Circulatory Death (DCD) UKDLI values (UKDLI: 9.07, UKDUI: 0.84, liver not transplanted), (UKDLI:29.1, UKDUI: 0.25, liver not transplanted) have been removed from the plot in order to visualise the trends more easily.

Table 3 suggests that changes to national liver offering scheme made on 20 March 2018 are associated with a borderline significant increase in both DBD and DCD non-utilisation. However, the authors suspect that this simple binary indicator (pre-change, post-change) may reflect changes in the overall donor pool (over and above the donor factors considered in the modelling process) over time and an increase in offering more marginal organs, rather than the effect of the offering scheme.

TABLE 5 Strengths and weaknesses of the developed UKDUI.

Strengths	Weaknesses
Can be used to assess the risk of non-use for offered organs. Previously, only indices based on the outcome of transplanted organs were available, however the risk of non-use and risk of poor outcomes post-transplant are not equivalent	Developed using UK data from 1 February 2016 to 31 January 2020 when use of machine perfusion and Hepatitis C donors was less common
Only data at time of offering is required to calculate the UKDUI, enabling the risk of non-use to be characterised for any organ at time of offer. Can be useful as entry criteria for studies that aim to target the most poorly utilised livers	Data/risk factors from further down the offering pathway are not included; e.g., long cold ischemia times or liver diagnoses upon retrieval would influence non-use but are not accounted for
Can be used to characterise liver non-utilisation across the UK as a whole. Centres that have particularly high or low non-utilisation rates, relative to the national average, can therefore be identified	Individual estimates of non-use for a particular donor do not account for variation associated with a particular centre or with an individual clinical decision-maker
Comprehensive statistical methods (including investigation of non-linear relationships) and model validation techniques have been used to produce and validate the UKDUI equations	UKDUI equations are complex and there are separate DBD and DCD equations but users are encouraged to use the UKDUI online tool [6]

The main driver for carrying out this study was the need to characterise risk of non-use when considering a UK national cohort of offered deceased donor livers. Up until now, indices based on transplanted livers have been used (UKDLI). We have shown that for both DBD and DCD donors, the UKDUI is generally better than the UKDLI at distinguishing between livers that are transplanted and those that are not (Figure 7). There have been studies outside of the UK which have aimed to characterise and predict the risk of non-use [8-16]; these are described and contrasted with the UKDUI in Table 6. Note that much of the existing literature focusses on the utilisation of retrieved organs as opposed to offered organs.

Only donor data available at the time of offering were included. This enabled us to produce a UKDUI that characterises perceived marginality at the time of offer and moreover, include data that were recorded consistently for livers that were 1) offered not retrieved, 2) retrieved not transplanted and 3) transplanted. In practice, further organ/donor information may have come to light during or after retrieval, for example, causing the transplanting surgeon to decline the organ; this is not captured in the UKDUI. As a result, there will be systematic variation in the data which is unaccounted for. However, the bias that would be caused by missing data for the cohort of offered not retrieved organs if we included later datapoints was considered more problematic than our chosen methodology.

Figure 6 showed there to be large discrepancies between the UKDUI and UKDLI values for livers less likely to be transplanted. There are two explanations for such discrepancy. The UKDLI is designed to describe the risk of graft failure if the organ was to be transplanted whereas the UKDUI is designed to describe the risk of not transplanting the organ. The discrepancy shown in Figure 6 could therefore suggest that transplant centres are declining some DBD livers that have a low risk of graft failure. The other explanation for such discrepancy is that the UKDUI contains more factors than the UKDLI meaning that the UKDUI is much more variable depending on donor characteristics. The UKDLI was constructed using data on transplants performed between 2000 and 2014 and perhaps if more recent data were used, the UKDUI and UKDLI could be in stronger agreement. Or perhaps the factors that influence graft survival genuinely are different (fewer) than the factors that influence liver utilisation decision making.

Future studies need to carefully consider which index is more appropriate to use. The UKDUI does not predict graft outcomes; it is designed to describe the risk of an offered liver not being transplanted. It should therefore be used in organ utilisation studies. However, the UKDLI would be more appropriate for studies looking at the graft outcome of transplanted livers. We therefore recommend that the UKDUI is used if wishing to assess the risk of non-use and that a transplant outcome-based index (such as the UKDLI) is used if wishing to assess the risk of poor transplant outcomes. There is increasing importance in using organ utilisation as both a trial endpoint and a focus for interventions. There are technologies which have shown promise in increasing utilisation (e.g., Normothermic Machine Perfusion [17, 18] and Normothermic Regional Perfusion [19]), and these technologies will be most efficient if targeted to the most poorly utilised donor organs. An accurate UKDUI allows us to do this both for inclusion criteria in the clinical trial setting, but also for efficient use in clinical practice. For instance, the UKDUI presented in this paper was used as inclusion criteria in the PLUS liver clinical trial (https://doi.org/10.1186/ISRCTN11552402). Studies in other organ areas have also started to focus on utilisation as an important endpoint, for example, the PITHIA kidney clinical trial [20]. Similar tools for these organs may help to target these interventions increasing efficiency. It should be highlighted that focussing on utilisation as a clinical endpoint alone does not give a full picture; increased utilisation is only a positive outcome if accompanied by adequate clinical outcomes.

Our developed UKDUI has many strengths; it has been developed on a large national dataset and validated in a randomised national subset which has shown the index to reflect UK liver utilisation between 1 February 2016 and 31 January 2020 well (Supplementary Material 5). The statistical models used to create the UKDUI were found to have good predictive ability (Table 3). It should be noted however that no external validation has

TABLE 6 Studies from outside the UK that aim to characterise and predict the risk of non-use for non-UK organs.

