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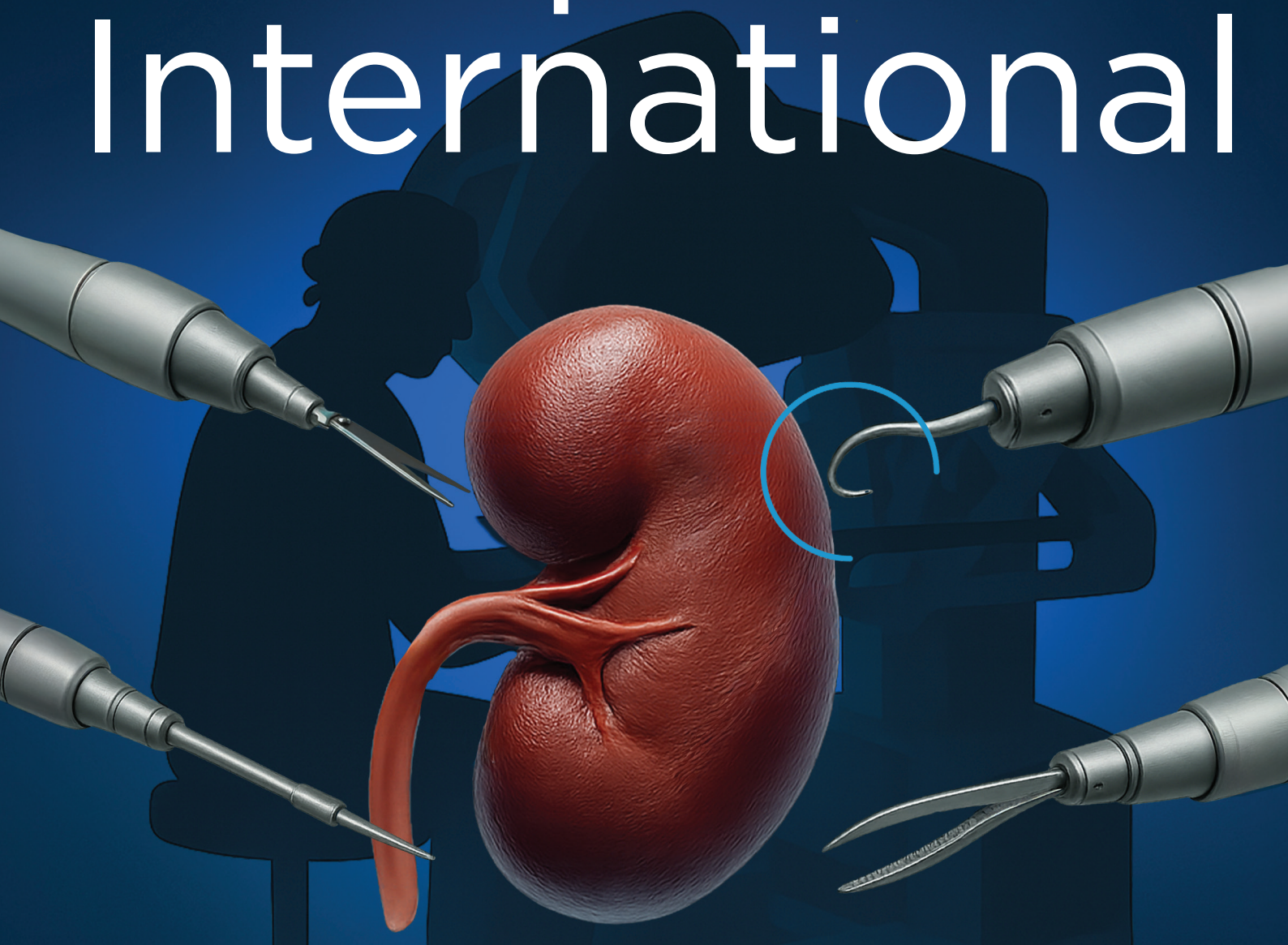

Robotic kidney transplantation

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NEWS AND VIEWS
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The 2025 Nobel Prize in Physiology or Medicine Honors the Immune Peacekeepers

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In an era marked by global conflict, polarization, and societal fragmentation, the Nobel Committee has chosen to honor three scientists (**Figure 1**) for their discovery of key cellular players involved in *Immune Tolerance* and homeostatic regulation. In their 1960 Nobel Lecture, Medawar and Burnet defined immune tolerance as "*a state of indifference or non-reactivity towards a substance that would normally be expected to excite an immunological response*", a definition that remains largely unchanged today (Glossary).

The laureates' seminal work led to the discovery and characterization of regulatory $CD4^+$ $FOXP3^+$ T cells (Tregs), now widely recognized as central orchestrators of peripheral immune tolerance, alongside other innate and adaptive immune cells. This breakthrough has laid the foundation for innovative therapeutic strategies across a broad range of clinical applications.

THE FIRST "GIANT" STEPS FORWARD

Shimon Sakaguchi was the first to provide decisive and widely accepted insights into these cells in 1995, turning the page on the previously ill-defined and controversial "suppressive T cells" of the 1980s. His seminal publication identified the constitutive expression of the high-affinity interleukin-2 receptor as a major phenotypic marker of regulatory T cells Tregs [1]. He also demonstrated their capacity to prevent autoimmunity in a mouse model [1].

In 2001, Mary Brunkow and Fred Ramsdell established a critical link between the human IPEX syndrome (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) and the murine Scurfy phenotype, both marked by severe autoimmune manifestations. They identified a shared genetic origin: mutations in the *FOXP3* gene located on the X chromosome [2, 3]. The emergence of FOXP3 as a master regulator of immune tolerance immediately raised compelling questions about its role in Tregs.

In 2003, Shimon Sakaguchi, Fred Ramsdell, and Alexander Rudensky independently, and almost simultaneously, published landmark studies demonstrating the essential role of FOXP3 in defining the identity and function of regulatory T cells [4–6].

This discovery marked the beginning of a remarkable surge of interest in these cells (**Figure 2**), a trend further accelerated by the development of novel molecular tools and the emergence of murine models enabling selective gene expression or deletion in Tregs. Tregs originate from two distinct developmental pathways, depending on the ontogenetic timing of their commitment to the regulatory lineage: either thymic-derived (tTregs) or peripherally induced (pTregs) [7–9]. The former possess a highly self-reactive T cell receptor repertoire and primarily function to maintain self-tolerance and prevent autoimmunity. In contrast, pTregs differentiate in response to exogenous

News & Views

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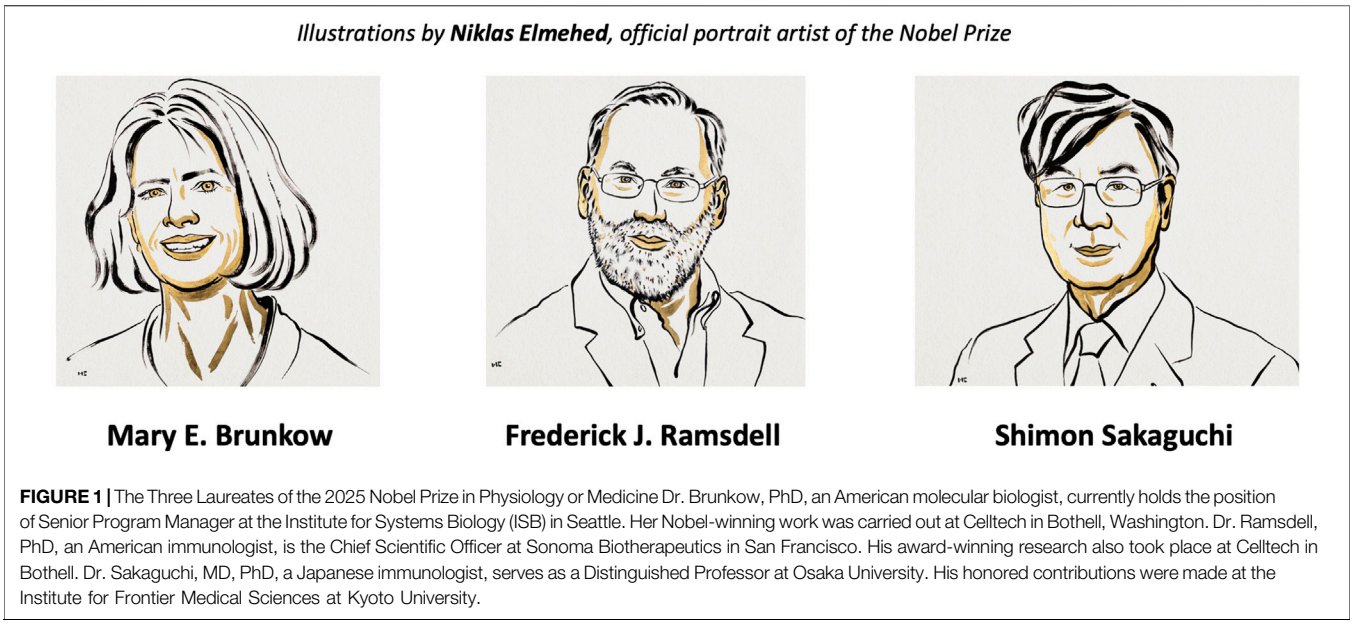

FIGURE 1 | The Three Laureates of the 2025 Nobel Prize in Physiology or Medicine Dr. Brunkow, PhD, an American molecular biologist, currently holds the position of Senior Program Manager at the Institute for Systems Biology (ISB) in Seattle. Her Nobel-winning work was carried out at Celltech in Bothell, Washington. Dr. Ramsdell, PhD, an American immunologist, is the Chief Scientific Officer at Sonoma Biotherapeutics in San Francisco. His award-winning research also took place at Celltech in Bothell. Dr. Sakaguchi, MD, PhD, a Japanese immunologist, serves as a Distinguished Professor at Osaka University. His honored contributions were made at the Institute for Frontier Medical Sciences at Kyoto University.

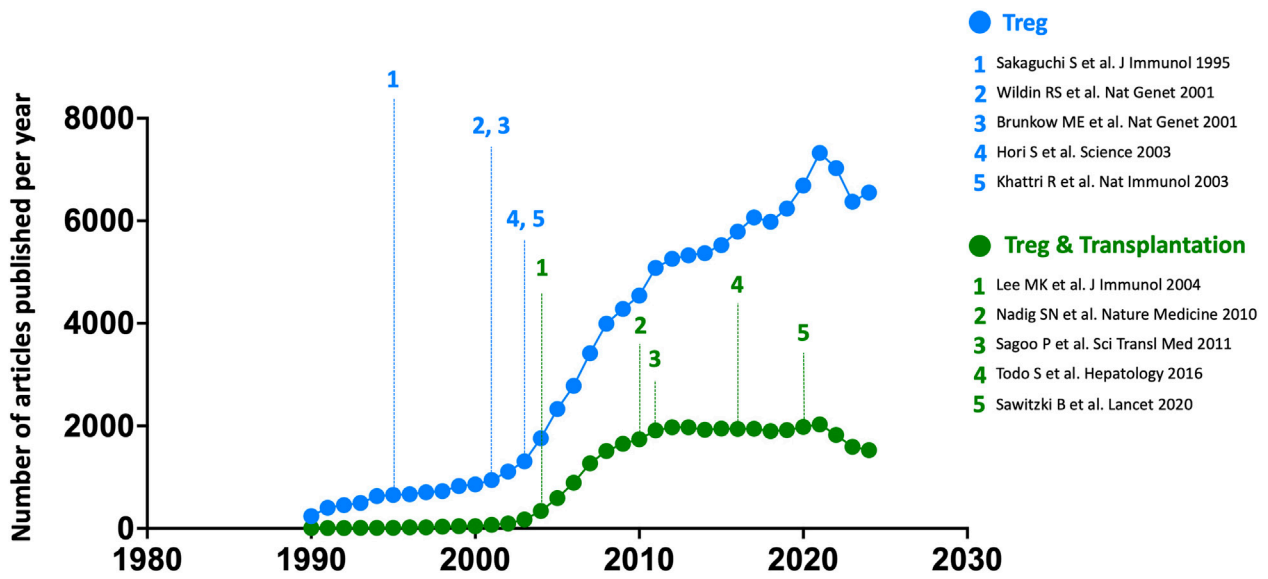

FIGURE 2 | Annual number of all articles published on Tregs, across all fields (blue) and specifically focused on transplantation (green), from 1990 to 2024. The five seminal papers by the three Nobel Prize laureates are numbered in blue along the chronological timeline, while five landmark studies in the field of transplantation are highlighted in green. Bibliographic data were extracted from the Web of Science platform (Clarivate Analytics) using the keywords [FOXP3] or [REGULATORY T CELL] for all fields, and [FOXP3] or [REGULATORY T CELL] combined with [TRANSPLANTATION] for articles specifically focused on Tregs in transplantation.

antigens within peripheral tissues, particularly in environments enriched in TGF-β. Notably, pTregs are key regulators of immune responses at mucosal interfaces, where they suppress immune reactions to dietary antigens and commensal microbiota [7, 8]. They also play a crucial role in preventing maternal immune responses against paternal antigens expressed by the fetus [10].

In this context, the evolutionary conservation of a specific regulatory element within the *FOXP3* gene among eutherian (placental) mammals, but not in marsupials or oviparous mammals, underscores the essential role of pTregs in mammalian evolution, ensuring maternal tolerance necessary for successful gestation and complete fetal development [10].

TREGS ARE UBIQUITOUS IN HUMAN IMMUNOPATHOLOGY

Human Treg subpopulations were first well characterized in a landmark paper by Makoto Miyara in Sakaguchi's laboratory [11]. Over the past two decades, dysregulated human regulatory

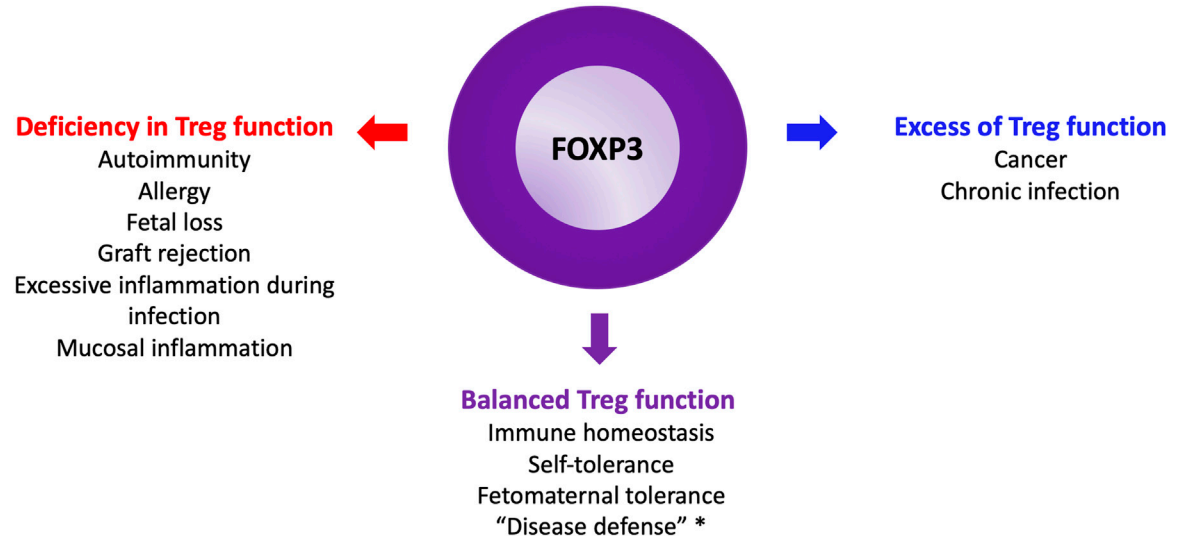

FIGURE 3 | The Yin and the Yang of Tregs. *: see glossary for definition.

T cell (Treg) function, whether excessive or insufficient, has been implicated across the full spectrum of immunopathology (**Figure 3**).

Beyond the extreme case of IPEX syndrome, Treg deficiency has been identified in various autoimmune diseases [15]. Shimon Sakaguchi's group demonstrated that single nucleotide polymorphisms linked to common autoimmune disorders are predominantly located in demethylated regions specific to naïve Tregs [16]. These regions shape the unique transcriptomic and epigenetic identity of Tregs, suggesting that impaired development or function of natural Tregs is a major driver of autoimmunity [16].

During healthy pregnancy, the Treg population expands alongside increased bioavailability of interleukin-2 (IL-2), a cytokine essential for Treg homeostasis [17]. A collapse in IL-2 signaling at the end of gestation coincides with the emergence of an inflammatory signature associated with parturition [17]. A recent study identified a subset of highly suppressive, activated CCR8-expressing Tregs at the decidual interface during the first trimester [18]. This population is reduced in recurrent pregnancy loss in humans and in murine models of spontaneous abortion. In mice, selective depletion of $CCR8^+$ decidual Tregs precipitates fetal loss, while their adoptive transfer protects against spontaneous abortion [18].

In the context of organ transplantation, Tregs play a pivotal role in suppressing alloimmune responses [19]. Their involvement in maintaining and propagating transplant tolerance has been well demonstrated in experimental models, offering a cellular basis for the phenomenon of *Infectious Tolerance* (Glossary) [12, 13]. In humanized mouse models, human Tregs can suppress both acute and chronic rejection, with enhanced efficacy when enriched for donor antigen-specificity [20, 21]. In clinical transplantation, the expansion and/or graft infiltration of Tregs in patients who achieve operational tolerance, either spontaneously or through therapeutic intervention [22], highlights their potential to reduce the need for long-term immunosuppression.

One of the earliest insights into the role of Tregs in anti-infectious immunity came from Shohei Hori, a key contributor to Sakaguchi's seminal 2003 study [4]. Hori demonstrated that Tregs play a crucial role in modulating the clinical manifestation of pneumocystis pneumonia by limiting inflammation [23]. In their absence, the infection took on a highly inflammatory and lethal course. Similarly, Rudensky's group identified amphiregulin-expressing Tregs involved in tissue repair; their impairment led to severe lung damage during influenza infection [24]. These findings support the concept of *Disease Tolerance* (see Glossary), where the host aims to both control the pathogen and minimize immune-mediated tissue damage [14]. Conversely, in chronic infections Tregs can be detrimental by impairing pathogen clearance [25].

Finally, a population of highly suppressive, activated $CCR8^+$ Tregs, similar to those found in the decidua, accumulate at tumor sites and contribute to the creation of an immune-privileged environment that enables cancer immune evasion [26]. Shimon Sakaguchi has shown that targeted depletion of CCR4+ Tregs or $CCR8^+$ Tregs can restore a robust, memory-driven anti-tumor immune response [27, 28].

TOWARD TARGETED THERAPIES

The field of oncology has embraced targeted therapies against intratumoral Tregs. The 2018 Nobel Prize in Physiology or Medicine was awarded to James Allison and Tasuku Honjo for their discoveries of the immune checkpoints CTLA-4 and PD-1, which laid the foundation for revolutionary cancer immunotherapies. While PD-1 inhibitors primarily target

intratumoral $CD8^+$ T cells, CTLA-4 blockade mainly disrupts Treg suppressive mechanisms [29]. In this regard, anti-CTLA-4 antibodies represent the first Treg-targeted immunotherapies. Another strategy involves depleting Tregs using anti-CCR4 antibodies, such as mogamulizumab, currently used to treat cutaneous lymphomas. Even more promising are anti-CCR8 therapies, with the potential to transform cancer immunotherapy [30].

Conversely, several academic and industrial research groups are developing novel therapeutic strategies to induce stable, suppressive Tregs from conventional T cells. Until recently, culturing T cells with TGF-β and IL-2 yielded only transient FOXP3 expression, resulting in an unstable regulatory phenotype. In this context, Shimon Sakaguchi's laboratory recently demonstrated the conversion of antigen-specific conventional T cells into stable, suppressive Tregs both *in vitro* and *in vivo* (in mice), either by inhibiting cyclin-dependent kinases 8 and 19 or abrogating CD28 signaling [31, 32]. Other teams are exploring chromatin-modifying agents to establish the epigenetic landscape characteristic of *bona fide* Tregs, essential for maintaining regulatory identity [33]. The therapeutic potential of this emerging class of immunomodulators is highly promising.

IL-2-based therapies exploit the high-affinity IL-2 receptor expression characteristic of Tregs, resulting in heightened sensitivity to low-dose IL-2 [34]. While low-dose IL-2 has shown clinical benefit in treating chronic graft-versus-host disease [35], it has also led to graft rejection in kidney (NCT02417870) and liver transplant [36] recipients due to limited specificity for Tregs. This narrow therapeutic window has spurred interest in IL-2 muteins: genetically engineered IL-2 variants designed to selectively activate Tregs [34, 37]. These modified cytokines are being developed primarily for autoimmune diseases, though they also hold promise for solid organ transplantation [34].

Regulatory cell therapy is attracting growing interest in treating autoimmune diseases, hematopoietic stem cell transplantation (HSCT), and solid organ transplantation. The Orca-T cell product, which includes donor-derived Tregs, has achieved breakthrough results in phase 2 [38] and subsequent phase 3 (NCT05316701) clinical trials, demonstrating a significantly lower incidence of moderate-to-severe chronic GVHD at 1 year among patients undergoing allogeneic HSCT. Orca-T is poised to become the first FDA-approved Treg-based cell therapy. In kidney transplantation, results from the ONE Study demonstrated the feasibility and safety of an autologous, polyclonal Treg therapy in kidney transplant recipients [39]. The findings suggest potential benefits, including reduced immunosuppressive requirements and a lower incidence of opportunistic infections [39]. In liver transplantation, a Japanese study showed that immunosuppressive drugs could be successfully discontinued following post-transplant cyclophosphamide pulses and donor-specific Treg therapy, with sustained results over long-term follow-up [40, 41].

Genetic enhancement of Tregs represents a promising strategy to potentiate regulatory cell therapy [42]. For example, Tregs can be redirected to the graft by engineering them to express a chimeric antigen receptor (CAR) specific for a donor-derived antigen, such as HLA-A2 [43]. Two clinical trials investigating HLA-A2–specific CAR-Tregs are currently underway in kidney (STEADFAST, NCT04817774) and liver (LIBERATE, NCT05234190) transplantation. Additionally, Tregs can be rendered resistant to tacrolimus through targeted deletion of the FKBP12 gene, preserving their function and proliferation in patients under immunosuppressive therapy [44]. Lastly, transgenic expression of an IL-2 mutein can enhance Treg expansion and suppressive capacity [45].

In summary, 30 years after the foundational work that shaped our modern understanding of regulatory T cells, their medical implications have proven profound, especially in organ transplantation. We extend our warmest thanks to the three laureates for their groundbreaking contributions and congratulate them on this well-deserved recognition.

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

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

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APPENDIX

Please see the glossary for definition.

Glossary:

1- Immune tolerance refers to the immune system's ability to remain unresponsive to molecules, cells, or tissues that would otherwise trigger a response. It involves various mechanisms that help distinguish between self and non-self, while also preventing excessive or inappropriate reactions to environmental factors such as dietary antigens and gut microbiota. Depending on where it is induced, immune tolerance is classified as either central tolerance, which occurs in the thymus and bone marrow, or peripheral tolerance, which takes place primarily in lymph nodes and other tissues.

2- Infectious tolerance refers to the capacity of *bona fide* Tregs to convert effector cells into new Tregs, thereby extending immune tolerance from one antigen to another. This mechanism supports the ongoing induction of tolerance in new cohorts of T cells over the lifespan of a tolerated graft. The concept was first introduced by Hermann Waldmann in 1993 [12], and was later linked to regulatory T cells in 2011 [13].

3- Disease tolerance refers to a paradigm proposed by Ruslan Medzhitov, in which an important defense strategy against infection involves mitigating bystander tissue injury caused by pathogen-specific immune responses [14].

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Living-Donor Kidney Transplantation: Comparison of Robotic-Assisted Versus Conventional Open Technique

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The aim was to compare intraoperative, postoperative and functional outcomes of patients undergoing living donor RAKT versus OKT. A retrospective analysis of all living donor's kidney transplantation performed in a tertiary center between 2013 and 2024 comparing RAKT with OKT was performed. All recipients in the OKT group were eligible for a RAKT. A total of 400 patients (200 RAKT and 200 OKT) were included. Recipients were younger in the RAKT cohort (48.0 versus 51.5 years, p = 0.045). Median operative time was significantly longer in the RAKT group (185.5 versus 120.0 min, p < 0.0001). Intraoperative complications rate was similar in both study group. A significantly higher proportion of recipients receiving OKT undergone post-operative surgical complications (p < 0.0001) and major post-operative complications (8.0% versus 19.5%, p = 0.001). Seven patients required graft nephrectomy during the early post-operative period (of whom all were in the RAKT group). Median length of hospitalization was significantly longer in the OKT group (7.0 versus 9.0 days, p < 0.0001). 1-, 3- and 5-years patient and graft survival were comparable between the RAKT and OKT cohorts. The postoperative opioid requirement was not evaluated. Our analysis confirms the safety and efficacy of RAKT in the setting of living donors, in comparison to conventional OKT.

Keywords: living donor kidney transplantation, robotic-assisted kidney transplantation, open kidney transplantation, delayed graft function, surgical complications

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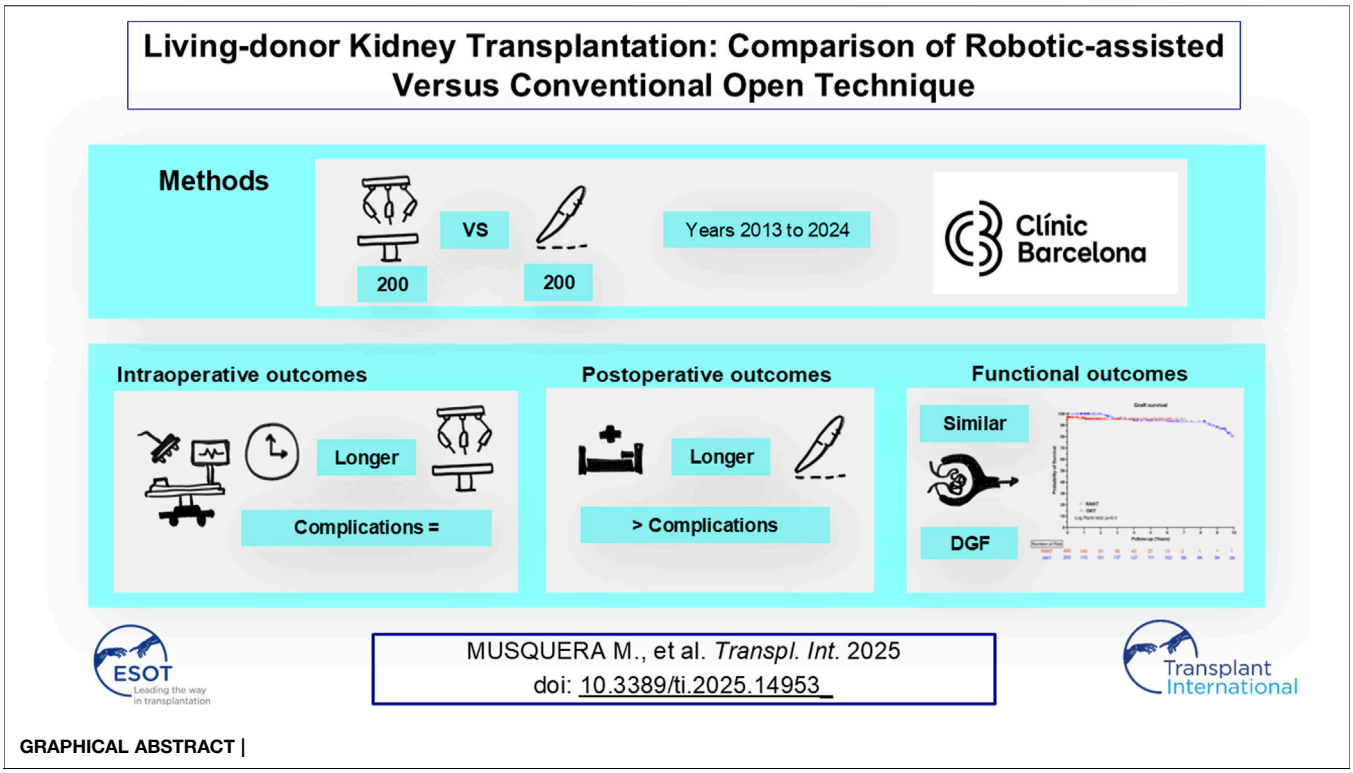
INTRODUCTION

Kidney transplantation (KT) is considered the preferred treatment for patients with end-stage-renal disease, owing to greater survival rate and better quality of life in comparison with dialysis [1–4]. Since the initial successful case in 1954, conventional open kidney transplant (OKT) surgery with anastomosis of the graft vessels to the recipient's iliac vessels has become the standard procedure [5].

Abbreviations: BMI, Body Mass Index; DGF, Delayed graft function; EAUiaiC, Intraoperative Adverse Incident Classification by the European Association of Urology; eGFR, estimated Glomerular filtration rate; IQR, Interquartile range (IQR); KT, Kidney Transplantation; LDN, Living-Donor Nephrectomy; LESS, LaparoEndoscopic Single Site; LOH, Length of Hospitalization; MRA, Multiple Renal Arteries; OKT, Open Kidney Transplantation; POD, Post-Operative Day; RAKT, Robotic-Assisted Kidney Transplantation; WIT, Warm Ischemia Time.



GRAPHICAL ABSTRACT |

Over the last 30 years, the minimally invasive surgery has revolutionized surgical practice resulting in a rapid dissemination of the laparoscopic surgery. However, in the field of kidney transplantation, the technical difficulties in performing vascular anastomosis in the pelvis using laparoscopic instruments and two-dimensional vision has limited its expansion.

The introduction of the da Vinci ® robotic surgical system (Intuitive Surgical Inc, Sunnyvale, CA, USA) has filled the gap, enabling the precise intracorporeal vascular anastomosis required for kidney transplantation. Indeed, robotic-assisted surgery provides advantages over standard laparoscopic surgery, such as high-definition 3D imaging, increased magnification and multiple degrees of freedom of instruments. The first used of the da Vinci ® platform was reported by Hoznek et al [6] in 2001, as an adjunct to open kidney transplantation. This first case demonstrated the feasibility of robotic-assisted vascular anastomosis in a kidney transplant using an open approach. A few years later, Giulianotti et al [7] reported the first pure robotic-assisted kidney transplantation (RAKT) performed in the USA. Then, Menon et al [8, 9] standardized the surgical technique of RAKT, using a transperitoneal approach. The first three European pure RAKTs were performed in July 2015 by Doumerc et al [10], Breda et al [11] and our team [12]. Various studies have confirmed that RAKT is a safe procedure, associated with good short-term functional outcomes [4, 13–15], feasible in obese patients [16] and using grafts with multiple vessels [17].

Despite the RAKT technique has been standardized and its feasibility demonstrated in several clinical scenarios, there is still a lack of data directly comparing perioperative and postoperative outcomes between RAKT and OKT.

To fill this gap, we sought to compare intraoperative, postoperative and functional outcomes of patients undergoing living donor RAKT versus OKT.

PATIENTS AND METHODS

Patient Population and Study Design

A retrospective analysis of all living donor kidney transplantation performed at the Hospital Clínic in Barcelona, Spain, between January 2013 and May 2024 was conducted after approval by the Hospital Clínic Institutional Review Board (HCB/2020/0713). We started our program on RAKT in July 2015. Since then, more than 200 living-donor RAKT has been performed and has become the benchmark technique for living donor kidney transplantation in our institution. In this study we included the first 200 consecutive cases.

The exclusion criterion for a RAKT were the following: a) medical history of complex abdominal surgeries, b) severe atherosclerotic plaques at the level of external iliac vessels at the preoperative computed tomography angiogram, c) prior bilateral kidney transplantation.

For this study, in order to mimic the RAKT conditions, the exclusion criterion in the OKT cohort including: a) orthotopic KT, b) KT on vascular prosthesis, c) severe atherosclerotic plaques at the level of external iliac vessels at the preoperative computed tomography angiogram, d) prior bilateral kidney transplantation. All computed tomography angiogram were reviewed to check the indication for robotic approach. Thus, all recipients in the OKT group were eligible for a robotic-assisted kidney transplantation.

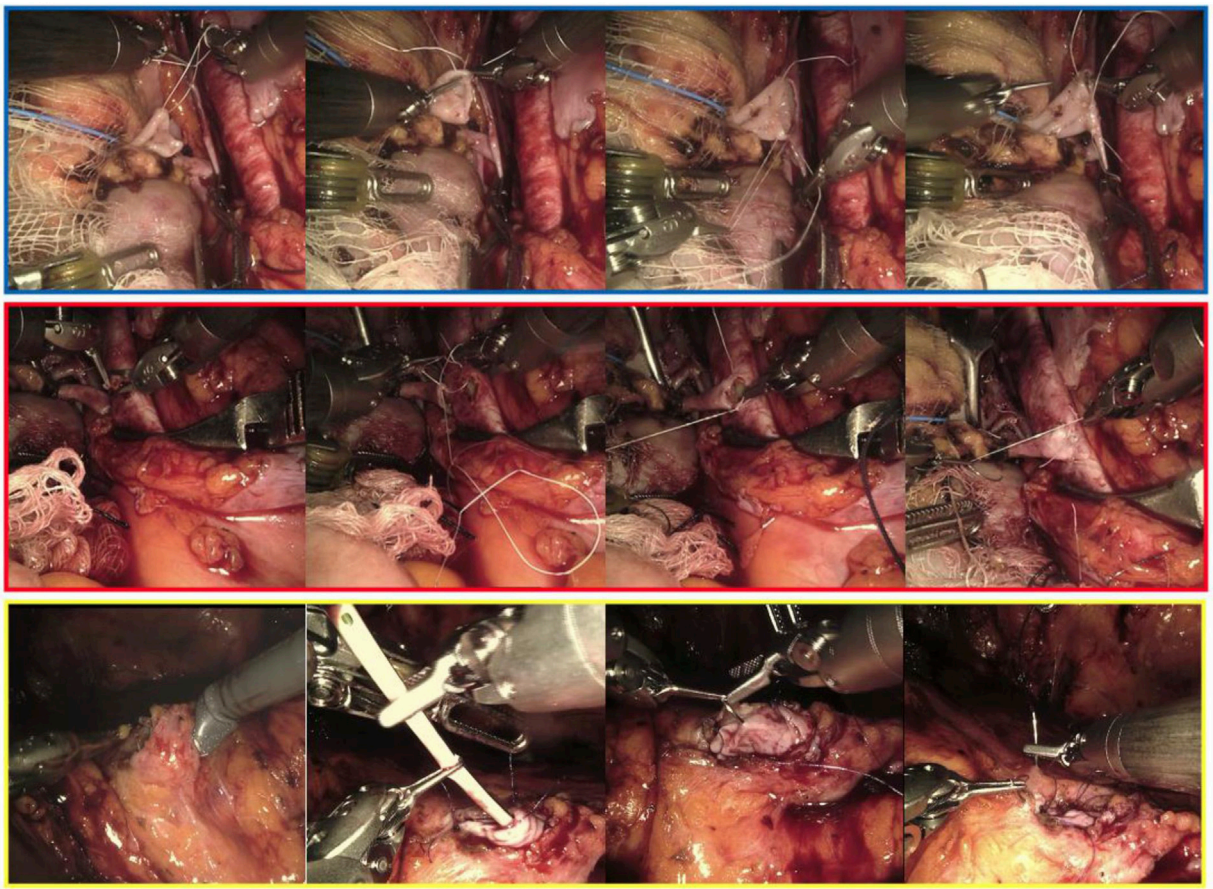


FIGURE 1 | Intraoperative snapshots showing the main phases of the venous (framed in blue), arterial (red) and uretero-vesical anastomosis during living donor robotic-assisted kidney transplantation.

Surgical Procedure and Immunosuppression

All donors and recipients' surgeries were performed following a simultaneous process, in two different operating rooms.

Robotic-Assisted Kidney Transplantation

RAKTs were performed using the da Vinci Xi Surgical System (Intuitive Surgical Inc., Sunnyvale, CA, USA) in a four-arm configuration, with a 0° lens and a 30° Trendelenburg tilt. The cases were performed by one senior surgeon, who had extensive experience in robotic surgery, robotic-assisted kidney transplantation and open kidney transplantation. In our institution, the RAKT technique followed the principles of the Vattikuti-Medanta technique, using a transperitoneal approach [9, 18]. Briefly, during back-table preparation, the graft is prepared with care to ligate any possible source of bleeding. Then, grafts were wrapped in ice-gauze jackets with marking stitches at the lower pole to maintain orientation before implantation. A small window is created into the gauze for artery and vein exposure. In case of multiples arteries, the surgeon may use different techniques in order to reconstruct the renal artery or decides to perform separate arterial anastomoses during robotic procedure. The graft was then introduced through a Pfannenstiel or periumbilical incision using a GelPoint device. Vascular anastomoses were completed in an end-to-side fashion to the external iliac vessels using a 6-0 GORE-TEX suture (Gore Medical, Flagstaff, AZ, USA) (**Figure 1**). Graft reperfusion was assessed by intraoperative Doppler-US. Uretero-vesical anastomosis is then completed using extravesical approach, according to modified Lich-Gregoire technique with a doble-J stent (**Figure 1**). Over time, specific modifications have been made: a) pneumoperitoneum reduction from 12 to 10 mmHg after graft reperfusion in order to reduce possible graft damage [19], b) modification of the graft introduction approach: replacement of the periumbilical incision by the Pfannenstiel incision (allows a quick open conversion if necessary), c) in selected cases, transvaginal approach for graft introduction could be used, d) modification of the organ preservation solution: the historically Ringer's lactate solution was replaced by histidine-tryptophan-ketoglutarate solution after first cases of RAKT in order to minimize cell damage.

Open Kidney Transplantation

OKTs were performed following conventional retroperitoneal technique via Gibson incision. Vascular (vein and artery)

TABLE 1 | Preoperative baseline donors- and graft-related characteristics.

Donors- and graft-related characteristics		Overall population n = 400	RAKT n = 200	OKT n = 200	*p*
Age (yr) *(median, IQR, Range)*		55.0 (48.0–62.0) (26–77.0)	55.0 (47.0–62.0) (26.0–77.0)	55.0 (49.0–62.0) (32.0–76.0)	0.7
BMI (kg/m^2) *(median, IQR, Range)*		25.6 (23.2–27.9) (18.8–35.4)	25.5 (23.0–27.5) (19.1–35.4)	25.9 (23.4–28.3) (18.8–34.4)	0.2
Male *(n, %)*		116 (29.0%)	59 (29.5%)	57 (28.5%)	0.9
Donor eGFR (ml/min/1.73 m^2) *(median, IQR, Range)*	Preoperative	90.0 (82.0–90.0) (58.0–148.0)	90.0 (85.0–90.0) (58.0–148.0)	90.0 (79.0–90.0) (60-0–93.0)	**0.01**
	POD 30	57.0 (50.0–64.0) (33.5–92.0)	57.3 (49.3–64.6) (33.5–92.0)	56.5 (50.8–61.7) (37.0–90.0)	0.5
Living donor type *(n, %)*	Biological related	228 (57.0%)	124 (62.0%)	104 (52.0%)	0.1
	Biological unrelated	172 (43.0%)	76 (38.0%)	96 (48.0%)	
Pair exchange *(n, %)*		33 (8.3%)	11 (5.5%)	22 (11.0%)	0.1
ABO incompatible kidney transplantation *(n, %)*		83 (20.8%)	36 (18.0%)	47 (23.5%)	0.2
Right-sided graft *(n, %)*		46 (11.5%)	19 (9.5%)	27 (13.5%)	0.3
Number of artery *(n, %)*	n = 1	331 (82.8%)	160 (80.0%)	171 (85.5%)	0.1
	n = 2	67 (16.8%)	40 (20.0%)	27 (13.5%)	
	n = 3	2 (0.5%)	0 (0%)	2 (1.0%)	
Number of veins *(n, %)*	n = 1	387 (96.8%)	196 (98.0%)	191 (95.5%)	0.3
	n = 2	13 (3.2%)	4 (2.0%)	9 (4.5%)	
Number of ureter *(n, %)*	n = 1	397 (99.3%)	199 (99.5%)	198 (99.0%)	0.9
	n = 2	3 (0.8%)	1 (0.5%)	2 (1.0%)	
Surgical approach for living donor nephrectomy *(n, %)*	Pure laparoscopic with pfannenstiel or infraumbilical extraction	327 (81.8%)	175 (87.5%)	152 (76.0%)	**0.0002**
	Pure laparoscopic with transvaginal extraction	49 (12.3%)	22 (11.0%)	27 (13.5%)	
	LESS	22 (5.5%)	2 (1.0%)	20 (10.0%)	
	Open	2 (0.5%)	1 (0.5%)	1 (0.5%)	
Living-donor nephrectomy warm ischemia time (min) *(median, IQR, Range)*		2.8 (2.0–4.0) (0.6–11.7)	2.8 (2.1–3.5) (0.6–11.0)	2.8 (2.0–4.3) (1.2–11.7)	0.3

RAKT, Robotic-assisted kidney transplantation; OKT, Open kidney transplantation; BMI, Body Mass Index; eGFR, estimated Glomerular filtration rate; POD, Post-operative day; LESS, LaparoEndoscopic Single Site. Bold values indicate statistically significant results ($p < 0.05$).

anastomoses were performed using 6/0 Prolene suture (Ethicon, Johnson & Johnson Medical, Somerville, NJ, USA). Ureterovesical anastomosis was performed using intravesical approach, according to Leadbetter Politano technique without doble-J stent. The cases were performed by four different senior surgeons.

Immunosuppression

All patients received triple immunosuppression therapy, including calcineurin inhibitor, steroids and either mycophenolic acid or an mTOR inhibitor. Induction was either basiliximab or antithymocyte globulin, accord to immunological risk.