Organ	Name of index	Comparison with UKDUI
Liver (US)	Liver discard risk index (USDSRI)	A liver discard risk index (USDSRI) [8] was published in 2018 with the aim to predict the chances of liver non-use in the US. The major advantage of this index was the concept of grading livers according to the USDSRI at time of offer and preferentially offering those with higher chances of non-use to US transplant centres with a more 'aggressive' approach to organ acceptance. Although this is not the designed purpose of the UKDUI, it could be considered for similar organ offering concepts in the UK. The USDSRI and UKDUI were both developed using logistic regression and there is a lot of agreement between the two indices in terms of which factors influence non-use (e.g., donor age, sex, BMI, ALT, Hepatitis C status, Hepatitis B status, cause of death, bilirubin) despite representing two very different organ offering systems (US versus UK). One major difference is that the USDSRI represents both DBD and DCD donors in one equation; the effect of donor type is incorporated through one value that shifts the estimate up or down by a specified amount. The UKDUI, on the other hand, acknowledges that the factors that influence liver non-utilisation in the UK, as well as the effect of these factors, differ between DBD and DCD donors. The USDSRI also treats all factors as categorical variables whereas the UKDUI has a mixture of categorical and continuous variables Another important difference is that the USDSRI includes donors that underwent procurement surgery only
Liver (Italy)	Donor Rejected organ pre-transplantation (DROP) score	A donor Rejected organ pre-transplantation (DROP) score [9] was published in 2022 which aimed to predict the risk of liver non-use for DBD donor organs offered in Italy. Importantly, the index predicts non-use due to liver-related reasons only. The following (donor) factors as well as a term representing a nuance of the organ offering scheme were included in the index, many of which are also included in the UKDUI; age, weight, height, diabetes, Hepatitis C status, Hepatitis B status, hypotension, creatinine, ALT, AST, bilirubin Liver-related reasons for non-use were defined as; pre-procurement liver blood tests and/or imaging; gross anatomy; procurement histology, and poor perfusion. Liver-unrelated reasons for graft discard were defined as; donor tumours, donor infections, and pre-procurement donor cardiac arrest. Similarly to the UKDUI, a logistic regression model was used but for the DROP score, only liver-related reasons were treated as an event; liver-unrelated reasons were classed as a non-event along with livers that were transplanted. The logistic regression model was therefore considered a cause-specific logistic regression model under a competing risks scenario Similarly to the UKDUI, only donor factors at time of offering were considered as risk factors
Pancreas (Eurotransplant)	Pre-procurement pancreas suitability score (P-PASS)	The pre-procurement pancreas suitability score (P-PASS) was published in 2008 [10] and aimed to identify 'suitable' offered pancreas donors. The score consists of donor factors only; patient age, BMI, the length of stay in the intensive care unit (ICU), the occurrence of cardiac arrest, and serum levels of sodium, amylase, lipase, adrenaline, and dopamine Unlike the UKDUI, statistical modelling was not used to produce the score; the assignment of weights and points was based on medical expertise and literature review. Due to the time of its development, the P-PASS was developed primarily for DBD offered livers; no account for DCD donation was made Logistic regression was used to assess the relationship between P-PASS and the odds of accepting an offered pancreas. Using pancreas acceptance as the outcome variable, this analysis suggested that donors with a P-PASS score of ≥17 were three times more likely to be declined
Kidney (US)	US kidney donor utilisation index (USKDUI)	In 2019 a kidney donor utilisation index (USKDUI) [11] was published with the aim to predict the chances of non-use for procured kidneys in the US. Similarly to the UKDUI, a logistic regression model was developed and the following factors were found to be significant upon kidney non-use; age, hypertension, diabetes, classification as public Health service increased risk, creatinine, Hepatitis C, Stroke cause of death, BMI, donation after cardiac death, Black race, drug use (nonintravenous), current smoker, cancer, kidney donor profile index The USKDUI was then used at the centre level by multiplying each of the parameter estimates by the proportion of donor kidneys at each centre with each characteristic DBD donors and DCD donors were included in the same model but a binary factor was incorporated to represent the difference in non-use by donor type Unlike the UKDUI, this index was applicable to procured organs as opposed to offered organs

(*Continued*)

TABLE 6 Continued

Organ	Name of index	Comparison with UKDUI
Lung (US)	Predictors of older donor lung utilisation	In 2020 a study was published [12] which identified the factors associated with the utilisation of lungs from 'older' solid organ donors in the US. Older donors were considered as aged >55 years. Both DBD and DCD donors were included in the same model. While not used to produce an index directly, logistic regression was used to identify the following factors associated with utilisation; sex, age, BMI, ethnicity, cigarette use, cocaine use, alcohol abuse, hypertension, diabetes, donor type, cause of death, lung function (PaO2/FiO2) ratio
Liver and kidney (US)	Use of machine learning for predicting kidney and liver discard	In 2023, a study was published [13] which aimed to predict organ utilisation/discard for livers and kidneys separately and compared six different machine learning techniques; random forest, XGBboost, FCNN, Naive Bayes, logistic regression with Lasso, ridge logistic regression (logistic regression was considered a machine learning technique). The two best performing methods in terms of predictive ability were found to be XGBoost and random forest. Interpretability is limited with some of these traditional machine learning methods and an index is not producable but if prediction is theprimary purpose then machine learning is worth consideration
Kidney (US)	Using machine learning to identify factors, additional to the existing kidney donor risk index, that influence kidney discard	A study was published in 2025 [14] which emphasised the importance of having an interpretable and easy-to-implement model for the prediction of non-use of retrieved kidneys The model included all factors included in the existing US kidney donor risk index (USKDRI) [15] as a minimal set of variables and then additional factors were added 1) through random forest machine learning and 2) logistic regression. Cold ischemia time and warm ischemia time were included as factors meaning that this model could not be used at time of offer or be used to predict offered organs that were not retrieved. Models were developed both with and without biopsy information For the model excluding biopsy information, in addition to the KDRI variables, the following factors were found to be influential upon kidney non-use: creatinine, age, hypertension, arginine, BMI, hisotry of smoking, donor type, coronary angiogram, height
Kidney (US)	Probability of discard or delay (PODD)	The probability of discard or delay (PODD) was published in 2010 [16] for US kidneys from donors where at least one kidney had been retrieved. This index aimed to identify factors that influenced whether a kidney would be 1) discarded (retrieved not transplanted) or delayed (cold ischemia time >36 h) or 2) transplanted Logistic regression was used to model this outcome variable. As two kidneys were studied from most donors (leading to non-independence), donor-level clustering was accounted for using a clustered sandwich estimator of the variance–covariance matrix The following (donor) factors were included in the model; sex, age, blood group, BMI, cancer, history of smoking, hypertension, myocardial infarction history, diabetes, insulin treatment, donor type, cause of death, human T lymphocyte virus, cytomegalovirus, Hepatitis B, Hepatitis C, CDC high risk donor, pumped, sclerosis, creatinine DBD and DCD donors were included in the same model/equation and the authors investigated different cutoffs for PODD values in order to predict a kidney that was 'easy to place' or 'hard to place'

been performed; the period following 31 January 2020 covers the COVID-19 pandemic during which time liver utilisation was substantially impacted. Furthermore, as the UKDUI was used as an inclusion criteria for recruitment of livers into the PLUS clinical trial (https://doi.org/10.1186/ISRCTN11552402) between 11 April 2022 and 3 April 2023, the liver utilisation landscape will have differed during the trial period due to increased use of machine perfusion.

Of course, attitudes towards risk and organ utilisation may differ between clinicians and between transplant centres, and this may also be affected by waiting list composition. The developed UKDUI provides a useful summary of liver non-utilisation across the UK as a whole.

Use of machine perfusion during the study period was fairly low, relative to the current UK landscape, so future work could be applied to investigate how the probability of non-utilisation changes in the presence of machine perfusion, or any other 'new' factor of interest, once the known risk factors incorporated in the UKDUI are adjusted for.

For those wishing to use the UKDUI but have missing data for some of the donor factors included in the UKDUI equations, it is suggested that the values presented in SDC 6 are imputed. While the UKDUI equations are complex, users are encouraged to use the UKDUI online tool [6].

In addition to providing a tool to help understand donor case mix, this UKDUI offers utility as a clinical audit tool; it will enable future studies to adjust for the risk profile (risk of non-utilisation and perceived marginality) of offered livers. In doing so, studies will be able to quantify and compare behaviour between transplant centres and even between clinicians' individual willingness to accept organs. Risk adjustment using the UKDUI will also help to quantify trends in liver utilisation over time. Future studies may find value in validating the

UKDUI in a different healthcare environment (e.g., USA or Eurotransplant).

Equation 1:

$$UKDUI_{DBD} = \frac{\exp(\eta_{DBD})}{1 + \exp(\eta_{DBD})} \quad (1)$$

$$\begin{aligned}\eta_{DBD} = &-4.3888 + (0.8005\, if\ HepB\ positive)\\ &+ (3.2254\, if\ HepC\ positive)\\ &+ (0.7601\, if\ past\ history\ of\ diabetes)\\ &+ (0.2157\, if\ post\ NLOS)\\ &+ (0.4792\, if\ past\ history\ of\ tumour) + 0.030043\, age\\ &+ 0.042627\, bilirubin + 0.005034\, alk\ phos\\ &+ (0.3155\, if\ moderate\ alcohol\ consumption)\\ &+ (1.1254\, if\ heavy/very\ heavy\ alcohol\ consuption)\\ &- (0.3342\, if\ stopped\ consuming\ alcohol)\\ &+ (0.2501\, if\ blood\ group\ A) + (0.2428\, if\ blood\ group\ B)\\ &+ (1.3751\, if\ blood\ group\ AB)\\ &+ (0.4115\, if\ cause\ of\ death\ CVA)\\ &- (0.0484\, if\ cause\ of\ death\ Anoxia)\\ &+ (0.7446\, if\ cause\ of\ death\ Other\ (excluding\ Trauma))\\ &+ BMIspline + ALTspline\end{aligned}$$

Post-NLOS: liver offered on or after 20 March 2018

Equation 2:

$$UKDUI_{DCD} = \frac{\exp(\eta_{DCD})}{1 + \exp(\eta_{DCD})} \quad (2)$$

$$\begin{aligned}\eta_{DCD} = &-5.4499 + (0.3026\, if\ past\ history\ of\ smoking)\\ &+ (3.2712\, if\ HepC\ positive)\\ &+ (0.4152\, if\ past\ history\ of\ diabetes) + (0.3163\, if\ male)\\ &+ (0.2354\, if\ post\ NLOS)\\ &+ (0.5582\, if\ past\ history\ of\ tumour)\\ &+ (0.4415\, if\ past\ history\ of\ hypertension)\\ &- (0.4145\, if\ past\ history\ of\ cardiac\ or\ respiratory\ arrest)\\ &+ 0.000652\, ALT + 0.016575\, sodium + 0.004917\, alk\ phos\\ &+ 0.002071\, creatinine\\ &+ (0.2510\, if\ moderate\ alcohol\ consumption)\\ &+ (1.0362\, if\ heavy/very\ heavy\ alcohol\ consuption)\\ &- (0.3321\, if\ stopped\ consuming\ alcohol)\\ &+ (0.2293\, if\ blood\ group\ A) + (0.2847\, if\ blood\ group\ B)\\ &+ (1.5143\, if\ blood\ group\ AB)\\ &+ (0.1481\, if\ cause\ of\ death\ CVA)\\ &+ (0.7689\, if\ cause\ of\ death\ Anoxia)\\ &+ (0.9891\, if\ cause\ of\ death\ Other\ (excluding\ Trauma))\\ &+ BMIspline + agespline + ITUspline\end{aligned}$$

Post-NLOS: liver offered on or after 20 March 2018

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The analyses described in this article were carried out at NHSBT, who maintain the UK Transplant registry on behalf of transplant centers in the United Kingdom. NHSBT are reliant on the General Data Protection Regulation Article 6(1)(e) - Performance of a public task. This lawful basis requires specific exemptions under Article 9(2)(h) and also (i) and (j). This allows NHSBT to use patient identifiable information for service evaluation without the consent of patients. In order to maintain data minimisation under GDPR, data may only be released on request. Requests to access these datasets should be directed to Jennifer.Mehew@nhsbt.nhs.uk.

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

JM conducted the statistical analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author SK has previously received consultancy fees from OrganOx limited to support the design of clinical studies. Author PF is a co-founder and part-time CMO of OrganOx Ltd, a spinout company from the University of Oxford which was established to develop machine perfusion of the liver. The company had no part in the research described in this paper. The work was performed as part of the study design of the PLUS liver clinical trial (https://doi.org/10.1186/ISRCTN11552402). The PLUS trial was funded by the NIHR.

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.2026.16484/full#supplementary-material

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Simultaneous kidney–islet transplantation from a donor after circulatory death using normothermic regional perfusion

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Dear Editors,

Patients with insulin-dependent diabetes and advanced chronic kidney disease frequently require β-cell replacement therapy, either at the time of kidney transplantation or as a staged procedure thereafter. Two established strategies for β-cell replacement include whole-organ pancreas transplantation and pancreatic islet transplantation. Both approaches can be performed either simultaneously with kidney transplantation or sequentially. Simultaneous pancreas–kidney transplantation (SPK) remains the gold standard for individuals with type 1 diabetes and end-stage kidney disease. However, a substantial proportion of candidates are unsuitable due to prohibitive perioperative risks. In such cases, simultaneous islet–kidney transplantation (SIK) may be considered. The procedural risk associated with intraportal infusion of isolated pancreatic islets is lower compared to whole pancreas transplantation. While SPK achieves higher rates of insulin independence, SIK has demonstrated quite comparable benefits in terms of glycemic stability, prevention of severe hypoglycemia, patient survival, cardiovascular outcomes, and kidney allograft survival—alongside a markedly reduced burden of surgical and metabolic complications [1–3]. However, donors' and recipients' characteristics can impact the results of islet transplantation.

SPK and SIK were initially performed using organs and islets from donors after brain death (DBD). More recently, kidney, pancreas, islet-alone, and islet-after-kidney transplantations from controlled donors after circulatory death (DCD; Maastricht category III donors) have also been utilized [4, 5].

Herein, we report the first SIK performed in France using a kidney and islets from a controlled DCD in whom, according to the national French protocol, normothermic regional perfusion (NRP) was implemented to restore *in situ* circulation of abdominal organs [6].

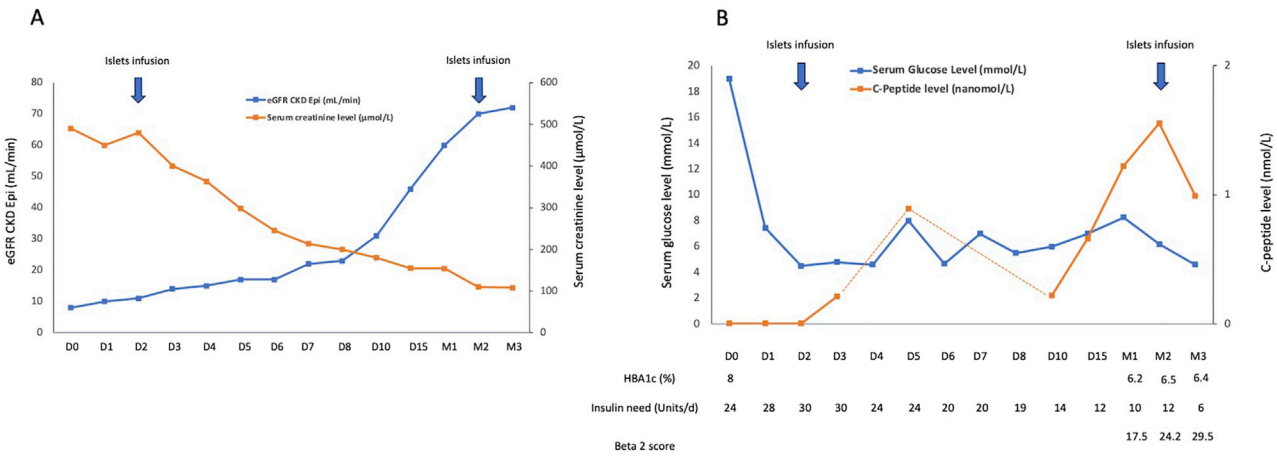

FIGURE 1
Outcome of kidney function **(A)** and glycemic parameters **(B)** after simultaneous islet kidney transplantation.