Study Variables and Outcomes

Donor-, graft- and recipient-related data's, intraoperative outcomes, early post-operative (≤ day 90) complications and functional outcomes as well as follow-up outcomes were retrospectively collected.

Warm ischemia time corresponds to the period between renal circulatory arrest and the beginning of cold storage after living donor nephrectomy. Total operative time was calculated from case start (incision time) until case end (closure). This included back-table time and any additional time waiting for donor nephrectomy to be completed. Delayed graft function (DGF) was defined as the need of dialysis in the first week following KT [20]. Estimated glomerular filtration rate (eGFR) calculation was performed using the Chronic Kidney Disease Epidemiology Collaboration formula [21]. Intraoperative complications were reported according to the Intraoperative Adverse Incident Classification (EAUiaiC) by the European Association of Urology (EAU) *ad hoc* Complications Guidelines Panel [22], while postoperative surgical complications were reported according to modified Clavien-Dindo system [23] and high-grade postoperative complications were defined as Clavien-Dindo grade ≥3. Patient and graft survival were assessed at 5 years and overall posttransplant.

Statistical Analysis

Quantitative data were expressed as medians with interquartile range (IQR) as well as range and were compared using the Mann-Whitney *U* test for nonnormally distributed variables. Qualitative data were expressed as numbers and percentage and were compared using chi-square and Fisher exact tests. Overall survival was estimated using the Kaplan-Meier method, and RAKT and OKT cohorts were compared via log-rank tests.

A *P* value of <0.05 was considered statistically significant. Statistical analyses were performed using S PRISM v.10.1.1 (GraphPad Software Inc., La Jolla, CA, USA) and IBM SPSS v29 (IBM Corporation, NY, USA).

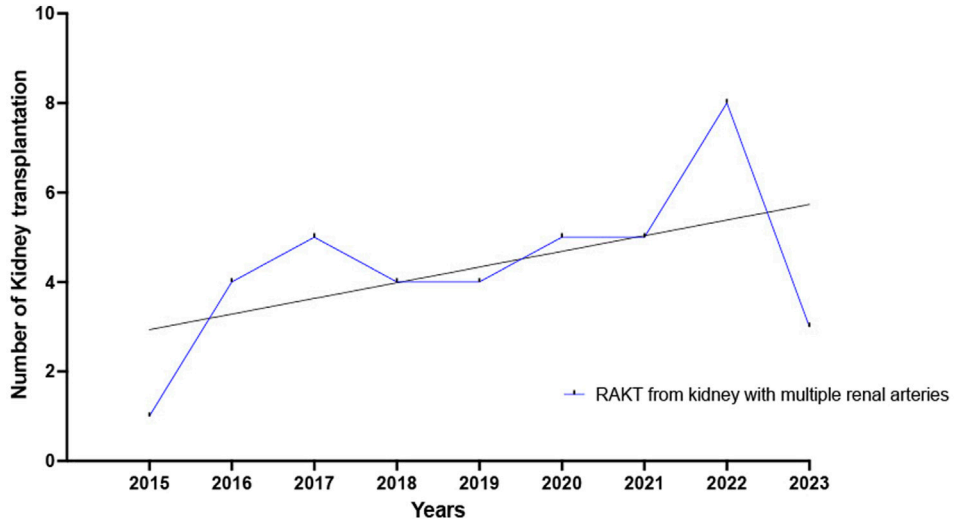


FIGURE 2 | Yearly number of RAKT with multiple renal arteries increased from 2015 to 2023.

TABLE 2 | Preoperative baseline recipients-related characteristics.

Recipients-related characteristics		Overall population n = 400	RAKT n = 200	OKT n = 200	*p*
Age (yr) *(median, IQR, Range)*		50.0 (38.0–60.0) (18.0–82.0)	48.0 (36.3–58.0) (18.0–77.0)	51.5 (41.0–61.0) (18.0–82.0)	**0.045**
BMI (kg/m^2) *(median, IQR, Range)*		24.7 (21.9–27.8) (15.4–44.7)	24.8 (21.9–28.4) (16.9–44.7)	24.6 (21.9–27.7) (15.4–39.4)	0.5
Male *(n, %)*		239 (59.8%)	122 (61.0%)	117 (58.5%)	0.7
Comorbidities *(n, %)*	High blood pressure	335 (83.8%)	167 (83.5%)	168 (84.0%)	0.9
	Diabetes mellitus	74 (18.5%)	17 (8.5%)	57 (28.5%)	**<0.0001**
	Dyslipidaemia	125 (31.3%)	49 (24.5%)	76 (38.0%)	**0.004**
Recipient nephropathy *(n, %)*	Autosomal dominant polycystic kidney disease	62 (15.5%)	34 (17.0%)	28 (14.0%)	0.3
	IGA-nephropathy	44 (11.0%)	21 (10.5%)	23 (11.5%)	
	Hypertensive nephropathy	22 (5.5%)	5 (2.5%)	17 (8.5%)	
	Diabetic nephropathy	37 (9.3%)	11 (5.5%)	26 (13.0%)	
	Glomerulonephritis	69 (17.3%)	43 (21.5%)	26 (13.0%)	
	Congenic uropathy	24 (6.0%)	9 (4.5%)	15 (7.5%)	
	Alport syndrome	5 (1.3%)	4 (2.0%)	1 (0.5%)	
	Lupus nephritis	5 (1.3%)	2 (1.0%)	3 (1.5%)	
	Haemolytic uremic syndrome	5 (1.3%)	2 (1.0%)	3 (1.5%)	
	Other/Unknown	127 (31.8%)	69 (34.5%)	58 (29.0%)	
Major previous abdominal surgery *(n, %)*		202 (50.5%)	87 (43.5%)	115 (57.5%)	**0.01**
Previous kidney transplantation *(n, %)*		61 (15.3%)	22 (11.0%)	39 (19.5%)	**0.03**
Preemptive recipient *(n, %)*		242 (60.5%)	125 (62.5%)	117 (58.5%)	0.5
Time on dialysis (months) *(median, IQR, Range)*		8.0 (4.0–18.0) (1.0–228.0)	6.0 (3.5–12.0) (1.0–36.0)	12.0 (4.8–32.5) (1.0–228.0)	**0.003**

RAKT, Robotic-assisted kidney transplantation; OKT, Open kidney transplantation; BMI, Body Mass Index. Bold values indicate statistically significant results (p < 0.05).

RESULTS

Finally, a total of 200 living donor RAKT were compared to the last 200 living-donor OKT whose recipients were eligible for a living-donor RAKT (i.e., exclusion criterion). The study periods were: July 2015 to May 2024 for the RAKT cohort and January 2013 to May 2024 for the OKT cohort.

Baseline Donor- and Graft-Related Characteristics

The baseline donor and graft-related characteristics in the RAKT and OKT cohorts were reported in **Table 1**.

Both study groups were comparable regarding donors' median age, median body mass index, gender, ABO incompatible KT proportion, KT from pair exchange

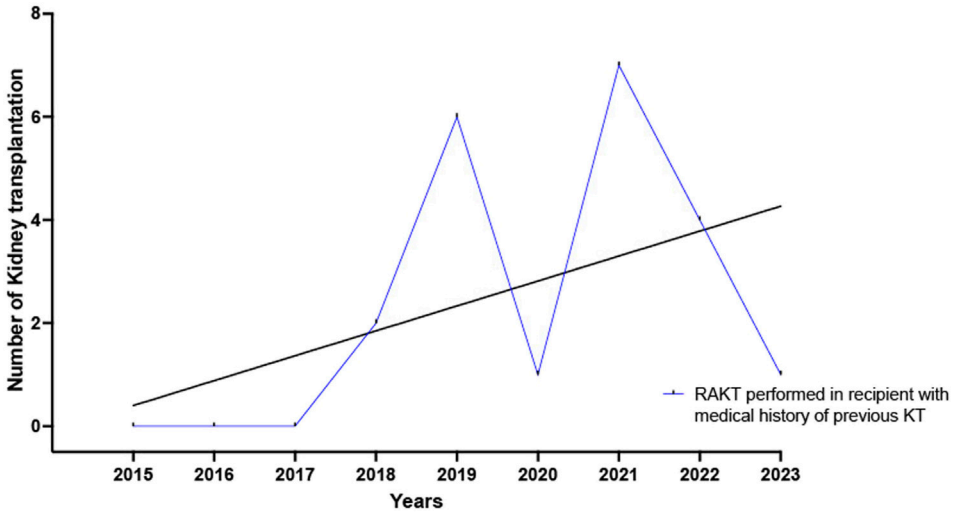


FIGURE 3 | Yearly number of RAKT performed in recipients who undergone a previous kidney transplantation increased from 2015 to 2023.

TABLE 3 | Intraoperative outcomes after robotic-assisted kidney transplantation (RAKT) versus open kidney transplantation (OKT).

Intraoperative outcomes		Overall population n = 400	RAKT n = 200	OKT n = 200	*p*
Transplant site *(n, %)*	Right iliac fossa	337 (84.3%)	175 (87.5%)	162 (81.0%)	0.1
	Left iliac fossa	63 (15.8%)	25 (12.5%)	38 (19.0%)	
Intraoperative complications *(n, %)*	EAUiaiC grade 0, 1 and 2	0 (0%)	0 (0%)	0 (0%)	0.1
	EAUiaiC grade 3				
	-Active bleeding	1 (0.3%)	0 (0%)	1 (0.5%)	
	-New vascular anastomosis without conversion	1 (0.3%)	0 (0%)	1 (0.5%)	
	EAUiaiC grade 4A	0 (0%)	0 (0%)	0 (0%)	
	EAUiaiC grade 4B				
	-Conversion due: a) Venous thrombosis	—	1 (0.5%)	—	
	c) Abnormal perfusion without requiring new vascular anastomosis	—	3 (1.5%)	—	
		—	3 (3.0%)	—	
	d) Abnormal perfusion requiring new vascular anastomosis				
	Total major intra-operative complications *(n, %)*	9 (2.3%)	7 (3.5%)	2 (1.0%)	
Operative time *(median, IQR, Range)*		157.5 (120.0–190.0) (50–325.0)	185.5 (170.0–211.0) (100.0–325.0)	120.0 (105.0–145.0) (50.0–240.0)	**<0.0001**

RAKT, Robotic-assisted kidney transplantation; OKT, Open kidney transplantation; EAUiaiC, Intraoperative Adverse Incident Classification by the European Association of Urology. Bold values indicate statistically significant results (p < 0.05).

proportion and right-sided graft proportion. The donors' preoperative eGFR was significantly lower in the OKT group.

Both study groups were comparable regarding living-donor nephrectomy (LDN) warm ischemia time, proportion of kidney transplantation with multiple renal arteries (MRA) and multiple renal veins (MRV) grafts. The yearly number of RAKT with MRA grafts increased from 2015 to 2023, **Figure 2**. Lastly, concerning the surgical approach for LDN, a higher proportion of pure laparoscopic with Pfannenstiel or infraumbilical extraction was performed in RAKT group (87.5% versus 76.0%, p = 0.0002) while a higher proportion of laparoendoscopic single site (LESS) surgery was reported in OKT group (1.0% versus 10.0%, p = 0.0002).

Baseline Recipient-Related Characteristics

The baseline recipient-related characteristics in the RAKT and OKT cohorts are shown in **Table 2**.

In the RAKT cohort, recipients were younger than recipients in the OKT cohort (48.0 versus 51.5 years, p = 0.045). Both study groups were similar concerning recipients' median BMI, gender and pre-emptive kidney transplantation proportion.

The proportion of medical history of diabetes mellitus (8.5% versus 28.5%, p < 0.0001) and dyslipidemia (24.5.0%

TABLE 4 | Early (POD 90) postoperative and functional outcomes after robotic-assisted kidney transplantation (RAKT) versus open kidney transplantation (OKT).

Early post operative outcomes (POD 90)		Overall population n = 400	RAKT n = 200	OKT n = 200	*p*
Overall length of hospitalization (days) *(median, IQR, Range)*		8.0 (7.0–11.0) (2.0–46.0)	7.0 (7.0–10.0) (2.0–29.0)	9.0 (7.0–13.0) (4.0–46.0)	<0.0001
Highest grade postoperative surgical complications (according to clavien-dindo classification) *(n, %)*	Grade 2				**<0.0001**
	-Bleeding requiring transfusion	102 (25.5%)	36 (18.0%)	66 (33.0%)	
	-Hematuria without endoscopic	43 (10.8%)	2 (1.0%)	41 (20.5%)	
	surgical revision	25 (6.3%)	2 (1.0%)	23 (11.5%)	
	-Wound infection	4 (1.0%)	4 (2.0%)	0 (0%)	
	-Ileus				
	Grade 3a				
	-Bleeding requiring radiological embolization	1 (0.3%)	1 (0.5%)	0 (0%)	
	Grade 3b				
	-Graft nephrectomy due to: a)	1 (0.3%)	1 (0.5%)	0 (0%)	
	Venous thrombosis	3 (0.8%)	3 (1.5%)	0 (0%)	
	b) Arterial thrombosis	3 (0.8%)	3 (1.5%)	0 (0%)	
	c) Acute rejection	7 (1.8%)	0 (0%)	7 (3.5%)	
	-Hematuria with endoscopic	25 (6.3%)	4 (2.0%)	21 (10.5%)	
	surgical revision	5 (1.3%)	2 (1.0%)	3 (1.5%)	
	-Reintervention due to urinary	7 (1.8%)	2 (1.0%)	5 (2.5%)	
	leakage	3 (0.8%)	0 (0%)	3 (1.5%)	
	-Reintervention due to paravesical bleeding/hematoma				
	-Laparoscopic marsupialization				
	-Abdominal evisceration				
	Grade 4a	0 (0%)	0 (0%)	0 (0%)	
	Grade 4b	0 (0%)	0 (0%)	0 (0%)	
	Grade 5	0 (0%)	0 (0%)	0 (0%)	
Major postoperative surgical complication (clavien-dindo grade ≥3) *(n, %)*		55 (13.8%)	16 (8.0%)	39 (19.5%)	**0.001**
Early functional outcomes (POD 90)					
Delayed graft function *(n, %)*		3 (0.8%)	3 (1.5%)	0 (0%)	0.2
Serum creatinine (mg/dL) *(median, IQR, Range)*	POD 7	1.3 (1.1–1.7) (0.3–8.6)	1.3 (1.1–1.6) (0.5–8.6)	1.3 (1.0–1.7) (0.3–8.1)	0.5
	POD 30	1.3 (1.1–1.7) (0.4–5.9)	1.4 (1.1–1.7) (0.7–4.0)	1.3 (1.1–1.6) (0.4–5.9)	0.1
eGFR (ml/min/1.73 m^2) *(median, IQR, Range)*	POD 7	60.0 (45.4–73.1) (6.2–95.0)	60.0 (45.5–71.0) (8.0–95.0)	60.0 (45.4–73.9) (6.2–92.0)	0.9
	POD 30	56.0 (45.0–70.0) (9.0–97.0)	56.0 (45.0–69.5) (15.0–90.0)	56.0 (45.0–73.8) (9.0–97.0)	0.3
Hemoglobin (g/L) *(median, IQR, Range)*	POD 7	98.0 (90.0–109.0) (66.0–159.0)	100.0 (90.0–111.0 (70.0–159.0)	97.0 (89.0–107.5) (66.0–149.0)	0.2

RAKT, Robotic-assisted kidney transplantation; OKT, Open kidney transplantation; POD, Post-operative day; eGFR, estimated Glomerular filtration rate. Bold values indicate statistically significant results (p < 0.05).

versus 38.0%, $p = 0.004$) was significantly higher in the OKT group. A significantly higher proportion of recipients receiving OKT had undergone previous major abdominal surgery (43.5% versus 57.5%, $p = 0.01$) or a previous kidney transplantation (11.0% versus 19.5%, $p = 0.03$). The yearly number of RAKT performed in recipients who undergone a previous kidney transplantation increased from 2015 to 2023, **Figure 3**. Lastly, recipients in the OKT group had a longer median times on dialysis (6.0 versus 12.0 months, $p = 0.003$).

Intraoperative Outcomes

The intraoperative outcomes of the RAKT and OKT cohorts are reported in **Table 3**.

The majority of KT were performed in the right iliac fossa. The median overall operative time was significantly longer in the RAKT group (185.5 versus 120.0 min, $p < 0.0001$). Overall, intraoperative adverse events were recorded in nine patients (2.3%). Intraoperative major post-operative complications rate was similar in both study group (3.5% versus 1.0%; $p = 0.1$). Seven (3.5%) open conversion occurred during RAKT.

Postoperative and Early Functional Outcomes

An overview of the early postoperative outcomes after RAKT versus OKT is provided in **Table 4**.

A significantly higher proportion of recipients receiving OKT undergone post-operative surgical complications ($p < 0.0001$) and major post-operative complications (8.0% versus 19.5%, $p = 0.001$). Seven (3.5%) patients required graft nephrectomy during the early post-operative period (of

TABLE 5 | Follow-up outcomes after robotic-assisted kidney transplantation (RAKT) versus open kidney transplantation (OKT).

Follow-up outcomes	Overall population n = 400	RAKT n = 200	OKT n = 200	*p*
Follow-up (months) *(median, IQR, Range)*	37.9 (14.3–83.8) (0.3–144.2)	21.5 (11.4–46.3) (0.3–86.4)	79.7 (24.0–116.2) (0.5–144.2)	**<0.0001**
KT-related surgical reinterventions after POD 90 *(n, %)*				
-Abdominal eventration requiring surgical treatment				0.9
a) Peri-umbilical	4 (1.0%)	4 (2.0%)	0 (0%)	
b) Pfannenstiel	0 (0%)	0 (0%)	0 (0%)	
c) Gibson	3 (0.8%)	0 (0%)	3 (1.5%)	
-Lymphocele marsupialization	5 (1.3%)	2 (1.0%)	3 (1.5%)	
-Ureteral reimplantation after marsupialization	1 (0.3%)	1 (0.5%)	0 (0%)	
-Ureteral stenosis	3 (0.8%)	1 (0.5%)	2 (1.0%)	
-TRAS requiring stenting	1 (0.3%)	1 (0.5%)	0 (0%)	
Serum creatinine at last follow-up (mg/dL) *(median, IQR, Range)*	1.4 (1.2–1.8) (0.4–17.6)	1.4 (1.2–1.7) (0.7–17.6)	1.4 (1.2–1.9) (0.4–6.1)	0.5
eGFR at last follow-up (ml/min/1.73m^2) *(median, IQR, Range)*	51.0 (41.0–64.5) (1.4–95.0)	52.5 (42.0–65.3) (1.4–95.0)	50.0 (36.5–63.0) (5.0–90.0	0.1
Graft survival				
1-year	97.7%	95.8%	99.5%	0.4
3-year	95.6%	95.1%	96.0%	
5-year	94.5%	95.1%	93.8%	
Patient survival				
1-year	99.2%	100.0%	98.4%	0.2
3-year	98.4%	98.9%	97.8%	
5-year	98.0%	98.9%	97.1%	

RAKT, Robotic-assisted kidney transplantation; OKT, Open kidney transplantation; POD, Post-operative day; KT, Kidney transplantation; TRAS, Transplant renal artery stenting; eGFR, estimated Glomerular filtration rate. Bold values indicate statistically significant results (p < 0.05).

whom all were in the RAKT group). Four (1.0%) patients required graft nephrectomy due to vascular thrombosis while three (0.8%) patients required graft nephrectomy due to rejection. Wound infection rates, hematuria and urinary leakage rates were higher in the OKT group. The median length of hospitalization (LOH) was significantly longer in the OKT group (7.0 versus 9.0 days, $p < 0.0001$). There were no significant differences between RAKT and OKT regarding delayed graft function rate as well as in the eGFR, serum creatinine and hemoglobin trajectories after transplantation.

Follow-Up Outcomes

Follow-up outcomes after RAKT versus OKT are shown in **Table 5**.

The median follow-up was significantly longer in the OKT group (21.5 versus 79.7 months, $p < 0.0001$). The proportion of reinterventions after POD 90 were comparable in both study groups. At last follow-up, the median serum creatinine and eGFR were comparable in RAKT and OKT group. One, three and five-years patient and graft survival were comparable between the RAKT and OKT cohorts, **Figure 4**.

DISCUSSION

During past 3 decades, minimally invasive surgery has increasingly permeated several fields, especially urology [24]. The widespread adoption of robotics worldwide has led to an increasing body of evidence supporting its noninferiority to open surgery and its benefits for both surgeons and patients for selected intervention [25, 26].

Thus, the transplantation community has been hesitant to such change, and OKT still remains the gold standard approach at most center worldwide [20].

Notably, in recent years, several groups have developed and standardized the technique of RAKT, aiming to reduce the morbidity of kidney transplantation [4, 13, 14, 16, 27]. To date, nearly all published data is based on descriptive series and few of them compared the results with the conventional open approach [28]. Thus, the influences of RAKT on short- and mid-term outcomes in kidney transplant recipients, as compared with OKT, remained undetermined.