A 45-year-old non-Human leukocyte antigen sensitized man (weight 53 kg) with a history of complicated, longstanding type 1 diabetes (onset at age 20) and on hemodialysis for 10 years was considered for SIK transplantation due to suboptimal continuous glucose monitoring metrics [HbA1c 8%; time in range (70–180 mg/dL) 36%; time <70 mg/dL 20%, including 5% < 54 mg/dL with hypoglycemia unawareness; and high glycemic variability (coefficient of variation 40%; target <36%)]. Due to extensive comorbidities, primarily ischemic cardiomyopathy and peripheral arterial disease, whole pancreas transplantation was contraindicated.

The donor was a 60-year-old man (BMI 27.5 kg/m^2, weight 66 kg) in whom life-sustaining therapy was withdrawn following a large ischemic stroke without neurological recovery after 4 days in the ICU. During procurement, the functional warm ischemia time was 28 min (2 min from mean blood pressure < 50 mmHg to circulatory arrest, followed by 26 min of asystole, including the required 5-min no-touch interval). Cannulation and radiologic verification required 21 min. Peak transaminases during NRP were twice the upper limit of normal (ULN), and lipase decreased from 3× to 2.5× ULN during NRP, which lasted 3.5 h.

Immediately after procurement, the kidney was preserved on a hypothermic perfusion machine (Organ Recovery system) without oxygenation. The cold ischemia time was 21.8 h, and the warm ischemia time (Time between withdrawal from machine perfusion and renal reperfusion) was 66 min. Kidney transplantation was performed by both urologists and vascular surgeons, as an iliofemoral bypass was required prior to graft implantation. The postoperative course was uneventful, with immediate recovery of urine output and graft function. Serum creatinine decreased from 490 µmol/L pre-transplantation to 108 µmol/L at month 3 (Figure 1A).

Abbreviations: BMI, Body mass index; DBD, donors after brain death; DCD, donors after circulatory death; IEQ, islet equivalents; NRP, normothermic regional perfusion; SIK, Simultaneous islet–kidney transplantation; SPK, Simultaneous pancreas–kidney transplantation; ULN, Upper Limit of the Normal.

The patient received induction therapy with anti-thymocyte globulins (Thymoglobulin®, 1.25 mg/kg/day for 4 days), followed by maintenance immunosuppression including tacrolimus (target trough level 8–12 ng/mL), mycophenolic acid (1 g twice daily), and corticosteroids (500 mg on day 0, 250 mg on day 1, then 20 mg/day until day 7, when discontinued).

The pancreas was sent to the Cell Therapy Unit at Montpellier University Hospital for islet isolation, which was completed in 5 h. The pancreas cold ischemia time was 5.5 h. Enzymatic digestion and continuous density gradient separation yielded 103,800 islet equivalents (IEQ; 1958 IEQ/kg), with 89% viability and 48% purity, meeting criteria for clinical transplantation of islets alone, simultaneously and after kidney. Islets were cultured for 24 h. Two days after organ procurement and kidney transplantation, the islets were prepared, packaged, and transported from Montpellier University Hospital to Toulouse University Hospital, where intraportal infusion was performed radiologically via percutaneous portal vein catheterization. Continuous intravenous insulin was administered to maintain strict euglycemia (target 0.8–1.2 g/L) during early engraftment. Anticoagulation included 70 IU/kg unfractionated heparin during infusion, followed by systemic heparin for 48 h (activated partial thromboplastin time 1.5–2× control), then prophylactic anticoagulation until day 7.

Endogenous insulin secretion became detectable within 24 h, with C-peptide levels increasing from 0 to 0.64 ng/mL on day 1 and reaching 4.7 ng/mL at month 2, consistent with effective engraftment (Figure 1B). Over the subsequent 2 months, mean glucose was 9.35 mmol/L; time in range (70–180 mg/dL) improved to 56%, time in hypoglycemia (<70 mg/dL) decreased to 3%, time <54 mg/dL to 0%, and no severe hypoglycemia occurred. At month 2, he received a second islets infusion (244,099 IEQ) obtained from DBD. Daily insulin requirements and glycated hemoglobin decreased over time (Figure 1B).

Islet isolation from DBD pancreases generally yields higher β-cell quantities and, consequently, higher transplantation eligibility rates compared to controlled DCD, likely due to the initial period of warm ischemia [7]. However, in most studies, controlled DCD donors did not benefit from NRP, which is mandatory in France and not routinely

implemented in many countries. Nevertheless, it was previously shown that abdominal NRP after controlled DCD improves pancreatic islet isolation yield {Doppenberg, 2025 #2883}. In the present, although the IEQ infused the first time was relatively low, it allowed to improve the glycemic control and the later was again improved by the second infusion. Both *in vitro* and clinical studies have demonstrated that when a sufficient number of islets is infused, viability and function are comparable between controlled DCD and DBD sources, resulting in similar insulin secretion and glycemic control [7].

In summary, this case report confirms that SIK using organs from DCD donors is feasible and effective, potentially expanding access to β-cell replacement therapy for patients with insulin-dependent diabetes and advanced chronic kidney disease. The use of NRP may improve β-cell yield from donor pancreases following circulatory death.

Data availability statement

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

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. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article because Not requested according to the French law.

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Imputed HLA typing as a practical approach to molecular mismatch risk stratification in kidney transplantation

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Dear Editors,

Human leukocyte antigen (HLA) compatibility between donor and recipient is a key determinant for successful transplant outcomes [1]. Compared to conventional whole-antigen mismatch, molecular mismatch (mMM) more accurately predicts the risk of donor-specific antibody (DSA) development and allograft rejection in kidney transplant recipients [2]. Specifically, HLA-DR/DQ single-molecule eplet mismatch has been validated across multiple cohorts as a prognostic biomarker for primary alloimmunity [3]. However, eplet analysis requires high-resolution genotyping, which is often unavailable in historical cohorts and under-resourced settings. Although imputed haplotypes have shown inaccuracies, particularly in non-Caucasian populations and class II alleles [4, 5], imputation may preserve clinically meaningful mMM risk classification [6].

We investigated the impact of imputation on mMM risk assessment in an ethnically diverse cohort of Southeast Asian kidney transplant recipients to demonstrate proof of concept for a cost-effective alternative to high-resolution HLA typing, potentially applicable in resource-limited settings.

This single-center cohort comprised 32 living- and 19 deceased-donor adult kidney transplant pairs transplanted between September 2023 and November 2024, yielding 97 unique HLA samples, as five of the deceased donors each donated to two recipients. The cohort comprised predominantly Chinese (54%), followed by Malay (20%) and Indian (17%). Approval was obtained from the NHG Domain Specific Review Board (2024/00118), and the study complied with the Declaration of Helsinki.

Recipients and donors underwent high-resolution HLA genotyping by next-generation Sequencing (NGS; AllType, OneLambda, Canoga Park, CA). We transformed the NGS data, retaining the first field and removing all subsequent fields. Serological splits were considered for HLA-B*14, -B*15, -B*40, -B*55, -B*56, -C*03, -DRB1*03, and -DQB1*03. No individual had an HLA-DRB1*01:03 allele. This dataset was then imputed using HaploStats, which derives the most probable alleles based on haplotype frequencies in reference populations in the National Marrow

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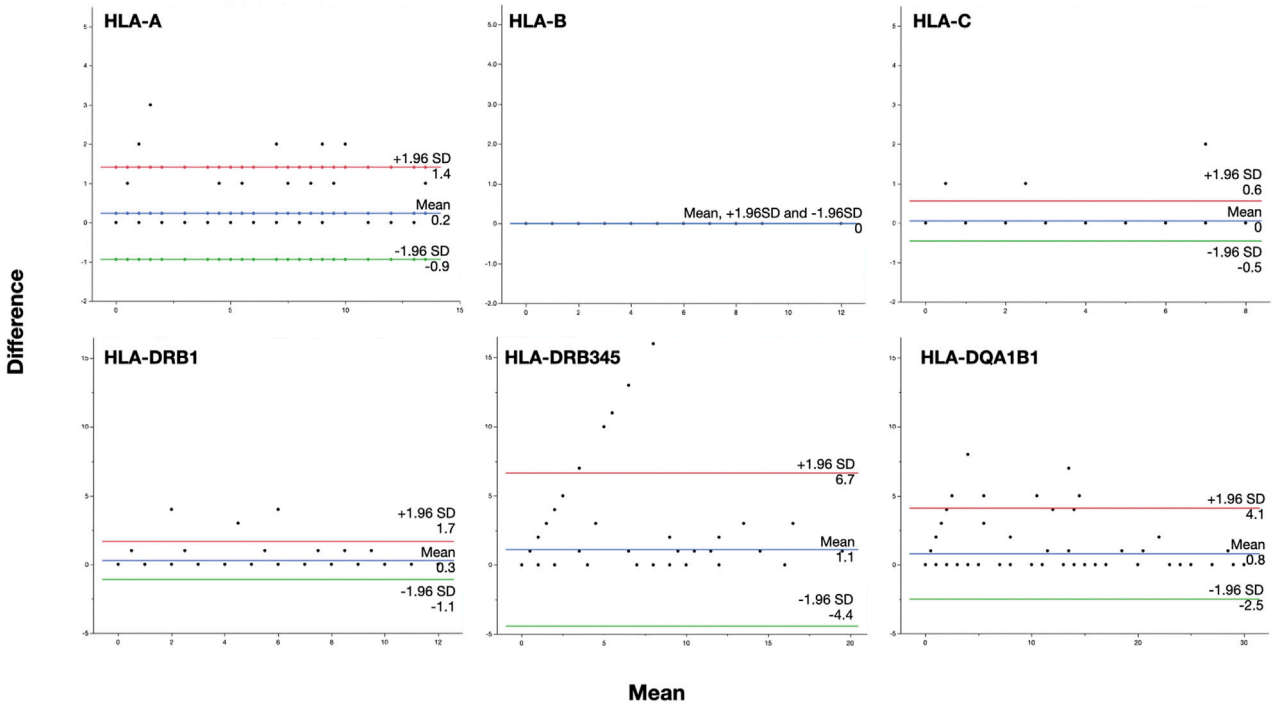

FIGURE 1
Bland-Altman plots of single-molecule eplet mismatches at each HLA locus. Bland-Altman plots showing agreement between donor-recipient single-molecule eplet mismatches calculated by NGS typing and imputation at each HLA locus. Each point represents the difference between methods plotted against their mean. The blue lines indicate the mean bias, and the red and green lines indicate the 95% limits of agreement (mean difference ±1.96SD). For the HLA-B locus, the mean bias and 95% limits of agreement are all zero. HLA, human leukocyte antigen; NGS, next-generation sequencing; SD, standard deviation.

Donor Program (NMDP) 2014 full dataset, to generate two-field genotypes for HLA-A, -B, -C, DRB1, -DRB345, and -DQB1 loci, selecting reference panels best aligned with each individual's self-identified race. Alleles from the top-ranked phased genotype were selected across all HLA loci. The most probable HLA-DQA1 alleles were assigned using published haplotype frequency standards describing HLA-DRB1-DQB1-DQA1 associations [7, 8]. Null alleles associated with common haplotypes were considered, including the DRB1*07:01-DRB4*01:03N-DQB1*03:03 and DRB1*15:02-DRB5*01:08N-DRB5*01:02 haplotypes. HLA-DP was excluded from Haplostats because HLA-DP typing has historically been limited and inconsistent. HLA-DP also has higher recombination rates and weak linkage disequilibrium with HLA-DR and HLA-DQ, making phasing of HLA-DP from HLA-A-B-C-DR-DQ haplotypes unreliable.

Single-molecule eplet mismatch was evaluated at each locus using HLAMatchmaker (ABC version 4.0 and DRDQDP version 2.2), except HLA-DP. Recipients were categorized into three alloimmune risk groups according to thresholds previously published by Wiebe et al. [2]: Low-risk (maximum HLA-DR eplet mismatch <7 and HLA-DQ <9), Intermediate-risk (any HLA-DR and maximum HLA-DQ 9-14), and High-risk (any HLA-DR and maximum HLA-DQ ≥15). We quantified the concordance of alleles and mMM risk categories using weighted kappa coefficients, and the agreement of single-molecule eplet mismatches using Bland–Altman plots.

Allele-level concordance between NGS and imputed alleles was 80% (95% CI 74%–85%, Cohen's κ = 0.77, 95% CI 0.71–0.84) for HLA-A, 89% (95% CI 83%–92%, κ = 0.88, 95% CI 0.82–0.93) for HLA-B, 92% (95% CI 87%–95%, κ = 0.91, 95% CI 0.87–0.95) for HLA-C, 83% (95% CI 77%–88%, κ = 0.82, 95% CI 0.76–0.87) for HLA-DRB1, 60% (95% CI 54%–67%, κ = 0.54, 95% CI 0.47–0.61) for HLA-DRB345, 86% (95% CI 80%–90%, κ = 0.84, 95% CI 0.78–0.89) for HLA-DQB1, and 88% (95% CI 83%–92%, κ = 0.87, 95% CI 0.82–0.92) for HLA-DQA1. Overall concordance was 87% (95% CI 84%–89%, κ = 0.87, 95% CI 0.84–0.89) and 79% (95% CI 76%–82%, κ = 0.79, 95% CI 0.76–0.82) for Class I and Class II alleles, respectively. The most frequently mis-imputed alleles were DRB4*01:03 (40/40, 100%) and DQB1*02:02 (12/12, 100%). Re-imputing DRB4*01:01 as DRB4*01:03 improved HLA-DRB345 concordance to 80%.

Despite allele-level inaccuracies, pairwise comparisons showed strong agreement between NGS- and imputation-derived single-molecule eplet mismatch counts at most loci (R^2 > 0.95) except HLA-DRB345 (R^2 = 0.67, Figure 1). HLA-DR/DQ mMM risk classification was generally consistent between NGS and imputed genotyping. By NGS, 12 (24%) donor-recipient pairs were classified as low risk, 25 (49%) as intermediate risk, and 14 (27%) as high risk.

Abbreviations: DSA, donor-specific antibodies; HLA, human leukocyte antigen; mMM, molecular mismatch; NMDP, National Marrow Donor Program.

All recipients classified as low- or high-risk by NGS were similarly classified by imputation. Reclassification occurred only among five intermediate-risk pairs, with three reclassified as low-risk (i.e., an underestimation of risk) and two as high-risk (an overestimation of risk). Alloimmune risk categories were preserved in 90% of recipients (κ = 0.85, 95% CI 0.73–0.97) when all DRB4*01:01 alleles were imputed as DRB4*01:03. There was no significant difference in the misclassification rate between deceased-donor (n = 3/19, 16%), living-related (n = 1/24, 4%), and living-unrelated (n = 1/8, 13%) subgroups (p = 0.36).