To the best of our knowledge, this is the largest study from a European center comparing RAKT and conventional OKT from living donor. Our study confirmed the safety and efficacy of RAKT in the setting of living donors. While overall operative time was longer in the RAKT cohort, functional outcomes (DGF rate, serum creatinine and eGFR trajectories, patient and graft survival) were similar in both study groups. We reported higher surgical post-operative complication rate in the OKT cohort. The main complications in the OKT cohort were hematuria and transfusion. This higher rate of hematuria is directly related to the type of uretero-vesical anastomosis. It is well known that the intravesical approach and the lack of ureteral stent are a risk factor of postoperative hematuria due to large cystostomy from which bleeding can arise [29]. However, 7 cases of hematuria required an endoscopic management. In addition, reintervention to perform a new uretero-vesical anastomosis rate was higher in OKT cohort, but similar with rates reported in the literature [30]. Wound complications (i.e., wound infection, evisceration and eventration) were similar in the OKT and RAKT groups and were not related to obesity.

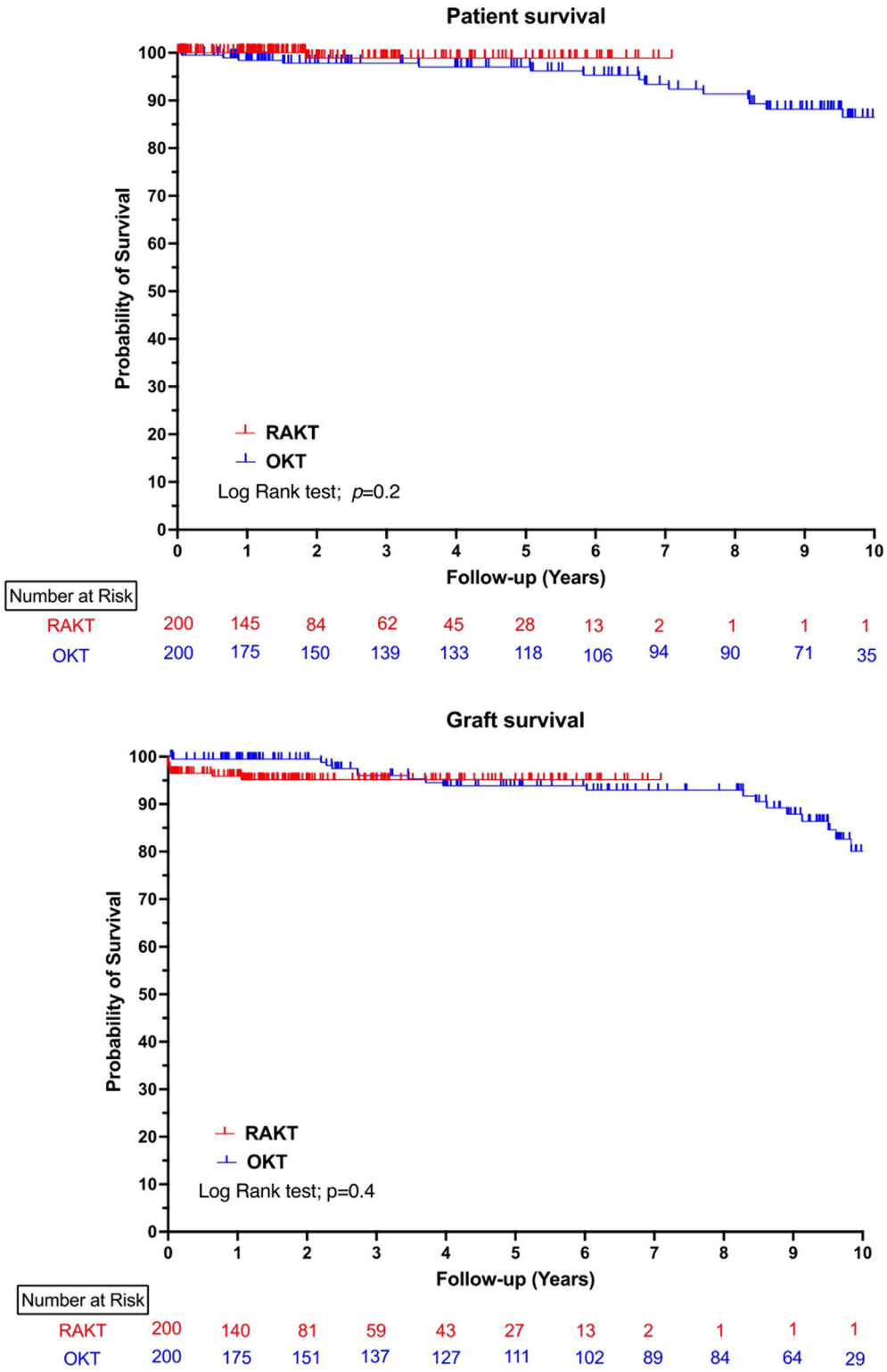


FIGURE 4 | Ten-years patient and graft survival in robotic-assisted kidney transplantation and open kidney transplantation cohorts.

Finally, the length of hospitalization was also shorter in the RAKT group (7.0 versus 9.0 days). This LOH is comparable with the average LOH reported in European countries [31, 32]. The hospital policies and the absence of ambulatory facilities may explain the longer LOH at our centre than that in other countries such as USA [33].

In the RAKT cohort, the four graft nephrectomies due to vascular thrombosis included one venous thrombosis (which occurred at the beginning of the RAKT experience) and three arterial thrombosis (one of which was due to arterial dissection during LDN). Seven conversions to open surgery occurred in the RAKT group, half of them in the first 50 cases. After the first kidney graft lost due to vein thrombosis (the 4th case), intraoperative eco-doppler US is performed to ensure the optimal graft perfusion, and to adapt the transplant position according to the resistance indexes.

Our results are consistent with the published literature. Recent systematic reviews [28, 34, 35] and series [36–39] comparing RAKT and OKT from living donor reported a lower incidence of surgical site infection in the RAKT cohort and similar midterm and clinical efficacy in comparison to OKT. However, those studies included fewer patients.

The present study is not devoid of limitations. First, this study is a retrospective and nonrandomized study with potential selection bias. Second, due to his single-institutional nature, our results may not be generalizable to all clinical scenarios. Third, The post-operative opioid requirement was not evaluated whatever the group, while several studies have demonstrated a decrease in opioid consumption using to the robotic approach [40, 41].

Thus, this study adds to a body of evidence supporting use of minimally invasive kidney transplantation techniques as equivalent to traditional open approaches regarding graft survival and patient survival and as potentially superior in terms of perioperative morbidity. Multicentric randomized controlled trial comparing the robotic and conventional approach should be essential to confirm these results but difficult to perform now with this excellent RAKT outcomes.

CONCLUSION

This study is the largest study from a European center comparing RAKT and conventional OKT from living donor. This confirms the safety and efficacy of RAKT in the setting of living donors. The combination of reduced post-operative complications rates and equivalent mid-term functional outcomes encourage the use of robotic-assisted approach.

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 Approval by the Hospital Clínic Institutional Review Board (HCB/2020/0713). 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

MaM: Participated in research design, writing of the paper, performance of the research and in data analysis. TP: Participated in research design, writing of the paper, performance of the research and in data analysis. TA: Participated in research design, performance of the research and in data analysis. CM: Participated in acquisition of data and data analysis. EC: Participated in acquisition of data and data analysis. MaM: Participated in acquisition of data and data analysis. ML: Participated in acquisition of data and data analysis. BL: Participated in acquisition of data and data analysis. IR: Participated in acquisition of data and data analysis. AV: Participated in acquisition of data and data analysis. MR: Participated in acquisition of data and data analysis. NS: Participated in acquisition of data and data analysis. FD: Participated in research design, in acquisition of data and data analysis. IR: Participated in research design, in acquisition of data and data analysis. BT: Participated in acquisition of data and data analysis. CM: Participated in acquisition of data and data analysis. LP: Participated in research design, performance of the research and in data analysis. AA: Participated in research design, performance of the research and in data analysis. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research 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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Vascular Access Management After Kidney Transplantation Position Paper on Behalf of the Vascular Access Society and the European Kidney Transplant Association

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There is no consensus on whether to ligate or preserve uncomplicated vascular access (VA) after kidney transplantation (KT), as International Guidelines do not address this issue. Enhanced survival rates of kidney grafts may elevate the risk of cardiac morbidity and mortality due to prolonged exposure to the hemodynamic effects of arterio-venous fistulas (AVF). Although VA ligation reduces left ventricle (LV) mass, its impact on cardiovascular (CV) morbidity or mortality is unclear. High-flow VAs can complicate KT patients, and immunosuppressive medication may increase these complications. Despite preserving VA for future hemodialysis (HD) use, central catheters are used in nearly two-thirds of patients. Detecting transplant patients who can undergo AVF ligation and reconstruction when returning to HD allows for flexible decision-making with a multidisciplinary approach, personally tailored to patients at their discretion. Therefore, an algorithm involving Doppler ultrasound and cardiac evaluation is advisable.

Keywords: ligation of arteriovenous fistula, kidney transplantation, AVF flow reduction, hemodialysis, kidney failure

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INTRODUCTION

The management of vascular access (VA) after kidney transplantation (KT) is a complex and unresolved issue, particularly in recipients with good allograft function and uncomplicated VA. While preservation is appropriate in cases of poor graft function or need for plasma exchange, the optimal strategy for managing a functioning VA in stable KT recipients is not yet clear. With improved graft survival—averaging 11.7 years for deceased donors and 19.2 years for living donors [1]—clinicians are increasingly confronted with the challenge of balancing future dialysis needs against potential VA-related complications, including cardiovascular morbidity.

Data from over 16,000 patients in the US Renal Data System show that only 40% had an arteriovenous fistula (AVF) in place at the time of hemodialysis (HD) re-initiation after graft failure, while nearly two-thirds started HD with a central venous catheter (CVC), despite efforts to preserve VA [2]. Meanwhile, cardiovascular disease remains the leading cause of death in KT recipients with a functioning graft, with a fivefold higher incidence compared to the general population [3, 4]. AVFs may contribute to this risk through their hemodynamic effects; evidence from randomized and observational studies has shown reduced left ventricular (LV) mass following AVF ligation [5, 6], but its effect on cardiovascular outcomes remains uncertain.

Clinical decisions regarding VA management are influenced by factors that are not yet fully defined, including the risk of future complications and the feasibility of reconstructing ligated AVFs for future HD access. This underscores the need for a multidisciplinary approach, where patient involvement and informed decision-making are crucial. Yet, surveillance and routine VA evaluations after KT are underutilized, with only 29% of physicians performing such assessments [7]. Moreover, no international guidelines currently address VA management in KT recipients.

This position paper, developed by the Vascular Access Society (VAS) and the European Kidney Transplant Association (EKITA) Section of the European Society of Transplantation (ESOT), reviews current evidence and provides a structured algorithm to support VA monitoring and individualized decision-making in KT patients.

CURRENT MANAGEMENT OF VASCULAR ACCESS AFTER KIDNEY TRANSPLANTATION

There is no consensus on managing VA in asymptomatic patients after kidney transplant (KT). Generally, nephrologists monitor VA and refer to specialists if complications arise. A multinational survey revealed no consensus about ligation of AVF after KT, and most centers do not have a defined protocol for management of AVF after KT [7]. Data on the current practice of VA management after KT and guideline recommendations are scarce. Post-transplant VA ligation is rare, occurring in 4.6% of patients according to the United States Data System [8]. The rate varies among transplant centers: 11% of centers performed ligation on over 10% of KT recipients within a year, while 43% did not perform any ligations among 248 centers. Ligation is typically for patients with steal syndrome or complications like infections and aneurysms. A significant association exists between longer durations on HD (up to 5 years) and AV access ligation after adjusting for donor factors [8]. Longer patency times may increase complications and the need for VA ligation. US data also shows that KT AV access ligation does not affect kidney graft outcomes or reduce all-cause mortality.

The type and placement of VA are also important. Synthetic grafts typically thrombose spontaneously within the first year after KT. Upper-arm AVFs are more likely to require ligation due to local problems than forearm AVFs [9]. The brachiocephalic fistula typically results in higher cardiac output than forearm AVF, leading to a greater incidence of steal syndrome and aneurysm formation [10]. Cephalic arch stenosis can cause giant aneurysms and perforation over time. The frequent stenosis site is a proximal swing segment for patients with basilic vein transposition, which can again cause aneurysmatic complications [11, 12]. Therefore, patients with proximally located AVFs should be evaluated more carefully for ligation or flow reduction.

IMPACT OF ARTERIOVENOUS ACCESS ON THE HEART AND CIRCULATION

The presence of AVFs and grafts significantly influences the CV system. These effects can be categorized based on timing: early or acute changes, which occur immediately after creation, and chronic or delayed changes, which develop over weeks or months (**Table 1**, adapted and modified from Basile and Lemonte [13]).

ACUTE CARDIAC EFFECTS OF AVF CREATION

Creating an AVF induces an immediate decrease in peripheral vascular resistance, significantly increasing blood flow through the newly created AVF (**Figure 1** Basile et al. [15]). Increased blood velocity raises the tangential pressure on the arterial wall, known as wall shear stress (WSS). WSS stimulates endothelial cells to produce vasodilatory substances like nitric oxide (NO), leading to an expansion in the vessel diameter, a reduction in systemic pressure, and the desired decrease of WSS [16]. This new hemodynamic condition places greater demands on the heart; i.e., the heart should increase its work to maintain the blood pressure and equalize the inflow with the outflow to distant organs [17]. As heart rate and stroke volume increase, so does cardiac output (CO) [the amount of blood pumped by the heart in liters per minute]. The increased stretching of cardiac myofibrils also results in elevated production of natriuretic peptides [ANP and BNP] [18]. The diameter of the feeding artery directly influences the newly created conditions of a hyperdynamic circulation. According to Poiseuille's law, a larger artery diameter will cause a higher flow through the AVF [19]. Likewise, the amount of AVF flow [Qa] and the functional condition of the myocardium influence the type and extent of changes that will manifest over time. In addition to the artery's diameter, the flow through the AVF also depends on the size of the anastomosis. Flow may decrease due to the presence and onset of stenosis, but it may also gradually increase over months and years of presence. Aneurysm formation in arteriovenous conduit is more common among younger patients with native AVF due to arterial dilatation and anastomotic remodeling [20, 21].

CHRONIC CARDIAC EFFECTS OF ARTERIOVENOUS CONDUITS

Once created and matured, the AVF continuously affects the heart and circulation. Although the adverse effect of the AVF

TABLE 1 | Early and late effects of the AVF on the heart and circulation.

Acute effects [days]	Chronic effects [weeks and months]
↓ Systemic vascular resistance	↑ Left ventricular end-diastolic volume
↑ Heart rate, ↑stroke volume	↑ Left ventricular mass and size
↑ Cardiac output	↑ Atrial chamber size
↑ ANP and BNP	Diastolic and systolic dysfunction
↑ Pulmonary flow and pressure	Pulmonary hypertension

Adopted from Basile and Lomonte [13].

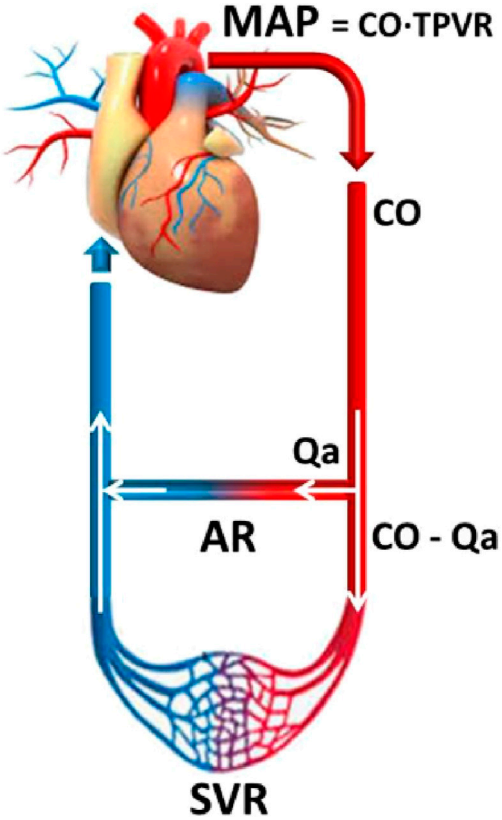

FIGURE 1 | As blood is pumped out of the left ventricle into the arteries, pressure is generated. MAP is determined by CO, TPVR and CVP, according to the following relationship, which is based upon the relationship between flow, pressure and resistance [14]: MAP = (CO TPVR) + CVP. Because CVP is usually at or near 0 mmHg, this relationship is often simplified to MAP = CO TPVR. AR and SVR are connected in parallel Basile C, et al. [13].

on the heart depends on the AVF flow (Qa), it also depends on the heart itself, as the heart is often affected by several structural and functional alterations in patients with chronic kidney disease (CKD). Therefore, no universal definition of a "safe" Qa exists, but values >1,500–2000 mL/min are usually considered as high and potentially detrimental to the heart [16, 22]. The effects of high Qa act in concert with water overload and include dilatation of all chambers, secondary valvular regurgitation, left ventricular hypertrophy, diastolic dysfunction, and pulmonary hypertension [23]. While water overload and various metabolic and endocrine changes resolve after a successful KT, the effects of fistula flow persist and may contribute to increased patient morbidity and possibly mortality. Nonetheless, direct evidence for this is still lacking. However, some previous studies revealed an early decline in left ventricular mass index (LVMI) and LV end-diastolic diameter (LVEDD) following AVF ligation [23, 24]. Rao et al. conducted a randomized controlled trial (RCT) involving two groups of patients 12 months post-kidney transplantation [5]. Both groups had initial cardiac MRI. One group underwent arteriovenous fistula (AVF) ligation, while the other was a control. A follow-up cardiac MRI 6 months later revealed a noteworthy reduction in left ventricular mass of 22.1g (95% confidence interval: 15.0–29.1) in the AVF ligation group. In comparison, the control group experienced a slight increase of 1.2 g (95% CI: −4.8–7.2) ($P < 0.001$). This result highlights the potential benefits of AVF ligation in improving cardiac health in kidney transplant recipients. Furthermore, another prospective RCT conducted by Hetz et al. showed that performing prophylactic ligation of a high-flow arteriovenous fistula (AVF) with a flow rate greater than 1,500 mL/min in asymptomatic KT recipients with stable renal function led to a reduction in both proBNP levels and systolic pulmonary arterial pressure (PAP) values [14]. Notably, none of the patients in the group that underwent AVF ligation developed high-output heart failure (HOHF). In contrast, among the patients who did not receive AVF ligation, 5 out of 13 (38.5%) developed HOHF ($p < 0.013$), indicating that *de novo* heart failure in KT recipients was more frequent in patients with the presence of a functioning AVF (adjusted hazard ratio 2.14). A recent 10-year observational cohort study of 1,330 kidney transplant patients found that those with AVF had a higher incidence of *de novo* heart failure (HF), at 58 cases per 1,000 person-years (95% CI 50–67), compared to 33 cases per 1,000 person-years (95% CI 27–41) in those without AVF, meaning that *de novo* HF was associated with the presence of an AVF [adjusted hazard ratio (aHR) 2.14 (95% CI 1.40–3.26), Moreover, the presence of an AVF was also associated with the composite CV outcome [aHR 1.91 (95% CI 1.31–2.78) [25]. Clinical presentation of the heart changes in CKD patients includes heart failure [HF] of any phenotype [with reduced, mildly reduced, or preserved ejection fraction or high-output HF] and pulmonary hypertension [15]. The progression of HF often leads to a gradual decrease in CO and to its so-called normalization of the CO to a value without the presence of an AVF, which inevitably leads to reduced blood supply to peripheral organs. This situation is called "systemic steal" and results in hypoperfusion of various organs [26]. A recent meta-analysis by Yasir et al., which included over 18,000 transplant patients, adds further evidence to previous studies. It confirms that ligation of symptomatic AVFs in high-output heart failure patients is safe and effective. Additionally, the review identified an AVF flow to cardiac output ratio greater than 0.3 as a predictive marker for the risk of acute heart failure [27].

IMMUNOSUPPRESSION AND VASCULAR ACCESS-RELATED ANEURYSMAL COMPLICATIONS

Studies suggest immunosuppressive medication may promote arterial and venous remodeling. [28–30]. Viscardi et al. reported larger AVF venous aneurysms with intense T-lymphocytic infiltrate in patients on immunosuppressive therapy [30], which are prone to thrombosis and significant thrombophlebitis requiring surgery [31]. Brachial artery aneurysm (dilatation of brachial artery >10 mm or more than 50% increase in longitudinal diameter) can be frequent and was detected in 21% of transplant patients [32]. Brachial artery aneurysm can cause ischemia of the arm and frequently requires major vascular surgery for arterial repair. AVF flow volume of more than 1,500 mL/min is associated with a 4.5-fold risk of brachial artery aneurysm formation [32]. The high flow causes upregulation of the local production of vasodilator agents and matrix metalloproteinases 2 and 9, resulting in loss of vessel wall vasoconstriction. Increased blood flow of AVF causes an increase in wall stress and a decrease in wall thickness. Elastic fiber degeneration and increased calcium and phosphate deposition can also affect the long-term [21, 33]. Ligation or flow reduction of the VA augments or prevents the increase of the brachial artery size [34]. Various case reports have shown that aneurysmal degeneration of the inflow artery is a potential serious complication and is mainly associated with immunosuppression [35–38]. These complications predisposed by immunosuppression support a strategy to close AVFs in KT patients with high blood flow, large aneurysms, and good kidney allograft function.