Our findings are consistent with previous studies evaluating the impact of imputation on eplet mismatches. Cohen et al. reported a strong correlation for both class I and class II single-molecule eplet mismatches across races [6]. Senev et al. reported no difference in eplet mismatch load for 91.3% of imputed class I alleles, with 95.8% differing by at most 1 eplet. Although only 53.9% of imputed class II alleles had the same eplet mismatch load, 83.7% were within one eplet difference [5]. More importantly, the impact of imputation on alloimmune risk categorization was modest: 90% of recipients remained in the same category, and none were reclassified from low to high risk or *vice versa*. Although this cohort is underpowered to estimate the rate of clinically meaningful misclassification, these findings are consistent with those of Cohen et al., who reported that only 1/35 recipients changed from low- to intermediate risk, indicating that imputation preserved accurate mMM risk categorization.

In previous studies of imputation accuracy, cohorts were representative of European or North American populations. Few studies have been conducted in Southeast Asian cohorts that applied imputation to genotyped data using reference databases to derive Southeast Asian-centric reference panels [9, 10]. These reference-data limitations may account for the lower concordance for the imputation of Class II alleles. Our study, therefore, contributes to the existing literature by evaluating the performance of imputation tools in a multi-ethnic Southeast Asian cohort and by applying them to molecular mismatch.

Although next-generation sequencing remains the gold standard, our study provides exploratory data and proof of concept that imputation may be a reasonable and practical alternative for mMM risk classification in Southeast Asian populations, especially in historical cohorts and resource-limited settings where high-resolution data is unavailable or prohibitively costly. The use of transformed NGS-derived data, rather than genuinely low-resolution HLA typing, may limit the generalizability of the findings to routine clinical practice. Other limitations include the modest sample size, the absence of HLA-DP, given its emerging role in alloimmunity, and the lack of correlation with DSA and post-transplant outcomes. Future research should focus on developing region- and race-specific haplotype reference datasets to improve accuracy in multicultural populations. Nevertheless, imputation may represent a scalable approach to expanding access to mMM risk stratification.

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 NHG Domain Specific Review Board (2024/00118). 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

AH – Formal analysis, Writing – original draft, Writing – review and editing. AV – Supervision, Writing – review and editing. HS – Writing – review and editing. MD'C – Writing – review and editing. ZC – Writing – review and editing. AN – Writing – review and editing. W–KK – Writing – review and editing. AL – review and editing. EW – Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review and editing. All authors contributed to the article and approved the submitted version.

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Bidirectional portal vein reconstruction for type C anatomy in living donor liver transplant

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Dear Editors

Portal vein (PV) reconstruction remains a critical technical challenge in living donor liver transplantation (LDLT), particularly in the presence of complex anatomical variants such as Type C portal vein anatomy, characterized by multiple portal branches without a dominant trunk [1–3]. These configurations are associated with size mismatch, spatial separation, and unfavourable inflow geometry, increasing the risk of thrombosis and anastomotic stenosis.

Autologous Y-graft interposition has traditionally been used to reconstruct multiple PV branches and has demonstrated acceptable outcomes [4, 5]. However, this approach introduces additional anastomoses and may result in geometric distortion, turbulence, and functional narrowing, particularly in complex anatomical settings and Conjoined unification venoplasty (CUV) was subsequently developed to create a single wide conduit by unifying multiple graft PV branches, thereby improving inflow alignment and reducing anastomotic complexity [6–8]. Despite these advantages, graft-side reconstruction alone may not adequately address recipient PV limitations, especially in cases with a narrow or unfavorable recipient PV.

We report our experience with a bidirectional dual-patch PV reconstruction technique (Figure 1) that simultaneously optimizes graft and recipient PV geometry in LDLT with Type C anatomy. This approach combines graft conjoined unification venoplasty using a rectangular autologous PV patch with recipient PV augmentation using a triangular patch, enabling a wide, tension-free, and size-matched anastomosis without the need for interposition grafts.

Between January 2016 and January 2026, 1,385 LDLTs were performed at our center. Type C PV anatomy was identified in 32 donors (2.31%), of whom 25 required PV reconstruction. 16 patients underwent portal vein reconstruction using autologous Y-graft interposition,5 consecutive patients underwent bidirectional dual-patch reconstruction and constitute this series, Direct venoplasty was feasible in 4 cases due to proximity of portal vein branches & rest of the 7 cases where left lateral graft were taken where no reconstruction were needed. Patients with pre-existing PV thrombosis were excluded.

Our technique for bidirectional dual-patch PV reconstruction (Figure 1) is following recipient hepatectomy, an autologous PV segment was harvested from the explanted liver. On the back table, a rectangular patch was used to unify adjacent graft PV branches into a single enlarged orifice. The recipient PV was then augmented with a longitudinal incision and triangular patch venoplasty to increase luminal diameter and accommodate the reconstructed graft PV. End-to-end anastomosis was performed with continuous sutures, ensuring proper

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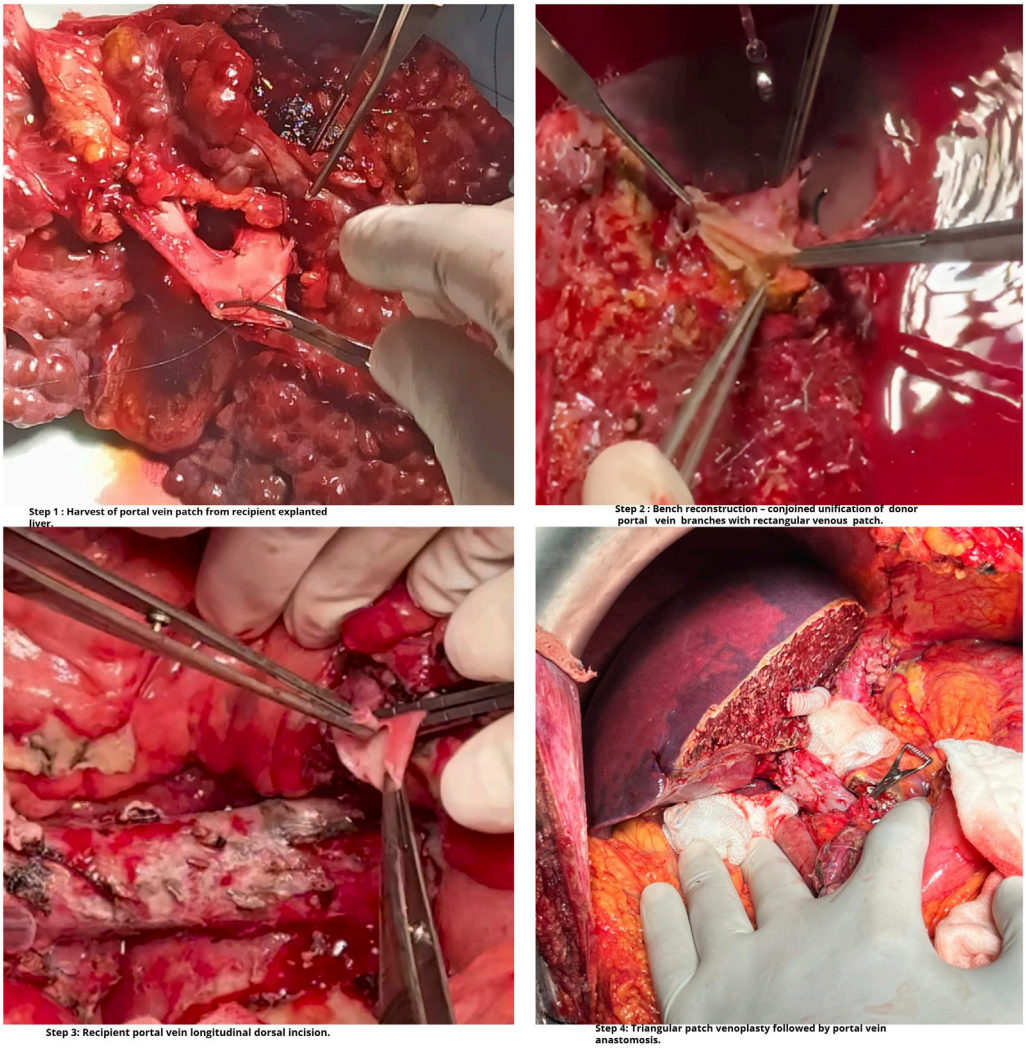