Malignancies confined to AVFs are rare but have been described in case series and reports. They present as angiosarcoma [39–41] and post-transplant lymphoproliferative disorder [42], confined to AVFs mostly in immunosuppressed patients. The most common presenting symptom was pain, with or without a mass. A comprehensive review revealed that of 22 unique patient cases, 19 were post-transplant, and 18 were on antirejection agents [43].

SURGICAL TECHNIQUES FOR THE INTERVENTION OF ARTERIOVENOUS FISTULAS AND GRAFTS

Revisions for reducing AVF blood flow post-KT include distal inflow, plication, or banding. Short interpositions with small-diameter prosthetic grafts show 58% primary and 71% secondary patency over 3 years [44], while distal inflow revisions demonstrate 48% and 84% [45]. AVF aneurysmography is associated with improved patency and decreased VA abandonment compared to interposition grafting at 2-year follow-up [46]. Some techniques use real-time flow measurements for precise adjustment during surgery [47, 48]. Possible complications include reoperation to reduce blood flow, early and late thrombosis, and infection. Long-term outcomes for transplant patients remain unpredictable, especially with an estimated graft survival of over 10 years.

Therefore, AVF ligation is almost certainly the most viable surgical option. The main risk of ligation, particularly for large AVFs, is that the massive reduction in blood flow in the draining AVF vein leads to thrombosis and the development of thrombophlebitis, which may cause significant discomfort. Therefore, in addition to disconnection of the AVF near the original arteriovenous anastomosis, excising particularly large or aneurysmal segments of the draining vein may be necessary. For this reason, timely management can prevent the loss of venous capital and prohibit the use of draining venous segments [forearm cephalic or upper arm cephalic vein] for future AVF creation. The complication rate of ligation of the VA is relatively limited, as approximately 5% of patients experience post-operative complications, including hematoma and wound infections [49].

LIGATION OF VA AND RECONSTRUCTION IN THE FUTURE FOR HEMODIALYSIS: SWITCH OFF AND ON

Considering the cardiac burden and the VA-related complications after KT, the ideal option would be to pause the patency of VA and reintroduce it at the time of switch to HD. Whether thrombosed from a juxta-anastomotic occlusion or surgically ligated right at the anastomosis, reconstructing an occluded AVF is possible for kidney recipients returning to dialysis, even years after occlusion. Forearm AVFs often have early anastomotic stenosis, but matured venous conduits enable successful reconstruction in most cases. Weyde et al. reported that 85 out of 112 forearm AVFs were successfully reconstructed with a one-year primary patency rate of 57.6% [50]. Another series presented the creation of a new VA after kidney failure for patients with an occluded AVF at the distal part of the dominant [87%] or non-dominant [29%] extremity [31]. Other series also present the reconstruction and immediate cannulation of the ligated/thrombosed AV fistulas at the time of switch to HD [51, 52]. The perioperative complication of ligating an uncomplicated forearm AV appeared very low [53, 54]. Reconstructing brachiocephalic AVFs at HD initiation post-KT is possible but uncommon.

Reconstructing ligated or thrombosed AVFs at HD resumption would reduce the need for CVC placement, as the venous conduit can often be cannulated immediately. Forearm AVFs can thrombose up to the antecubital fossa, but if 10–15 cm of venous conduit remains, reconstruction of inflow and outflow is feasible with thrombectomy even years later. Notably, many transplant patients with lower arm AVFs have opportunities for ligation and reconstruction. VA specialists should evaluate this option to enable more informed decision-making involving patients.

PATIENT PERSPECTIVE

Individualized care for CKD patients and access to predialysis information are crucial in nephrology. Current CKD guidelines underline the patient-centered care, with the proper access, at the right time, for the right patient and reason [55]. The European Renal Best Practice remarks that patients prioritized adverse effects of AV accesses and involvement in care, while clinicians focused on options and technical aspects like maturation and patency [56]. Living with a buzzing AVF can cause discomforting psychological and aesthetic

influence on KT patients. Among KT recipients, 23% considered ligation (2/3 for esthetics, 1/3 for heart health), 39% opposed it, and 39% had no opinion [57]. In this regard, the information from the vascular access specialist about the possibility of ligating AVF and reconstructing in the future at the time of switch to HD can have an important impact on the patient's decision for VA ligation. Some studies highlight the importance of an individualized approach to the VA after a successful kidney transplant [58].

IMPACT OF ARTERIOVENOUS ACCESS ON THE KIDNEY ALLOGRAFT

In CKD patients, creating an AVF has been linked to a slower decline in GFR. Golper et al. found that GFR decline dropped from −5.9 to −0.5 mL/min/year after AVF creation in 123 patients ($P < 0.001$), though without a control group [9]. A larger nationwide cohort of 3026 US patients in 2017 revealed GFR decline slowing from −5.6 to −4.1 mL/min/year post-AVF surgery ($P < 0.001$) [59]. Hahn Lundstrom compared GFR decline between 435 patients with VA and 309 patients with peritoneal catheter, finding both groups benefited similarly, revealing the benefit of multidisciplinary follow-up [60]. Recently, a Canadian study including a propensity-score matched cohort of future peritoneal dialysis patients without access surgery concluded that the VA placement increased the patients' awareness of their CKD condition [61]. The last two studies suggest that the key is multidisciplinary follow-up rather than hemodynamic changes.

Theories behind reduced GFR decline include ischemic preconditioning, arterial blood pressure control, and increased venous return to the lungs [62]. Ischemic preconditioning releases erythropoietin, nitric oxide, and adenosine into circulation, protecting organs from ischemic injuries [62–64]. AVF creation significantly lowers central systolic [-8%] and diastolic [-9%] blood pressure [65]. Increased venous return to the lungs boosts oxygen delivery to peripheral organs, including the kidney parenchyma [62, 66]. Considering the adverse long-term effects of hypertension on renal function, AVF ligation and the resulting rise in systemic blood pressure might negatively impact renal allograft function in KT recipients [67, 68].

The first study at KT was published in 2010 by Vajdič and coworkers, who compared kidney graft function and survival between patients with a functioning AVF 1 year after transplantation with patients with a non-functional AVF [69]. The total population included 311 patients, with a mean age of 47 ± 11 years. In a crude analysis, patients with a functioning AVF had worse renal function at 1 year [69 ± 21 mL/min/1.73 m^2] than those with non-functional AVF [74 ± 19 mL/min mL/min/1.73 m^2, $P < 0.05$]. Also, the 5-year graft survival was higher in patients with a non-functioning AVF [75%] than in those with a functioning one [60%]. In a more recent paper published in 2017, Weekers et al analyzed the impact of AVF ligation in a retrospective cohort of 285 kidney transplant recipients with a mean age of 50.2 ± 14.3 years divided into three groups: (no AVF, closed AVF, and left-open AVF). The lowest GFR slope was evident in patients who had their AVF closed [-0.081 mL/min/month] in comparison with the other two groups [-0.183 mL/min/month for patients without AVF and −0.164 with patients with left-open AVF] [70]. In line with this observation, no significant effect of access ligation on GFR was observed in the randomized clinical trial on the impact of access ligation on left ventricular hypertrophy [5].

The conflicting data from these studies do not provide clear-cut information replicating the findings observed in the general population with CKD. Ideally, a large multinational clinical trial in which patients are randomized for closure or left-open AVF after transplantation would provide the best option to prevent renal function deterioration. However, considering the potential benefit of AVF ligation on CV structure [6], this putative trial should also focus on CV events and patient survival.

PROBABILITY OF STILL HAVING A FUNCTIONAL AVF AT THE TIME OF ALLOGRAFT FAILURE

The natural progression of VA following KT was described in a retrospective cohort study of 626 patients. The study reported AVF patency rates of 82%, 70%, and 61% at 1, 3, and 5 years, respectively [31]. Their conservative approach included AVF examination at each clinical visit and ligation only in severely problematic cases. AVF ligation was performed in 24% of patients. Of 127 patients, 53 (40.1%) restarted HD with their original pre-transplant AVF, 12 (9.1%) with a newly constructed AVF, and 7 (9.4%) had the original AVF ligated and reconstructed. The rate of having a functioning AVF at the time of allograft failure in KT patients was 66%, 55% and 14.8% in presented cohorts from Scotland, Italy, and Canada [71–73], illustrating that local preferences and practices have a significant impact on VA management and outcomes. The Canadian study revealed that the 12-month predialysis and 24-month postdialysis VA creation rate was 16% and 47%, respectively [73]. Reports from the US show that nearly two-thirds of patients restart HD with catheters [2]. Therefore, transplantation nephrologists may be so focused on saving the kidney graft that they can postpone management to create AVF when switching to HD [74, 75].

THE PROS AND CONS OF LIGATING A FUNCTIONAL VASCULAR ACCESS AFTER TRANSPLANTATION

As mentioned previously, solid data regarding the long-term clinical effects of a functional VA after KT are scarce, and no international guidelines on the management of kidney transplant recipients provide guidance on post-transplant VA management [55, 56, 67, 76–78]. A multicenter survey showed that disagreement among experts among respondents was considerable regarding the decision to ligate AVF after KT, as in four out of eight cases, less than 70% of respondents agreed on the arteriovenous fistula management strategy [7]. Having a functional VA may facilitate rapid access to HD treatment in patients experiencing post-transplant complications, such as delayed graft function or allograft failure, avoiding the need

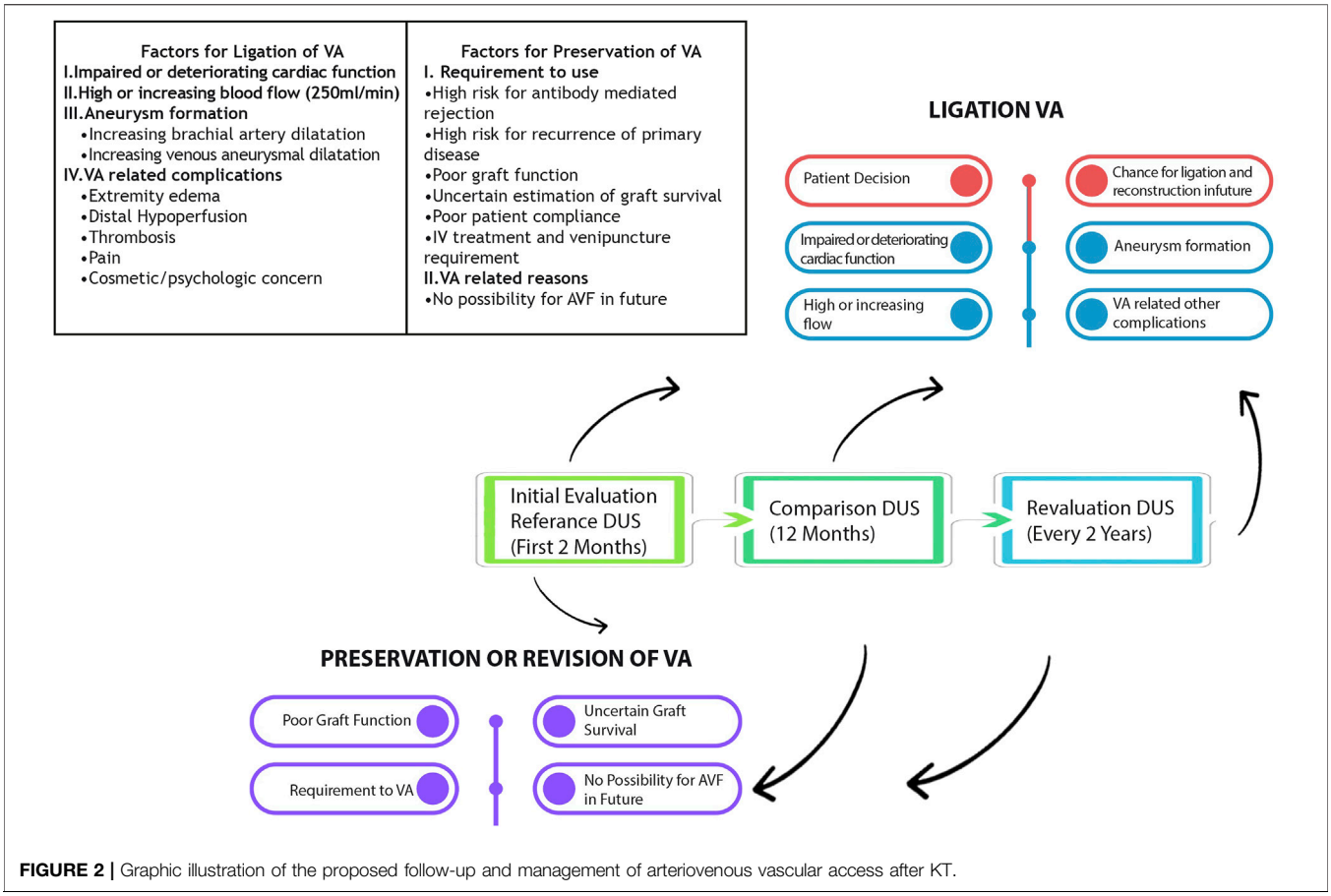

FIGURE 2 | Graphic illustration of the proposed follow-up and management of arteriovenous vascular access after KT.

for placing a CVC, which causes an increased risk of infection [79, 80]. Moreover, having an AVF may permit a straightforward initiation of pharmacological or apheresis treatments in patients with poor quality peripheral veins or VA problems developing immune-mediated post-transplant complications, such as episodes of antibody-mediated rejection and recurrence of glomerulonephritis [81]. Belatecept maintenance treatment through AVFs is a good example of IV treatment use of AVFs after KT, which prevents the risk of complications introduced by a port catheter.

In kidney transplant recipients with stable allograft function, ligation of the AVF may reverse maladaptive heart alterations such as right ventricular [RV] dilatation [82], AVF-associated volume overload leads to LV hypertrophy and cardiac remodeling [83], and diastolic dysfunction with structural heart disease [82–84]. Although unproven, this may mitigate the adverse CV clinical effects associated with a long-lasting AVF, such as LV hypertrophy [85], contributing to the increased risk of CV mortality observed among KT patients [86, 87].

Ligation may also reduce the risk of high-output cardiac failure secondary to high-flow AVF [23]. Unger et al. reported that AVF surgical ligation reduced LV end-diastolic diameter and mass indexes 2 months after surgery in stable KT patients. However, diastolic and mean arterial BP were marginally augmented in these patients after AVF ligation [88]. One randomized clinical trial on the cardiac effects of VA ligations has been published [5]. This Australian study included 63 adult patients who underwent successful KT at least 12 months prior to the intervention. MRI assessed cardiac dimensions at baseline and 6 months later. The primary outcome was LV mass reduction at 6 months, which decreased by 22.1 g in the group with AVF ligation and increased by 1.2 g in the control group [$p < 0.001$]. The cardiac output decreased from 6.8 L/min at baseline to 4.8 L/min at 6 months [$p < 0.05$] upon AVF ligation. The closure group also observed significant decreases in LV end-diastolic volumes, LV end-systolic volumes, atrial volumes, and NT pro-BNP. Subsequent follow-ups of the patients who underwent AVF ligation revealed a further reduction in LV mass 5 years after AVF ligation [6]. This trial confirms that ligation of AVF in stable post-transplant patients improves LV remodeling.

Late AVF complications in patients following KT are quite common [31, 32]. Preventing the increase in the size and the result of increasing blood flow from the brachial artery is important. Surgical intervention can cease or decrease the diameter of the brachial artery [34]. Therefore, increased blood flow through the AVF, brachial artery aneurysm, and following complications, including venous aneurysm formation, can be prevented by timely ligation or flow-reducing surgery of the VA.

PROPOSED PROTOCOL FOR MANAGEMENT OF VASCULAR ACCESS AFTER TRANSPLANTATION

Effective VA management after KT involves a surveillance protocol. Our proposed protocol is depicted in **Figure 2**. Initially, the complete VA-related medical history should be documented. Use Doppler ultrasonography to screen VA in the first 2 months post-KT, assessing blood flow, brachial artery dilatation, venous conduit dilatation, and aneurysms. If the duplex ultrasonography reveals a blood flow ≥1 L/min, cardiac evaluation is required to estimate VA-related cardiac morbidity, also considering other comorbidities such as diabetes mellitus and hypertension. Echocardiography should establish baseline cardiac parameters for comparison with follow-up measurements at the end of the first year post-KT. Follow AVG conservatively unless there are cardiac complications, as they usually thrombose spontaneously. Monitor atypical VA conduits and upper arm VAs more carefully due to their risk of aneurysms. Refer VAs with cardiac or access-related complications to specialists immediately. Consider ligation of non-complicated VAs by the end of the first year post-KT.

Evaluating the ligation of VA 1 year post-KT is crucial for several reasons. First, it allows assessment of kidney graft survival, ensuring preservation of VA in recipients with poor outcomes. A banding operation can reduce VA blood flow to preserve it for recipients requiring VA after KT. Second, most of the spontaneous thrombosis of the VA occurs during the first year after KT. Finally, a one-year follow-up helps monitor changes in VA blood flow, aneurysm progression, and their impact on cardiac health.

The evaluation of VA in the initial year after KT should include Doppler ultrasound and examination by a VA specialist. The VA specialist should identify the VA likely to cause future complications. The VA with increasing blood flow, causing increasing brachial artery dilatation, and aneurysm size of venous conduit compared to the initial duplex Ultrasound evaluation should be referred for ligation if the estimated graft survival is over 10 years. Determining if the VA can be reconstructed after ligation is crucial for transplant failure cases, particularly with non-complicated forearm AVFs. A multidisciplinary team, including a nephrologist, cardiologist, and VA specialist, should decide on preservation and ligation in consultation with the patient. In case of preserving the VA, the evaluation should be repeated every 2 years or earlier in case of cardiac complications or VA-related problems, especially when the blood flow of the VA is higher than 1.5 L/min.

CONCLUSION

The VA of KT transplant recipients is a modifiable factor that could significantly impact their burden of cardiac disease. Recent studies have demonstrated that ligation of VA results in a substantial and permanent reduction of cardiac hypertrophy. Prospective studies are necessary to evaluate whether AVF closure in asymptomatic patients offers benefits for CV mortality.

High-flow VAs can also cause arterial and venous aneurysmal complications in KT patients, which can be enhanced using immunosuppressive medication. Therefore, implementing a VA surveillance program is essential for improving VA management post-KT. Detecting the subset of transplant patients who may benefit from technical interventions such as ligation and reconstruction of AVFs, particularly when switching back to HD, allows for more informed and patient-involved decision-making regarding VA ligation.

Although the proposed algorithm is not entirely evidence-based, it represents the best management strategy for detecting cardiac and VA morbidity after KT. This approach can contribute valuable data that is currently missing from the literature. Given the favorable prognosis of allografts today, the decision to ligate VA can be considered more liberally, even without VA-related complications, for patients with well-functioning grafts. The decision to maintain or ligate the VA should be made by a multidisciplinary team, with active participation from the patient in the decision-making process.

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Intensive Care to Facilitate Organ Donation: Insights From the French Guidelines

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Intensive care to facilitate organ donation (ICOD) is being discussed internationally without reaching a consensus. The aim of this paper is to share with the community the recently published French ICOD guidelines, focusing on two main ethical issues: the ethical acceptability of antemortem interventions during the ICOD process, and the ethical acceptability of considering controlled donation after circulatory death during the ICOD process. These issues raised by the tension between end-of-life care and the possibility of OD deserve to be addressed as they challenge the consideration of ICOD as a routine part of end-of-life care.

Keywords: intensive care to facilitate organ donation, devastating brain injury, brain death, controlled donation after circulatory death, antemortem intervention

INTRODUCTION

Intensive care to facilitate organ donation (ICOD) has been defined in the Spanish guidelines as the initiation or continuation of intensive care in patients with a devastating brain injury, in whom medical and surgical treatments for curative purpose have been deemed futile and who are considered possible organ donors with the aim of incorporating the option of donation after brain death (DBD) into their end-of-life care plan [1, 2]. ICOD supports the concept that donation should considered as a routine at the end of life [3–5]. This strategy has been developed mainly in Spain [1, 2, 6, 7] and is being discussed internationally without reaching a consensus [8–14]. The idea that the intensive care measures are not solely made in the best interests of the patient, but must also consider the interests of a third party, in this case the patient awaiting for transplantation, is challenging [15, 16].

In France, ICOD was mentioned as early as 2010 in expert recommendations on stroke management with a weak agreement [17]. However, no specific French recommendations on this topic have existed until now. The French ICOD guidelines have just been published, taking into account the specific framework and the professional codes (Supplementary file 1) [18]. A working group was set up that included experts in intensive care medicine and organ donation (OD), as well as experts in the humanities and representatives of healthcare system users and of donors' families. The French guidelines are organized into several sections. The first section addresses the key elements required to implement an ICOD procedure within a healthcare facility. This includes prior institutional reflection on staff information and training; identification by the OD team of relevant partner departments (such as hospital emergency departments, neurology and neurovascular

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intensive care units); and the collaborative development and formalization of a local protocol with the OD team, partner departments, and ICU staff. A second section defines the ICOD pathway and describes the successive steps involved, which we presented in the first part of this manuscript. All the authors participated in this national-level working groups organized by the *Agence de la Biomédecine* to develop these recommendations.

As each country has its specific legal regulations, medical codes, and cultural backgrounds [19], we would like to share these guidelines with the community by focusing on the two main issues: are antemortem intervention for donation ethically acceptable within the ICOD pathway ? How should controlled donation after the circulatory determination of death (cDCD) be integrated within the ICOD pathway?

THE FRENCH ICOD GUIDELINES

In the French guidelines, ICOD is defined as the process by which a patient with a devastating brain injury and a severe coma (Glasgow Coma Scale score <8 or rapidly worsening coma), for whom no therapeutic plan is available (i.e., whom medical and surgical treatments for curative purpose have been deemed futile [20]), and who has a high likelihood of progressing to brain death (BD), is admitted to intensive care unit (ICU) solely for the purpose of OD. This process relies on a multidisciplinary approach and includes the evaluation of the clinical context, logistical support, and several discussions with the patient's relatives- including an *early interview* to inform about ICOD and to seek consent and authorization. This process involves the patient, their relatives, and the caregivers in end-of-life support. The *early interview*, as part of an ongoing communication, is defined as a discussion between the caregivers and the relatives with the aim of raising the possibility of post-mortem organ and tissue donation, and documenting any refusal expressed by the patient during his or her lifetime, as well as the relatives' agreement with this approach. Legally, France applies an opt-out system: everyone is presumed to be a donor unless they have expressed their refusal to be a donor during their lifetime. This refusal can be expressed in three ways: registration on a national refusal registry (which can only be consulted after death has been formally declared), written testimony, or oral testimony. In practice, an interview with the relatives is always conducted. Its purpose is first to gather any possible testimony of refusal expressed by the patient during their lifetime, to comply with the legal framework. Beyond this legal requirement, engaging with relatives is also essential to ensure that the donation process remains acceptable to them, to avoid conflicts, and to preserve trust through full transparency in what is an emotionally very difficult moment. In France, as in many other countries, national guidelines and best practice recommendations explicitly require that these interviews be systematically conducted by the organ donation personnel. This ensures both compliance with the legal framework and alignment with international standards aiming to optimize donation discussions.

The French definition of ICOD differs slightly from the original Spanish definition in several important respects. In Spain, ICOD is understood to include both the initiation and continuation of intensive care for the purpose of OD. In contrast, the French guidelines specifically address the management of patients with devastating brain injury who are not yet in the ICU but rather in partner services (such as emergency departments or neurology units), who, in the vast majority of cases, are not intubated at the time of initial assessment, and for whom a decision has been made not to admit them to the ICU for a therapeutic plan. They do not include the referral of patients who have already been admitted to the ICU after having been placed on invasive ventilation by emergency teams, either outside or inside the hospital, and for whom the ICU team has decided - either at the time of the initial assessment or after several hours or days of treatment - that no therapeutic plan is possible, but that intensive care could nonetheless be initiated solely for the purpose of OD [20]. For these patients already admitted to the ICU, it is recommended to prioritize discussing OD after the BD diagnosis, while informing the family of the imminent (i.e., no early interview). An early mention of OD should only occur if the family specifically inquires about the continuation of intensive care.

The process must follow a series of steps (**Figure 1**). Two conditions must be met prior to the ICOD process: (1) the absence of therapeutic plan must be established by the physician in charge in the partner department outside the ICU, with input from at least one expert (such as neurologist, neurosurgeon, neurointensivist) and with the involvement of the patient's caregivers; and (2) the patient's relatives must have been informed by the senior physician in charge of the diagnosis, the severity and life-threatening nature of the condition, the absence of a therapeutic plan, and the death to come. Caregivers must ensure that the relatives have fully understood this information. From this point, the process proceeds through four steps: (1) identification of the patient as a possible donor by the physician in charge outside the ICU; (2) referral to the OD team, who, in collaboration with the ICU physician, will assess the feasibility of OD; (3) discussions with the relatives, including an early interview regarding OD; (4) admission to the ICU for the sole purpose of OD, while providing appropriate end-of-life care. The physician in charge outside the ICU is encouraged to consult the OD team before making any statement regarding the presence of a contraindication or age limit, in order to avoid inappropriate exclusions that could result in the loss of potential donors.

The *early interview* must be conducted by at least two people, a senior physician–preferably the most experienced physician available for this type of interview - and a member of the OD team. It should take place in a room located close to the patient's care unit, designed to accommodate all relatives and caregivers, and providing a comfortable, quiet, and dedicated setting for the interview. The timing of the early interview requires caregivers to consider the relatives' experience and the patient's clinical condition, respecting the steps of the process. This interview must balance transparency in the information provided with acknowledgment of the uncertainties regarding the outcome of the process. It should be carefully prepared by the caregivers, including sharing all available information, defining roles, and agreeing on objectives. A summary of the interview must be

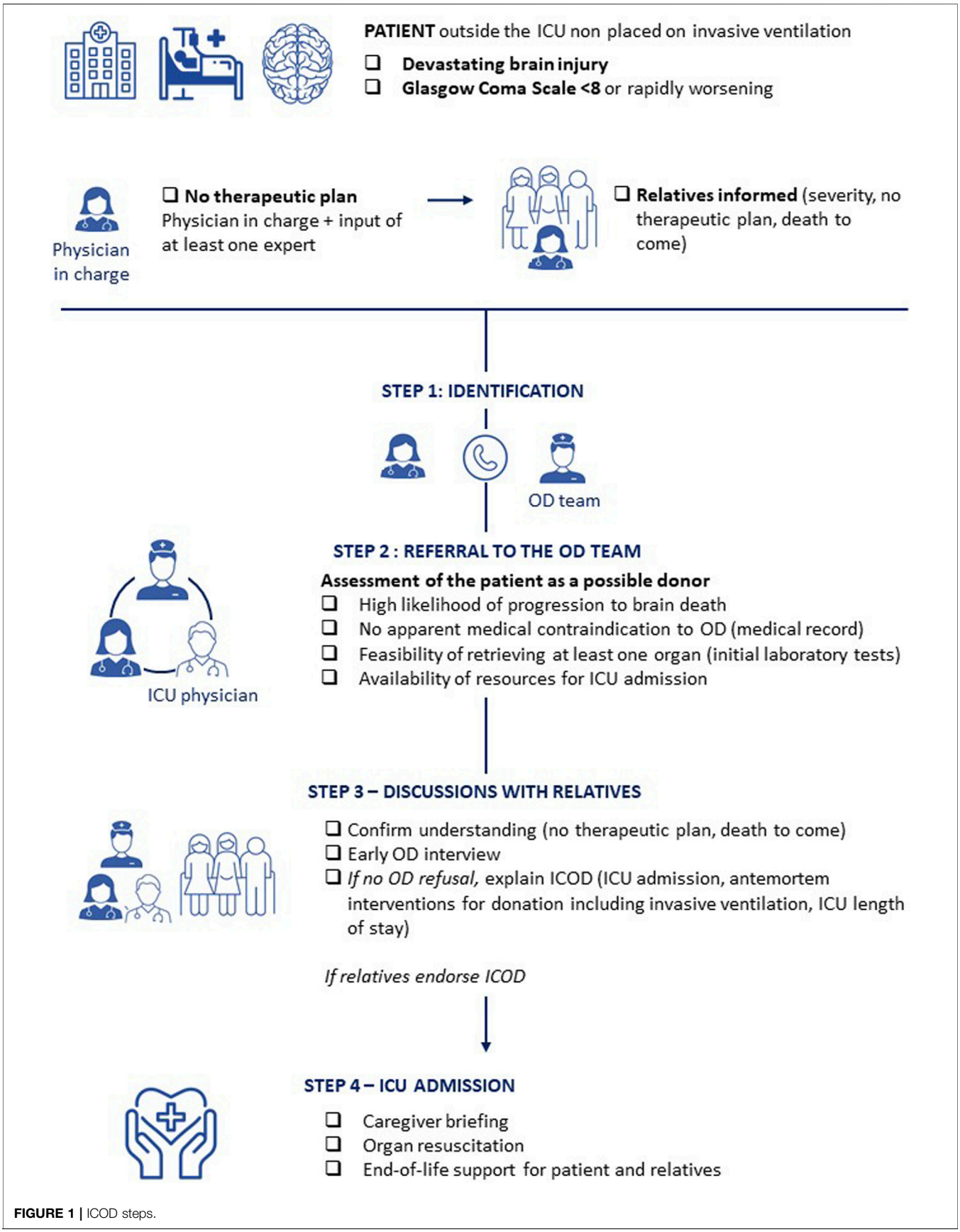

FIGURE 1 | ICOD steps.

documented in the patient's medical record, and the interview should be evaluated using a debriefing grid. During the early interview, if there is no refusal, the relatives are informed of the need for ICU admission and antemortem interventions for OD, including invasive ventilation, as well as the expected ICU length of stay, which will not exceed a few days. If relatives agree to this process, the patient is admitted to the ICU for the sole purpose of OD while ensuring appropriate end-of-life care.

All caregivers are briefed on the objectives of ICU admission, which include end-of-life care and organ resuscitation in view of potential OD. The presence of relatives should be facilitated throughout this end-of-life phase. Throughout the process, support for the relatives and ongoing reassessment of the ICOD pathway will be provided by ICU and OD team professionals. Relief of suffering must be ensured, even if suffering cannot be assessed due to the patient's neurological status.

We now propose a more detailed examination of two issues that emerged during the development of these guidelines.

ARE ANTEMORTEM INTERVENTION FOR DONATION ETHICALLY ACCEPTABLE WITHIN THE ICOD PATHWAY?

Antemortem interventions for donation refer to any clinical procedure or test performed before death with the purpose of facilitating OD, which would not otherwise occur in the absence of consideration of donation One of the main ethical concerns regarding ICOD The first issue is the acceptability of these interventions.

The identification of a patient as a possible donor by the physician in charge outside the ICU is the most critical step in the ICOD process. At this stage, the patient is both a person at the end of his or her life who requires palliative care and a potential organ donor. The initiation of intensive care measures for the purpose of OD, including invasive measures such as invasive ventilation, should be guided by the patient's wishes. Within the French legal and regulatory framework, the wishes of a patient who is unable to express them must be established by consulting any advance directives, as well as through testimony from the trusted person designated by the patient, or, failing that, from the relatives, regarding any wishes previously expressed by the patient.

In an opt-out system, it is essential to distinguish between presumed consent for OD and presumed consent for antemortem interventions. Presumed consent applies to post-mortem organ procurement and does not necessarily extend to antemortem interventions for donation, such as mechanical ventilation Even in situations where relatives report that the patient explicitly expressed support for OD, whether the patient also agreed to undergo antemortem interventions for donation remains a question that deserves careful consideration, particularly if these interventions may be associated with risks, burden, or suffering for the patient. These antemortem interventions, although intended to benefit recipients, offer no direct benefit to the dying patient and may conflict with the principle of non-maleficence. Some individuals may support OD but nonetheless oppose antemortem interventions for donation. The routine use of such interventions risks undermining public trust if they are perceived as prioritizing recipients' interests over the dignity of dying individuals. Striking a balance between respecting the patient's autonomy regarding OD and avoiding harm through invasive antemortem interventions is a delicate and ethically complex challenge.

The most critical situation for questioning the ethical acceptability of these antemortem interventions is when they become necessary for organ preservation before the patient's wishes can be established through consultation with their relatives.

On the one hand, to support the use of antemortem interventions for donation even before knowing the patient's wishes, one could invoke the French legal context of an opt-out system. In an opt-out system, as long as it there is no evidence that a patient has expressed opposition to OD, they are presumed to be a donor. Consequently, it could be argued that presumed consent might also extend to antemortem interventions for donation. This opt-out framework allows individuals to easily register their refusal, thereby simplifying and accelerating the OD process while aiming to increase the availability of organs for transplantation. By balancing the need for organ availability with respect for individual autonomy, this system supports the ethical principles of solidarity and medical necessity. This argument is supported by the fact that 80% of people in France say they are in favour of OD after their death [21]. Initiating such interventions in this situation is also a way of considering OD and transplantation as public health priorities. To support these antemortem interventions for donation even before knowing the patient's wishes, one might argue that admission to intensive care could improve the quality of end-of-life care for patients and their families, or provide additional time to confirm the initial prognostic assessment [12]. However, we challenge these claims, advocating instead for the development of high-quality end-of-life care strategies within emergency or neurology departments, together with the implementation of relevant and robust prognostic tools.

On the other hand, initiating antemortem interventions for donation even before knowing the patient's wishes carries the risk of violating the patient's potential refusal of OD or at least their preference not to be admitted to an intensive care unit at the end of their life solely for the purpose of OD, even if they had not explicitly opposed OD itself.

At this stage of the process, the guidelines distinguish between two situations: (1) if the patient does not present with cardiovascular or respiratory failure, the early interview with relatives must take place before any antemortem interventions for donation, such as invasive ventilation, are initiated. These interventions are only undertaken in the absence of any opposition expressed by the patient during their lifetime, in order to comply with the opt-out legal framework, and when the ICOD donation process is also acceptable to the relatives, so as to maintain trust and transparency during this sensitive time; (2) if, however, the patient presents with immediate

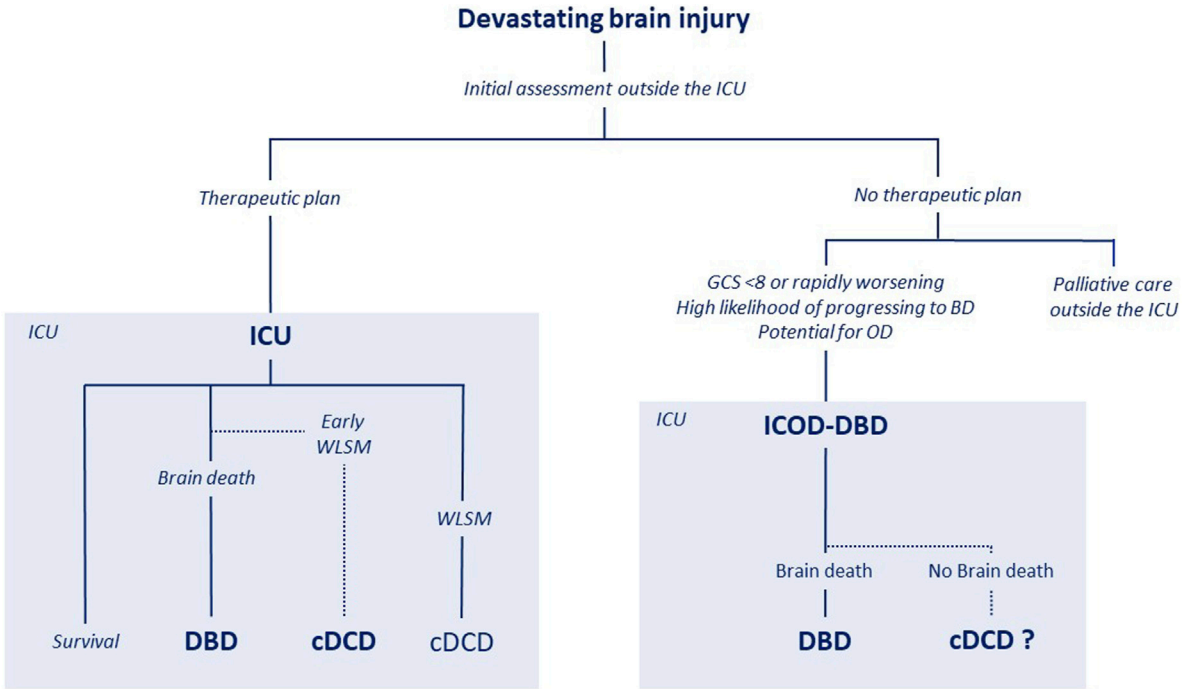

FIGURE 2 | ICOD, DBD and cDCD pathways.

cardiovascular or respiratory failure, antemortem interventions for donation may be initiated before the patient's wishes are formally confirmed during the early interview, provided that this decision is made in a transparent and collegial manner involving all caregivers. This approach is more cautious than the Spanish guidelines, which prioritize invasive ventilation and patient stabilization in such circumstances to maximize OD opportunities [2]. The French guidelines leave the possibility for caregivers to consider this strategy as ethically questionable. In any case, the priority must always be the relief of suffering. Invasive mechanical ventilation **is never considered as a means to relieve suffering.** In such cases, these interventions are not performed in the patient's best interest, particularly when they may prolong the dying process or cause discomfort. Their use may instead be considered within a **separate ethical framework**, namely, the preservation of organ viability for potential OD—which serves the interest of third parties (future recipients).

HOW SHOULD cDCD BE INTEGRATED WITHIN THE ICOD PATHWAY?

The second issue concerns the ethical acceptability of integrating controlled donation after the circulatory determination of death (cDCD) into the ICOD. For a clearer and more comprehensive understanding of the different pathways discussed throughout this manuscript, readers are invited to refer to **Figure 2**, which provides a visual summary and clarification of the key processes and decision points described in the text.

Currently, in both Spain and France, the ICOD pathway is primarily considered for patients with devastating brain injury who have a high likelihood of progressing to BD. The aim is to integrate DBD into end-of-life care planning–a process that could be considered as a ICOD-DBD pathway. Only in cases where progression to BD does not occur after several days of observation and reassessment in the ICU may cDCD pathway be considered as a secondary option. This situation may arise as evaluating the probability of progression to BD based on clinical and radiological criteria is not always straightforward, especially in elderly patients. Although advanced age may limit eligibility for certain types of OD, these patients may still be considered for OD under extended criteria or tissue donation. In assessing the likelihood of BD, the intensivist plays a key role. At the end of this period of observation and reassessment, if BD has not occurred, is it ethically acceptable to consider cDCD?

There is currently no international consensus regarding this pathway. The Spanish guidelines explicitly state that if a patient does not progress to BD, cDCD may be considered as an option and be offered to the family [2, 7]. In Spain, cDCD donors account for 20%–30% of actual ICOD donors [7, 22]. In contrast, the French guidelines specify that if the patient does not progress to BD, life-sustaining measures should be withdrawn according to the ICU protocol until death occurs. The French guidelines chose not to explicitly mention the possibility of cDCD as an outcome of an ICOD-DBD pathway, while nevertheless not excluding this alternative.

This choice reflects a precautionary approach intended to limit the risk of a potential shift toward a systematic ICOD-cDCD pathway, which raises two main concerns. First, there is a risk that prognostic evaluation—particularly of neurological outcomes in patients with brain injury—might be influenced by the potential of OD. In other words, OD could shape the prognostic judgment, leading to an early transition from a curative to a non-curative approach before a thorough neurological assessment has been completed. Second, there is a risk of progressively normalizing the integration of OD into end-of-life care, shifting from a palliative care model toward an organ-donation-driven end-of-life framework. Such a development would only be ethically acceptable if it fully respects the patient's wishes, guarantees the quality of end-of-life care, and preserves the interests of both families and healthcare professionals. This issue is central, as it challenges the future orientation of palliative care more broadly—at least for patients without contraindications to OD. Finally, it seems difficult to envisage integrating cDCD within the ICOD pathway while concerns about transparency and communication regarding cDCD remain significant in France. Should a patient with a high likelihood of progressing to BD be admitted to the ICU and placed on invasive ventilation solely for the purpose of OD? Yes. Should every end-of-life patient be admitted to the ICU and placed on invasive ventilation, only to subsequently withdraw life-sustaining measures under continuous and deep sedation for the sole purpose of OD? Not sure. Including the possibility of ICU admission solely for the purpose of OD within end-of-life care planning remains a challenging issue. Experts believe that the French medical community continues to hold ambivalent views on this issue. In practice, many of those patients will not be eligible for cDCD, given that the current age limit for cDCD in France is 71 years. Most patients under the age of 71 with severe coma related to devastating brain injury are already placed on invasive ventilation during the initial phase of management pending a full assessment of the clinical condition and prognosis. Moreover, the French healthcare system is organized in a specific way, with pre-hospital medical teams and a high capacity of critical care resources.