FIGURE 1
Surgical steps of bidirectional dual-patch PV reconstruction.

alignment and absence of tension. Intraoperative Doppler ultrasonography confirmed adequate portal inflow.

PV reconstruction was successfully completed in all patients without interposition grafts. No early PV thrombosis or clinically significant stenosis occurred. All recipients demonstrated satisfactory graft function, and PV patency was maintained during 6 months follow-up, with physiologic Doppler flow (mean velocity approximately 35 cm/s).

In contrast, in our limited experience of portal vein reconstruction using autologous Y-graft interposition in 16 cases, size mismatch, conduit buckling, and angulation-related inflow compromise emerged as the principal technical challenges. These complications necessitated surgical re-anastomosis in 3 cases (18.75%) and endovascular stenting in 1 case (6.25%). While Y-graft interposition remains an effective reconstructive strategy, it is technically demanding during bench preparation and portal vein reconstruction. Particularly in patients with chronic portal vein thrombosis, distorted portal venous morphology, and small-caliber main portal veins where Y-graft interposition may be technically challenging. This inherent fixed anatomical configuration may predispose to angulation-related inflow disturbances, potentially resulting in flow impairment and postoperative thrombosis, thereby requiring re-intervention in a subset of patients. These findings are comparable with previously reported series [6]. Although conjoined unification venoplasty (CUV) improves graft-side configuration, the resulting conduit may exceed the adaptive capacity of the recipient PV and wider common channel. These observations emphasize that successful PV reconstruction depends not only on graft-side unification but also on appropriate recipient PV accommodation. Asan medical center came up with conjoined unification venoplasty (CUV) method in 2014 which is a technical modification of conventional autologous Portal vein Y graft interposition introduced in 2001 [6–8]. To overcome these issues we came up with bidirectional dual-patch PV reconstruction.

However, the bidirectional dual-patch technique addresses both components of this problem by combining graft unification with controlled recipient PV enlargement we achieved adequate diameter of main PV, this strategy facilitates a harmonized inflow pathway with improved geometric alignment. This is particularly relevant in

LDLT, where partial grafts are exposed to increased portal inflow and are sensitive to disturbances in flow dynamics. Maintenance of a laminar, low-resistance inflow is essential to preserve endothelial integrity and support graft function [6–8].

In this small series, the absence of PV-related complications and sustained patency suggest that this technique is safe and reproducible. Although the number of patients is limited and follow-up duration is relatively short, the consistent hemodynamic performance supports further evaluation of this approach in larger cohorts. We are currently extending this experience through a comparative study evaluating the bidirectional dual-patch technique against Y-graft interposition to further define its relative advantages.

In conclusion, bidirectional dual-patch PV reconstruction represents a practical and physiologically sound option for managing Type C PV anatomy in LDLT. By restoring ideal graft–recipient portal venous geometry while eliminating the need for interposition grafts, this technique minimizes anastomotic complexity and has the potential to reduce flow-related complications. It should be considered a strong alternative to Y-graft interposition, and warrants further validation in larger, comparative studies with long-term follow-up.

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 Ethics Review Committee, Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences (PAQSJIMS), Gambat, Sindh, Pakistan. 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 Written informed consent was waived by the Institutional Review Board due to the retrospective nature of the study and the use of anonymized patient data.

Author contributions

SD conceived the study, performed surgeries, collected data, and drafted the manuscript. BA contributed to study design, data interpretation, and manuscript revision. AWD, MA, MU, and SHA contributed to data collection, literature review, manuscript preparation, and critical revision. All authors reviewed and approved the final 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.2026.16600/full#supplementary-material

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Both perfusion pressure and flow are critical in abdominal normothermic regional perfusion!

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KEYWORDS
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Dear Editors,

Abdominal normothermic regional perfusion (A-NRP) has emerged as a major advance in controlled donation after circulatory death (cDCD), improving organ utilization and post-transplant outcomes, especially in liver transplantation. Clinical series have shown lower rates of ischemic cholangiopathy and better graft outcomes when A-NRP is used instead of rapid recovery alone [1, 2]. Yet the hemodynamic monitoring of the reperfused abdominal compartment remains conceptually underdeveloped. In many settings, the adequacy of abdominal reperfusion is inferred mainly from extracorporeal pump flow and venous oxygen saturation sampled from the drainage line. We believe this is physiologically insufficient, because tissue perfusion depends on arterial pressure as much as on blood flow. In this regard, continuous arterial pressure monitoring of the reperfused compartment should be regarded as a critical requirement, because pressure, and not flow alone, makes organ perfusion effective [3, 4].

The rationale is grounded in fundamental hemodynamics. Organ blood flow is governed by the pressure gradient across the vascular bed and its resistance. Extracorporeal flow displayed by the pump is therefore only a circuit variable; it does not directly indicate whether an adequate driving pressure is being transmitted to the abdominal microcirculation. This issue is particularly relevant after death, when circulation is non-pulsatile and entirely pump-driven. Under these conditions, apparently acceptable circuit flow may coexist with inadequate arterial pressure if systemic vascular resistance is low. In such a situation, blood may circulate through the circuit while the pressure head required to perfuse ischemic tissues remains insufficient. In physiological terms, this corresponds to flow that is measurable, yet hemodynamically ineffective [4]. One may therefore wrongly assume that high blood flow necessarily implies adequate arterial pressure and tissue perfusion. Conversely, even apparently sufficient pressure may coexist with inadequate tissue oxygen delivery if cardiac output, or, here, circuit flow, is too low.