We have just discussed cDCD as a possible outcome of a DBD-ICOD pathway, in which a patient with a devastating brain injury does not progress to BD for medical reasons after several days in the ICU. However, it is also necessary to consider situations in which a patient with a devastating brain injury could be included directly in a cDCD pathway because a decision to withdraw life-sustaining treatment was made prematurely—whereas continued observation might have allowed progression to DD. This scenario represents an overlap between a DBD-ICOD pathway and, from the outset, a cDCD-ICOD pathway. This second situation raises two concerns: first, the risk of making end-of-life decisions too early, before gathering all prognostic information required for a robust neurological assessment; and second, the risk of contributing to a broader shift from DBD toward cDCD, which, at present, is associated with fewer utilized donors and fewer organs transplanted per utilized donor.

CONCLUSION

Organ donation is a public health priority, as the gap between patients awaiting transplants and those identified as potential donors continues to grow [23]. Integrating OD as a routine part of end-of-life care remains challenging. The issues arising from the tension between providing high-quality end-of-life care and the pursuit of OD are complex. Supporting patients and their relatives at the end of life must always take priority. Particular attention should be paid to communication and transparency in order to strengthen public trust in OD.

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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 authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

GENERATIVE AI STATEMENT

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REVIEW
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Current Usage of Extracorporeal Photopheresis in Solid Organ Transplantations in Europe: A Narrative Review

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Solid organ transplantation (SOT) faces significant challenges in managing allograft rejection, with current immunosuppressive therapies often associated with substantial adverse effects. Extracorporeal photopheresis (ECP) has emerged as a promising adjunctive treatment for rejection prevention and management in heart and lung transplants, with growing evidence supporting its use in kidney and liver transplants. Despite this, the availability of ECP and its place in standard treatment pathway is widely variable across Europe. This narrative review, supported by a European survey of 51 transplant clinicians, highlights the current usage of ECP in SOT. Findings reveal that ECP is primarily used for recurrent rejection in heart and lung transplants, with limited application currently in kidney and liver transplants. ECP has shown some efficacy in managing acute and chronic rejection, and stabilizing graft function. Barriers including lack of standardized protocols, availability of ECP, lack of high-quality clinical trial data and lack of a defined mechanism of action hinder its broader adoption. Future directions include the development of standardized protocols, multicenter registries, and further controlled clinical trials to define the role of ECP. Increased awareness, cost-effectiveness studies, mechanistic studies and equitable access are essential to integrate ECP into routine SOT management.

Keywords: transplant, extracorporeal photopheresis, solid organ transplant, ECP, solid organ transplantation (SOT), SOT

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INTRODUCTION

Prevention and management of allograft rejection urgently require more effective and safer therapeutic solutions. Current immunosuppressive therapies used in solid organ transplantation (SOT) are associated with substantial adverse effects, and there is a need for therapies that can provide immunomodulation while minimizing the negative impact of immunosuppression [1–4]. Extracorporeal photopheresis (ECP) is an immunomodulatory therapy currently recommended in international guidelines as an adjunctive treatment for the prevention and management of organ rejection in heart and lung transplantations, with growing evidence supporting its use in kidney and liver transplantations as well.

ECP involves the collection of leukocytes, their exposure to a photosensitizing agent (8-methoxypsoralen), ultraviolet A (UVA) light, and subsequent reinfusion into the patient [5]. This process has been shown to dampen immune responses, making it particularly valuable in the context of SOT, where balancing immune suppression to prevent rejection while minimizing infection risk is critical. Initially approved for the treatment of T-cell cutaneous lymphomas [6], ECP has since been used in graft *versus* host disease (GvHD) developed after allogeneic hematopoietic-cell transplantation and rejection of transplanted solid organs [7].

Despite the growing body of evidence supporting the use of ECP in SOT, access to ECP and its application remains inconsistent across European transplant centers [3]. Variability in clinical protocols, limited awareness among healthcare providers, lack of understanding of ECP mechanisms and the high upfront costs of ECP equipment are some of the barriers to its widespread adoption [8–10].

This narrative review is supported by a recent survey conducted by ESOT and Bryter Inc that aimed to understand current usage of ECP in solid organ transplantations in Europe. A 25-min online questionnaire was conducted May-August 2024 in accordance with privacy and data protection codes of conduct. The study complied with ethical and privacy principles for research such as the Declaration of Helsinki and GDPR. The usability and technical functionality of the electronic questionnaire had been tested before fielding the survey. The sampling frame consisted of transplant clinicians who were recruited through targeted lists provided by ESOT and were screened and profiled to ensure good representation of the European market. Transplant surgeons/cardiologists/nephrologists/pulmonologists, cardiac surgeons, general surgeons, nephrologists, and hepatologists involved in post-operative treatment and management of patients with solid organ transplantation (kidney, heart, lung, or liver) were invited to take part. Informed consent was obtained from participants at the beginning of the survey, and no personal or identifiable data was collected. Out of a total of n = 734, n = 51 completed the survey. The sample consisted of n = 51 clinicians across Europe: Belgium, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Romania, Spain, Switzerland, and the United Kingdom.

CURRENT USAGE OF ECP IN SOLID ORGAN TRANSPLANTATION

European Survey Findings

The European survey found center-based protocols are the primary clinical rationale for the approach taken regarding treatments to prevent post-transplant rejection across organ types (**Figure 1**). Clinical trial evidence informs protocols, and the majority of clinicians will take trial evidence into consideration when deciding on treatments.

Oral or IV steroids are the most prescribed first line treatment for T cell mediated rejection in solid organ transplant (**Figure 2A**). For acute antibody mediated rejection, plasmapheresis, IVIG and Rituximab are the most prescribed first line treatments (**Figure 2B**). Likewise for chronic antibody mediated rejection, IVIG, plasmapheresis and Rituximab are the most prescribed first line treatments (**Figure 2C**). ATG, Oral or IV steroids, Rituximab, and IVIG are the most prescribed first line treatments for recurrent rejection (**Figure 2D**). First line treatments prescribed are determined by rejection type; ECP is

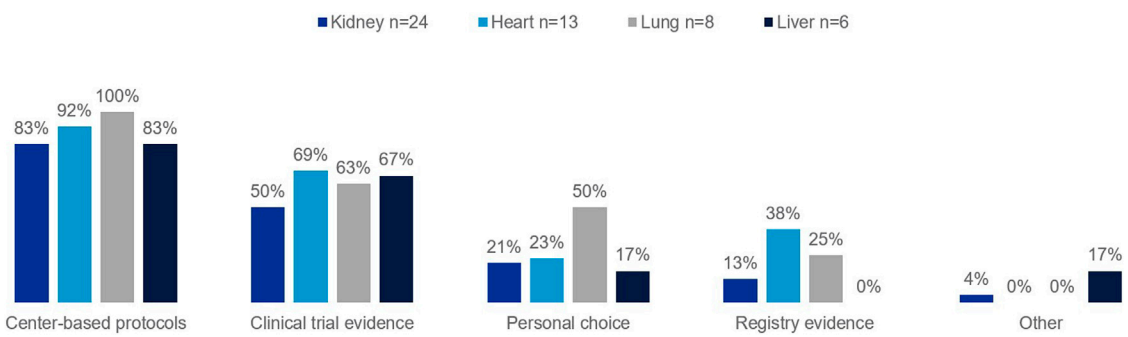

FIGURE 1 | Percentage of European clinicians using each of the following as part of their clinical rationale for approach taken regarding treatments to prevent against rejection in transplant recipients, by organ type.

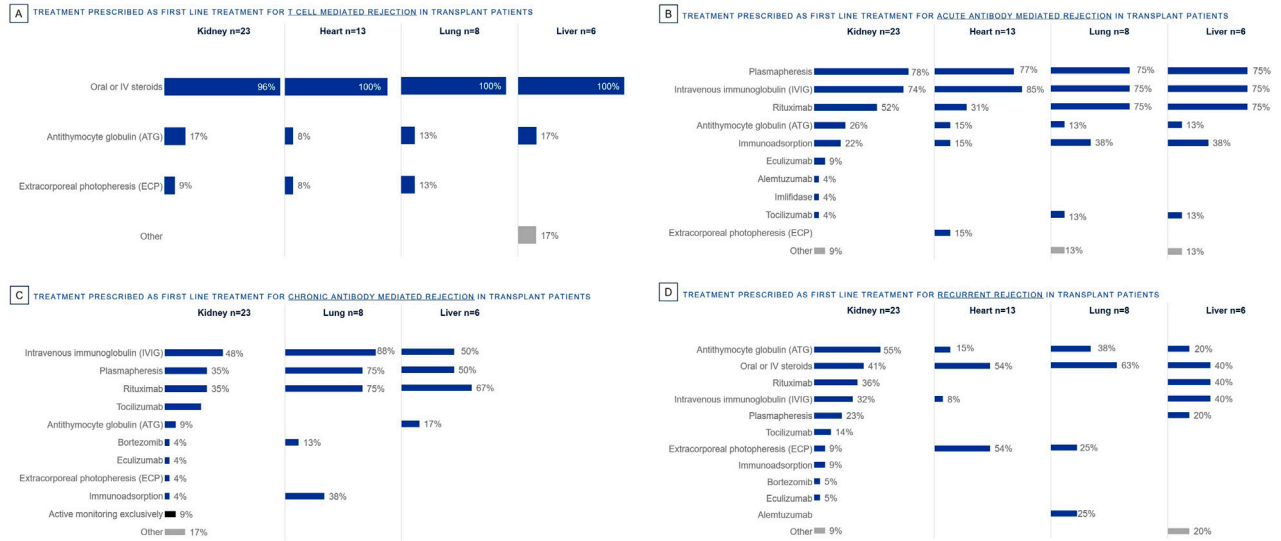

FIGURE 2 | Percentage of European clinicians using each treatment first line by organ type, for the following rejection types: **(A)** T Cell Mediated Rejection, **(B)** Acute Antibody Mediated Rejection, **(C)** Chronic Antibody Mediated Rejection, **(D)** Recurrent Rejection.

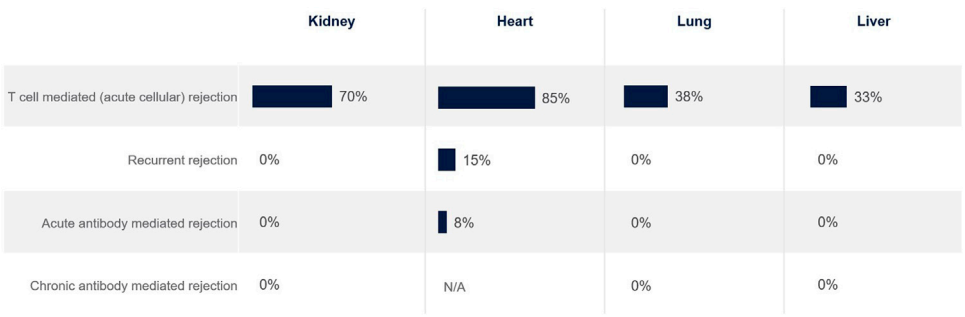

FIGURE 3 | Percentage of European clinicians 'very satisfied' with current treatments for transplant recipients, by organ type.

used only by some in first line, specifically in T cell mediated (lung 13%, kidney 9%, heart 8%), acute antibody mediated (heart 15%) or recurrent (heart 54%, lung 25%, kidney 9%) rejection.

Satisfaction with current treatments is very low for almost all rejection types, except for T cell mediated rejection in kidney and heart transplantation (but not lung and liver) (**Figure 3**). T cell mediated rejection often responds well to standard treatments, protocols are well-established and have clear diagnostic criteria. There is a major need for more efficacious and well tolerated treatments across all rejection types.

The top unmet needs in SOT tend to be grouped per rejection type rather than organ type (**Figure 4**). For T cell mediated rejection, top unmet needs were a lack of personalized treatment for rejection (kidney, lung), as well as risk of infection (heart) and lack of alternative therapies (liver). For acute antibody mediated rejection, top unmet needs were lack of clear diagnosis and disease definition (heart, lung), lack of alternative therapies (kidney), and lack of targeted therapies (liver). For chronic rejection, top unmet needs were ability to slow disease progression (kidney, heart, lung) and lack of treatment efficacy (liver).

Most clinicians surveyed were aware of ECP as a therapy option for kidney (69%), heart (63%), and lung (57%) transplants (**Figure 5**). Fewer were aware of ECP for liver transplants (24%).

The top barriers to the widespread adoption of ECP in SOT is the lack of standardized clinical protocols (kidney, heart, lung, liver) and reimbursement/cost challenges (lung) (**Figure 6**).

Those focused on heart and lung transplants have higher rates of routine access to ECP as a therapy option at their centers (77% and 63%, respectively), whereas the rate is lower for those focused on kidney and liver (42% and 33%, respectively) (**Figure 7**). Those with no access to ECP at all were those who treat kidney

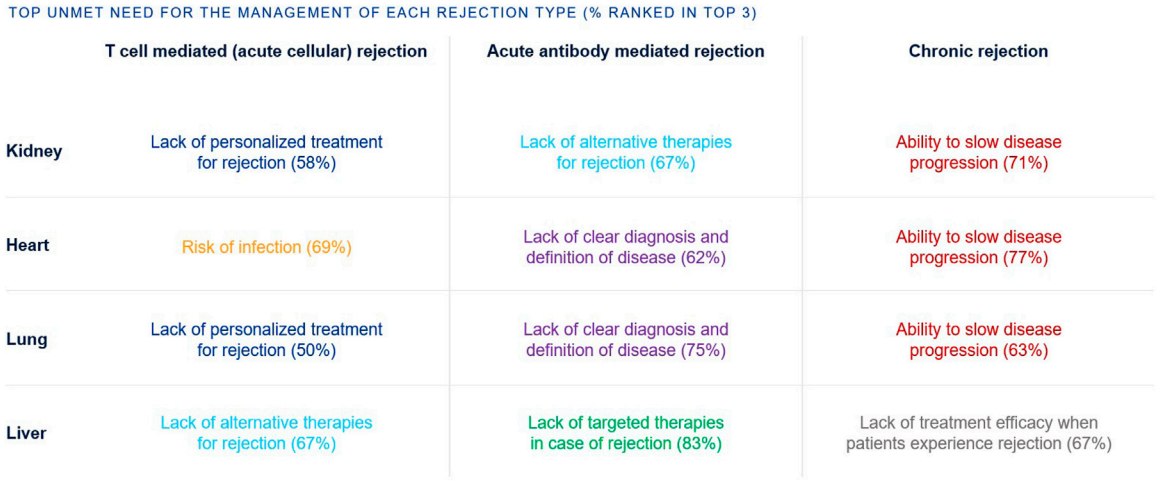

FIGURE 4 | Percentage of European clinicians ranking each unmet need in the top 3 unmet needs for the management of transplant recipients, by rejection type and organ type.

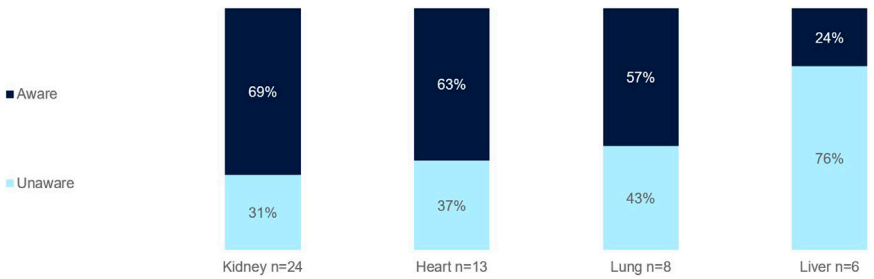

FIGURE 5 | Percentage of European clinicians aware of ECP as a treatment option for SOT per organ type.

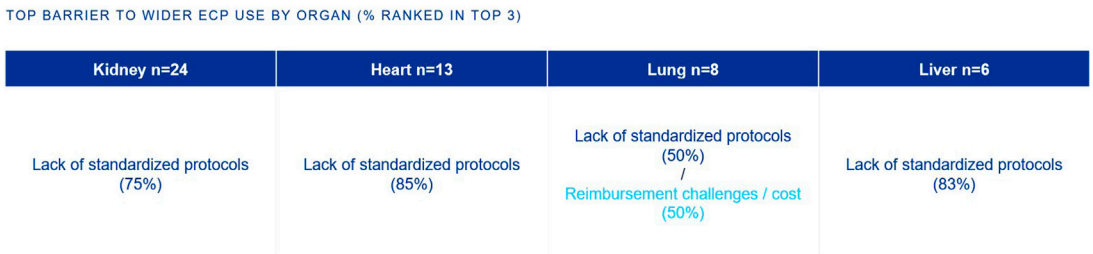

FIGURE 6 | Percentage of European clinicians ranking each barrier in the top 3 barriers to wider ECP use, by organ type.

(46%), liver (33%), and heart (8%). When asked what would encourage use of ECP in transplant management, top reasons included more robust clinical trial data and the development of a standardized protocol (**Figure 8**).

ECP in Solid Organ Transplantation

Heart Transplantation

A major cause of mortality and morbidity in heart transplant recipients is cardiac allograft vasculopathy (CAV) [11]. Acute rejection is also a significant risk in the first year following heart transplantation [12]. ECP has been widely studied in heart transplantation, particularly for acute cellular rejection (ACR) and antibody-mediated rejection (AMR). It is useful in cases where patients suffer from steroid-resistant or recurrent rejection or where reducing immunosuppressive drug toxicity is a priority. ECP has been employed as an adjunct therapy to dampen immune responses and decrease dosage of standard immunosuppressive regimens, which are associated with events

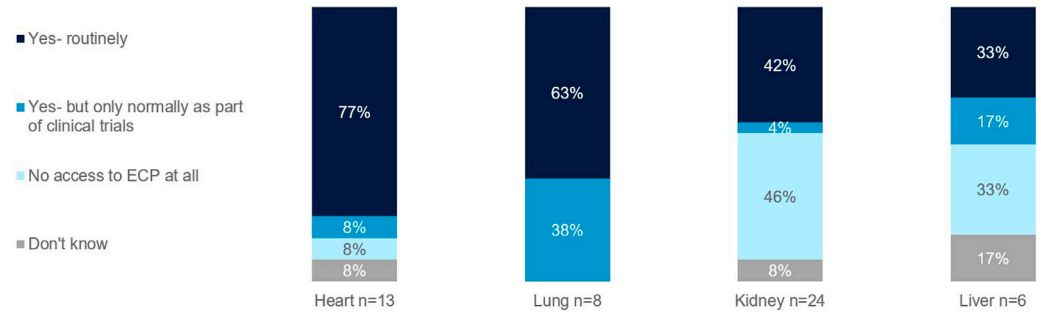

FIGURE 7 | Rates of routine access to ECP. Percentage of European clinicians treating transplants of the heart, lung, kidney, and liver.

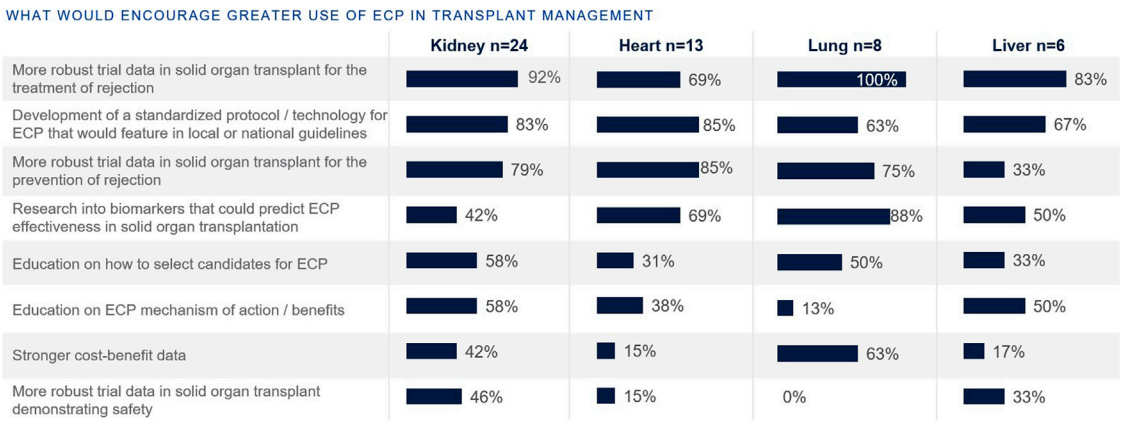

FIGURE 8 | Percentage of European clinicians agreeing each factor would encourage greater ECP use, by organ type.

such as renal insufficiency, increased infection, and neurotoxicity [11, 13].