The kidney illustrates why this distinction matters. Renal perfusion becomes pressure-dependent below the autoregulatory range, and autoregulation itself is altered in shock states and cannot be assumed to be preserved after circulatory arrest and warm ischemia [4]. Thus, during A-NRP, low arterial pressure may translate directly into inadequate renal cortical perfusion despite apparently satisfactory extracorporeal flow. The same concern likely

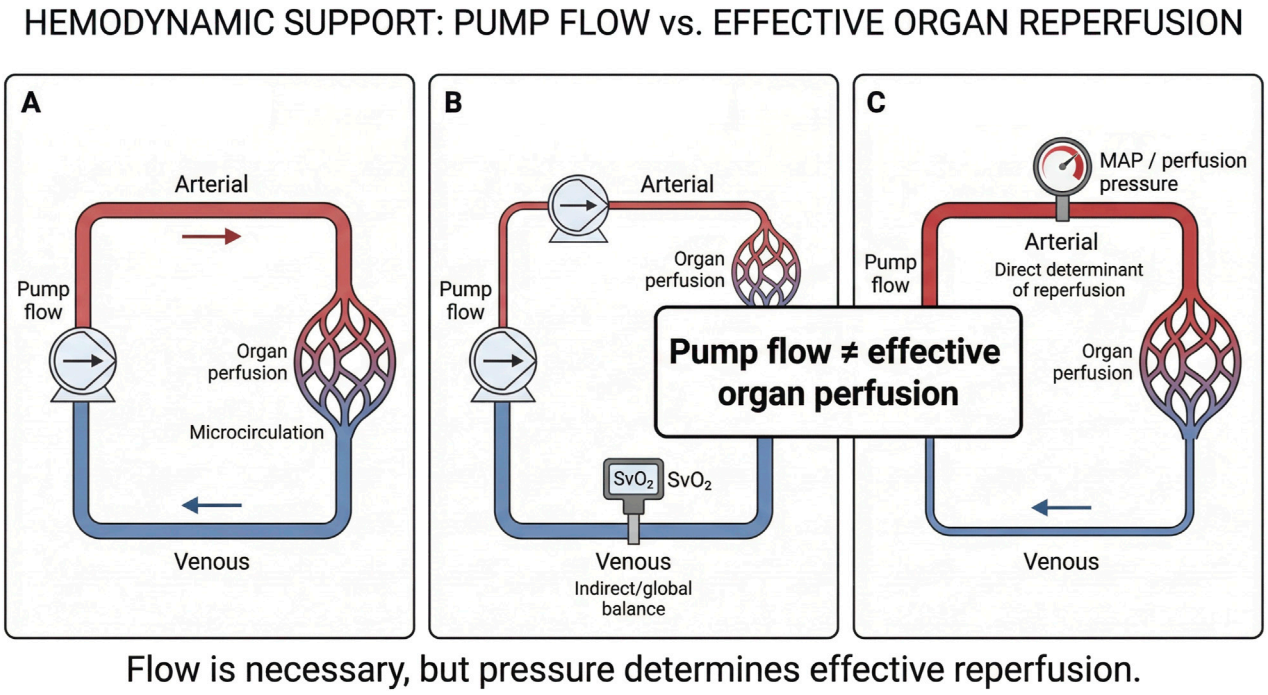

FIGURE 1
Conceptual framework for hemodynamic monitoring during abdominal normothermic regional perfusion (A-NRP). **(A)** Circuit overview. **(B)** Indirect monitoring. **(C)** Direct physiological target.

extends to the liver and splanchnic organs, whose recovery after warm ischemia depends on effective tissue oxygen delivery rather than simply on the presence of circulating blood in the aorta. Preserved macroflow is not synonymous with restored organ perfusion [4].

For the same reason, reliance on venous-line SvO_2 is problematic. SvO_2 is a global, flow-weighted average of oxygen extraction in the venous effluent reaching the sampling site. It is not an organ-specific perfusion marker. Low SvO_2 is certainly concerning, but normal or elevated mixed SvO_2 does not exclude regional hypoperfusion, heterogeneous flow distribution, impaired oxygen extraction, or microcirculatory shunting. Venous oxygen saturation can remain normal despite persistent tissue hypoxia, a phenomenon described as "covert tissue hypoxia" [5]. This is particularly relevant when perfusion is unevenly distributed, because well-perfused territories may dominate the venous signal and mask ischemia in more vulnerable organs.

As illustrated in Figure 1, extracorporeal pump flow does not necessarily translate into effective organ perfusion. While pump flow reflects circuit blood flow and venous-line SvO_2 reflects a global mixed venous signal, arterial pressure measured within the reperfused abdominal compartment more directly reflects the driving pressure for abdominal organ perfusion.

Evidence from extracorporeal circulation supports this concern. During cardiopulmonary bypass, mixed venous oxygen saturation has been shown to correlate poorly with regional venous saturations. McDaniel and colleagues demonstrated that normal mixed venous saturation did not exclude marked regional venous desaturation during bypass [6]. Dahn et al. showed that global venous oxygenation may coexist with depressed splanchnic venous oxygen saturation, indicating that visceral hypoxia may be missed when only systemic venous oxygenation is monitored [7]. Although these studies were not performed in A-NRP donors, their physiological message is directly transferable: global venous oxygenation is an indirect and potentially misleading surrogate for abdominal organ reperfusion.

Pump flow suffers from a similar limitation. It quantifies what the circuit delivers, not what the organ bed receives. If arterial pressure is low because resistance is low, a seemingly adequate flow can still fail to generate sufficient transorgan perfusion pressure. This is why coherence between macrocirculation and microcirculation cannot be assumed. In critically ill states, correction of global hemodynamic variables does not reliably restore microvascular perfusion, and the same principle likely applies to organs undergoing reperfusion after warm ischemia [8]. This blind spot may be even more pronounced in uncontrolled DCD, where longer no-flow and low-flow periods, more severe metabolic derangement, and greater vascular dysfunction are expected at the time NRP is initiated. Uncontrolled DCD donors undergoing NRP have been shown to display more severe metabolic derangement than controlled DCD donors, often requiring more aggressive corrective treatment during reperfusion [9]. A-NRP is intended to recondition organs, not merely to re-establish circuit circulation. Even at constant pump flow, a fall in vascular resistance in one abdominal territory may redistribute flow toward that organ at the expense of others. In this setting, total circuit flow alone cannot guarantee adequate and balanced reperfusion, because changes in regional resistance directly affect flow distribution and tissue perfusion.

Continuous arterial pressure monitoring of the reperfused abdominal compartment addresses this blind spot. It provides direct information on the driving force available to perfuse the

kidneys, liver, and gut and allows real-time adjustment of ECMO flow and vasopressors. In practical terms, this pressure should ideally be measured directly within the reperfused abdominal arterial compartment, for example, through a side port connected to the arterial return line or through an arterial catheter placed in the infradiaphragmatic arterial circulation. This approach is also consistent with broader NRP standardization efforts, which emphasize hemodynamic control and procedural reproducibility during A-NRP [3]. Published A-NRP protocols support maintaining a mean arterial pressure in the range of 60–65 mmHg to ensure effective abdominal organ perfusion [3, 10]. The principle nevertheless remains straightforward: if arterial pressure is not monitored within the reperfused compartment, one cannot be confident that all abdominal organs are being effectively and adequately reperfused. This does not diminish the importance of adequate extracorporeal flow; rather, it emphasizes that flow must be interpreted together with pressure.

We are not claiming that compartmental arterial pressure monitoring has already been proven, in isolation, to improve graft or recipient outcomes. Rather, we argue that it is physiologically indispensable if the objective of A-NRP is true organ reperfusion rather than simple extracorporeal circulation. Flow is necessary, but pressure is what makes flow biologically relevant and appropriately distributed. In A-NRP, direct monitoring of arterial pressure within the reperfused compartment should therefore be considered a logical next step toward more rational, physiology-guided donor management.

Data availability statement

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

Author contributions

RG and KB conceived the correspondence and drafted the manuscript. BA, FI, and YG critically revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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