In heart transplantation, acute antibody-mediated rejection is a significant cause of early graft dysfunction. ECP has been used as a rescue therapy in refractory AMR, with case reports and small studies suggesting improved hemodynamic stability and graft function [3]. The exact mechanism remains unclear but is likely related to the modulation of alloimmune responses and the lack of power in available studies limits the ability to draw strong conclusions. The American Heart Association also noted there are no published data conclusively demonstrating efficacy of ECP in AMR in SOT, and mechanistic understanding remains incomplete [14]. It notes that while ECP has been successfully used for recurrent rejection and acute cellular rejection, its role in AMR remains undefined and warrants further investigation. ECP is not included as a standard or first-line therapy for AMR in the American Heart Association's treatment algorithms, and only considered in refractory cases [14]. ECP is generally well received in steroid-refractory ACR in heart transplantation. Preliminary data in small sample sizes found ECP to be well tolerated and reduce the dose of standard of care immunosuppression, as well as a reduction in the number of rejection episodes [15, 16]. A retrospective chart review of 102 heart transplant patients treating rejection with ECP found 88.2% of patients remained rejection-free despite lower dose in standard of care immunosuppression and 92.3% had reduced rejection grades [17]. However, as well as limitations associated with the retrospective design, the effectiveness of ECP in comparison with other treatment options was not assessed due to the descriptive, single-arm design. A single center retrospective study on 22 patients assessed standard of care immunosuppression plus ECP, and found zero episodes of ISHLT grade 3R ACR and two episodes of 2R ACR episodes were reversed over the study period [18]. Furthermore, decreased rates of subsequential rejection episodes, and normalized allograft function were observed in patients completing the ECP course [18]. However, these findings were from a small sample in a single center, and large scale randomized clinical trials are required to validate this.

In heart transplantation, chronic rejection manifests as cardiac allograft vasculopathy. Studies have demonstrated that ECP can slow the progression of CAV by reducing immune-mediated endothelial injury [14, 17, 19, 20].

Savignano et al [11] performed a retrospective case series on 8 patients treated with ECP for recurrent rejection. Of the 8, 3 patients had negative biopsies with no rejection at the end of

treatment; 4 patients showed no response to ECP; 1 could not be evaluated [11]. A single-center study reported on 20 pediatric heart transplant patients who underwent ECP, showing that it can be safely applied in this population [21]. The study found a survival rate of 84% at 1 year and 53% at 3 years post-ECP initiation.

Lung Transplantation

Lung transplantation is associated with a high risk of chronic lung allograft dysfunction (CLAD), most commonly bronchiolitis obliterans syndrome (BOS) [13]. Current immunosuppression strategies and its modifications do not reverse BOS but instead aim to stabilize or slow its progression [13, 22]. In lung transplantation, although some studies suggest ECP benefit in reducing acute cellular rejection and CLAD, earlier reviews highlight that no randomized controlled trials have yet confirmed these findings, and most available data are from small, single-center, non-randomized studies, limiting generalizability and strength of evidence [23]. [24] There are currently no guidelines on early prophylactic ECP in lung transplantation, but this is presently being evaluated [25].

A recent randomized controlled trial evaluated the prophylactic addition of ECP to standard immunosuppressive therapy in lung transplant recipients, and demonstrated a significant reduction in ACR episodes, lymphocytic bronchiolitis, and CLAD within 24 months [26]. In this study, the ECP group also experienced fewer severe infections and adverse events compared to the control group [26]. This study was the first prospective RTC in lung transplant recipients evaluating early use of ECP in addition to standard triple immunosuppressive therapy. Although an RTC provides stronger evidence, this study had a small sample size (n = 31 per group) and only patients transplanted for COPD were included.

Further evidence is needed to confirm the impact of ECP in lung transplant AMR. One analysis has found that ECP is able to reduce circulating *de novo* donor-specific antibodies (dnDSA) (cleared in 88% of patients), and lung function was restored in 38% patients [27]. This was however a single-center retrospective analysis, and as such limits generalizability and lacks causality.

Chronic lung allograft dysfunction, including bronchiolitis obliterans syndrome, is a leading cause of late graft failure in lung transplantation. ECP has been investigated as a therapeutic option for CLAD/BOS [24]. ECP has been used as a second-line therapy for BOS, with studies reporting stabilization or improvement in lung function in some patients [28–32]. Stronger evidence comes from Benazzo et al [33] that assessed ECP use in 631 patients (87% BOS, 13% RAS) from 3 European centers and found long-term stabilization of lung function was achieved in 42% of patients with improvement in 9% [33]. This study was not free of limitations however; it was retrospective (indications of ECP may change over time and possibilities of miscoding data), data on AMR and DSAs were not included, and clinical practice might differ between the centers. Another retrospective study on 373 CLAD patients were initiated onto ECP after ≥10% decline in FEV1 from baseline. Statistical modeling revealed 5 different temporal CLAD phenotypes based on the FEV1 course and suggested predicting survival at ECP initiation appears feasible [34]. Again, there are limitations with the retrospective study nature. Jaksch et al. [13] demonstrated that ECP could stabilize or improve lung function in some patients with BOS, however this was a single center study on n = 51 patients and lacks generalizability [13]. Another retrospective study on early ECP in CLAD (n = 105) by Gautschi et al. (2024) recommended early initiation of ECP to slow lung function decline and improve survival rates [35].

Liver Transplantation

The benefits of liver transplantation vary by patient, with the potential for chronic rejection or late graft loss due to disease recurrence [36]. Most published experience with ECP in liver transplantation is limited to small case series, pilot studies, and anecdotal reports, with as of yet no randomized controlled trials or large prospective studies validating its effectiveness for prevention or treatment of rejection, or for improving long-term graft or patient survival [3, 8, 37].

ECP has been explored as an adjunct to delay calcineurin inhibitor introduction, prophylaxis of acute cellular rejection in high-risk or ABO-incompatible recipients, and as a strategy to reduce immunosuppressive burden in hepatitis C virus-positive patients. However, these applications remain investigational, and the reported benefits are preliminary, with outcomes such as rejection rates and virological response requiring confirmation in larger, randomized controlled trials [38]. Further studies found preliminary data that supported the finding that ECP potentially provides a low complication rate immunomodulation in liver transplantation [37, 39]. In rare complications such as graft-versus-host disease post-liver transplant, ECP has been used in individual cases, but the evidence again is limited to case reports and does not establish efficacy or impact on survival [40, 41]. Its role remains investigational, with limited data available.

Kidney Transplantation

There is a lack of clinical trials relating to ECP in kidney transplantation, with most of the current evidence for it use relating to case studies [13]. ECP has been explored as an alternative for T cell-mediated rejection when standard therapies such as corticosteroids and anti-thymocyte globulin are contraindicated or not tolerated, but its use is based on limited case series and small studies rather than randomized controlled trials [3, 8, 42]. Preliminary studies have shown that ECP can modulate cellular immunity in the long term and reduce acute glomerular lesions without causing major chronic lesions. Faenko et al. [43] suggests ECP contributes to activation of tolerogenic T-regulatory cells, maintaining long-term graft survival [43].

ECP has been used in combination with plasmapheresis, intravenous immunoglobulin (IVIG), and rituximab to treat refractory AMR in kidney transplant recipients. The immunomodulatory effects of ECP, including the induction of Tregs and suppression of B-cell activity, are thought to contribute to its efficacy. ECP was shown in one small study (n = 14) to stabilize the renal function in more than 70% of cases and significantly lower DSA levels [44].

In kidney transplantation, chronic rejection is less commonly treated with ECP compared to other organs. However, emerging evidence suggests that ECP may have a role in managing chronic antibody-mediated rejection (cAMR). A prospective observational study found that 72.7% of patients responded to ECP with stabilization of renal function for up to 3 years and even an improvement in GFR in seven cases of chronic rejection and any adverse reaction [44]. However, the overall clinical impact of ECP in kidney transplantation remains uncertain due to the lack of high-quality, large-scale studies.

Clinical Guidelines and Recommendations

Current clinical guidelines and consensus statements from major transplant societies and organizations, including the American Society for Apheresis and the American Society of Transplantation, recognize extracorporeal photopheresis as an adjunctive therapy for the prevention and management of rejection in heart and lung transplantation [8, 20].

In Europe, ECP is increasingly recognized as an adjunctive therapy for some patients at risk of rejection or experiencing allograft dysfunction after solid organ transplantation. The British Photodermatology Group (BPG) and the UK Cutaneous Lymphoma Group (UKCLG; formerly the UK Skin Group) support the use of ECP as a treatment for cardiac allograft rejection and rejection prophylaxis [7, 12, 45]. ECP is most commonly indicated for heart transplant patients with recurrent/refractory acute cellular rejection, those with intolerance or contraindications to standard immunosuppression, and for immunosuppression minimization [3, 8, 17, 18]. There is no universally accepted dosing protocol, and ECP is usually an adjunct to standard immunosuppressive regimens, but typical regimens involve 2-3 treatments per week for several weeks, then tapering based on response [18, 20].

The International Society for Heart and Lung Transplantation (ISHLT) also identifies ECP as an option for the treatment of chronic or resistant acute cellular rejection and for managing CLAD/BOS, especially in patients with recurrent rejection or intolerance to standard immunosuppression [25, 46, 47]. As of yet, ECP is not included in any major international, European, or United States liver or kidney transplant guidelines as a recommended therapy for rejection or immunosuppression minimization [3, 8], however ongoing research and clinical trials are exploring its role in managing rejection and reducing immunosuppressive drug toxicity in these settings.

ECP Efficacy and Outcomes Summary

Current standard of care immunosuppressive therapy in solid organ transplantation lacks in efficacy and has a cumulative side effect profile [48]. Standard of care immunosuppressive therapies can result in side effects such as infection, malignancy, cardiovascular diseases, and nephrotoxicity [3]. ECP is an immunomodulatory approach that provides a potential solution in both rejection treatment and rejection prophylaxis [3]. Currently however, the majority of data stems from single-center or case studies, and large-scale clinical trials are required to fully understand its potential. The effectiveness of ECP varies among different types of solid organ transplants, with the most evidence and guideline support seen in heart and lung transplants.

In heart transplantation, ECP is linked to high rates of rejection-free outcomes (up to 88%–83% in prevention and treatment groups), improvements in rejection grades on histology, and the safe reduction of immunosuppressive medications, particularly calcineurin inhibitors [17]. A small (n = 15) single center study found a significant proportion of patients (up to 64%) experience a reduction in donor-specific antibodies, along with decreases in gene expression profiling and donor-derived cell-free DNA [49]. However, survival rates are similar to registry data and do not surpass those achieved with standard therapy.

ACR and CLAD contribute to lung transplants having the worst long-term outcomes of all solid organ transplants [26]. Freedom from rejection and freedom from CLAD are significantly improved when ECP is added to standard immunosuppression [26]. It was also shown in a retrospective cohort study to slow the decline in forced expiratory volume in one second (FEV1), with a 63% reduction in the rate of FEV1 decline in cases of chronic rejection [50]. Other studies (including a randomized controlled trial in lung transplantation focused on ECP for prevention of rejection and chronic lung allograft dysfunction) reported stabilization or improvement in FEV1 [22, 26, 51]. Additionally, ECP promotes the reduction and clearance of donor-specific antibodies and antibodies targeting lung-specific antigens, which is associated with improved lung function and decreased levels of pro-inflammatory cytokines [3, 8, 23].

ECP provides measurable improvements in freedom from rejection, FEV1, and DSA reduction in heart and lung transplantation, but data are insufficient to support similar benefits in liver and kidney transplantation [3, 49]. In kidney and liver transplantation, ECP is considered investigational or reserved for refractory cases. There is insufficient evidence for reduction in ACR, improvement in DSA kinetics, or preservation of renal function, and ECP is not guideline-recommended for routine use in these settings [3, 17].

CHALLENGES AND UNMET NEEDS

Unmet Clinical Needs in SOT

The challenges of SOT are multifactorial, with different rejection types having a different set of unmet needs (**Figure 4**). The top unmet needs tend to be grouped by rejection type rather than organ type.

Although T-cell mediated/acute cellular rejection often responds well to increased immunosuppressive therapy, a minority of patients can be refractory and warrant the need for alternative therapies for rejection. Due to the nature of this rejection type, there is also a need for personalized treatments.

In antibody mediated rejection (AMBR) treatment resistance can also be observed, warranting the need for alternative therapies [52]. In SOT there is a risk of developing acute AMBR in patients who develop *de novo* DSA following transplantation or in

patients who have pre-formed DSA to HLA at the point of transplantation [52]. These patients who have developed acute AMBR may progress to chronic rejection and are highly associated with graft loss [52]. However, due to the complexity of its pathology and unclear cellular/molecular pathways, acute AMBR lacks a clear definition of the disease and therefore a clear diagnosis [52–54].

Chronic rejection is characterized by repeated injury of the graft vasculature and uncontrolled repair responses that can result in transplant vasculopathy [14, 52, 55]. Chronic rejection resulting in transplant vasculopathy is leading cause of re-transplantation with a significant impact on patient mortality and morbidity [56, 57]. Currently chronic rejection is irreversible, and a major unmet need is the ability to slow disease progression.

Limitations of Current Mechanistic Research on ECP in Transplantation

One of the most critical gaps in current knowledge is the incomplete understanding of the mechanism of action of ECP. Several mechanisms have been hypothesized as to how ECP modulates the immune system: early theories suggest apoptosis of treated leukocytes due to the combination of psoralen and ultraviolet A [58, 59], and later theories suggest transimmunization via differentiation of immature dendritic cells [60–62], modification of the cytokine profile [63–65], and stimulation of several T-cell lineages (in particular regulatory T-cells) [66, 67]. However, the precise pathways and cellular interactions remain unclear. This lack of mechanistic clarity hinders the ability to refine ECP protocols for specific transplant-related conditions and patient populations [8, 68]. There is increasing research attempting to elucidate the mechanism of action in order to extend the use of ECP and better target its use in current indications [61, 69].

Currently, ECP demonstrates organ-specific benefits, with the most evidence for DSA reduction and stabilization in lung transplantation, while results in heart, kidney, and liver transplantation are more equivocal/insufficiently established [3, 8, 17, 22, 23, 26, 49, 50]. DSAs are a critical marker of antibody-mediated rejection and graft survival in SOT. If ECP shows inconsistent or unclear results in reducing DSAs, clinicians may hesitate to recommend it as a reliable therapy, especially when other treatments (e.g., plasmapheresis, IVIG, or rituximab) have more established efficacy in DSA management.

Challenges in Implementing ECP in Clinical Practice Across Europe

Awareness of ECP as a treatment option in SOT is the first barrier to its use. Fewer clinicians surveyed were aware of ECP as a therapy option for liver transplants, as opposed to the higher awareness for heart, lung, and kidney transplants (**Figure 5**). This is likely due to the limited ECP research in the area and the fact that liver transplants are generally more immunologically tolerant compared to heart or kidney transplants, which may reduce the perceived need for adjunctive therapies like ECP. Acute and chronic rejection rates in liver transplantation are lower, and standard immunosuppressive regimens are often sufficient.

A top barrier to the widespread adoption of ECP in SOT is the lack of standardized clinical protocols (**Figure 6**). While ECP is recommended in international guidelines for specific indications there is significant variability in its application across transplant centers [3].

Access to ECP remains limited in many regions, including Europe. Access to ECP is unevenly distributed across Europe, with significant disparities between countries and even within regions of the same country. ECP requires specialized facilities and equipment, which are not widely available in all hospitals or regions. Larger transplant centers in urban areas are more likely to have the resources and infrastructure to offer ECP, while smaller or rural centers often lack access to this therapy. This geographic disparity creates inequities in patient care, as transplant recipients in underserved areas may not have the opportunity to benefit from ECP. Patients may need to travel long distances to access treatment, creating logistical and financial burdens. Furthermore, ECP sessions are time-consuming, often requiring several hours per session, with treatments typically repeated multiple times per week or month. This can be inconvenient for patients and resource-intensive for healthcare providers.

There are also access limits per organ type. The European survey found that those focused on heart and lung transplants have higher rates of routine access to ECP as a therapy option at their centers, whereas the rate is lower for those focused on kidney and liver (**Figure 7**).

A further barrier to ECP access is the high upfront cost of the equipment and treatment sessions. ECP requires specialized apheresis machines, trained personnel, and infrastructure, which can be prohibitively expensive for smaller or resource-constrained transplant centers. The medical literature acknowledges ECP's potential to reduce immunosuppression-related adverse effects and improve clinical outcomes in heart and lung transplantation, but explicitly notes that cost-effectiveness analyses are lacking and represent a major gap in current research [3, 8]. Additionally, reimbursement policies for ECP vary widely across countries and healthcare systems, with some systems failing to cover the full cost of treatment. This financial burden limits the availability of ECP, particularly in public healthcare systems or in regions with limited healthcare funding [1, 8]. The absence of formal cost-effectiveness studies means that the economic impact of ECP remains undetermined in all solid organ transplant settings [3, 8].

FUTURE DIRECTIONS

As research continues to demonstrate its efficacy in reducing acute and chronic rejection in heart, lung, kidney, and liver transplants, ECP is expected to become a more integral part of SOT protocols, especially for patients who are unable to tolerate standard immunosuppressive regimens [3, 8]. 59% of European clinicians surveyed agreed with the statement: "*It would be of benefit to my clinical practice if more ECP was used to treat transplant rejection in the future*".

More robust clinical trial data and the development of a standardized protocol would encourage use of ECP in transplant management (**Figure 8**). Randomized clinical trial data would provide more evidence for the clinical indication and efficacy in ECP, particularly of use to kidney and liver transplants where the use of ECP currently is less established. Indeed, ECP is being actively studied across a range of clinical settings, including solid organ transplantation, chronic rejection, GvHD, and autoimmune diseases. The ongoing phase II randomized control trial E-CLAD UK assesses ECP in CLAD, and will further collect long-term follow up data [70]. There are several more actively recruiting trials, including the EUROEXPORT-DSA trial from Medical University of Vienna that will assess ECP in subclinical antibody-mediated rejection after lung transplantation (NCT06112951), a study on the impact of ECP for the prevention of acute rejection in highly sensitized kidney transplant recipients from Fundacion Clinic per a la Recerca Biomédica (NCT04414735), and the phase IIb study by University of Miami on axatilimab in combination with ECP in chronic graft-versus-host disease (NCT06663722).

Furthermore, the development of standardized ECP protocols that are incorporated into national guidelines would promote the broader adoption of ECP by providing clear, evidence-based recommendations for its use in clinical practice. Currently, the variability in ECP protocols, including differences in treatment frequency, duration, and patient selection criteria, limits its implementation and creates uncertainty among clinicians. Furthermore, standardized protocols would facilitate more consistent data collection across institutions, enabling better evaluation of clinical outcomes and cost-effectiveness.

Establishment of multicenter registries to collect real-world data on the use of ECP in SOT is essential for evaluating its long-term efficacy and safety. Such registries would provide valuable insights into patient selection criteria, treatment protocols, and outcomes, thereby informing future policy and practice improvements [9].

Further awareness and expertise among healthcare providers regarding the benefits and mechanisms of ECP can encourage its adoption [71]. Future initiatives should include targeted educational programs and training workshops for transplant clinicians, nurses, and allied healthcare professionals.

Future research should focus on exploring the role of ECP in pediatric SOT recipients. While ECP has shown some promise in pediatric heart transplantation [21], data on its use in solid organ transplants in pediatric patients are limited. Given its use and efficacy in managing acute and chronic GvHD in pediatric patients following bone marrow transplantation [72–74], investigating its potential benefits in SOT could help establish evidence-based guidelines for its use in this patient population.

The successful integration of ECP into SOT management requires collaboration among transplant specialists, immunologists, policymakers, and industry stakeholders. Interdisciplinary efforts should focus on addressing logistical challenges, streamlining treatment pathways, and ensuring equitable access to ECP across diverse healthcare settings [4].

Cost-effectiveness studies have shown that ECP can reduce long-term healthcare costs by decreasing the need for high-dose immunosuppressive therapies and reducing the incidence of graft loss and associated complications [3]. However, these benefits are often not immediately apparent, leading to underinvestment in ECP programs.

LIMITATIONS

This review has a number of limitations that will now be discussed. The survey data used to support this review whilst targeted to be broad, may not be fully generalizable. The sample size was relatively small (n = 51) and limited to clinicians from specific European countries. This regional focus may not reflect the practices, challenges, or perspectives of transplant centers in other regions of the world. While the survey provides valuable insights into current practices and perceptions, it relies on self-reported data, which by its nature may be subject to recall bias or variability in interpretation. The design of a narrative review inherently does not have a full formal systematic search and exclusion strategy. Finally, significant evidence gaps remain regarding the efficacy, mechanisms of action, and optimal protocols for ECP in solid organ transplantation, particularly for kidney and liver transplants. These gaps highlight the need for further large-scale, multicenter randomized controlled trials to better understand the role of ECP in this context.

CONCLUSION

The approach to treatment in solid organ transplantation is primarily guided by established center protocols, evidence from experience, and to a lesser extent clinical trials. However, there is widespread dissatisfaction with current treatments across various organs and types of rejection. First-line treatments are selected based on the type of rejection, with extracorporeal photopheresis being used by some as a first-line option, especially for recurrent rejection in heart and lung transplants. There are significant unmet needs in managing solid organ transplant patients, particularly in treating rejection, managing immunosuppression, and improving diagnostics.

ECP is recognized as an effective adjunctive therapy for managing organ rejection in some recipients, particularly in heart and lung transplantations. ECP offers immunomodulatory benefits that can help reduce the need for traditional immunosuppressive therapies, which are often associated with significant side effects such as infections, malignancies, and nephrotoxicity. Awareness and access to ECP vary by organ, and its usage is currently low, unaided by mechanistic uncertainty. The main barrier to wider ECP use is the absence of standardized protocols across different organs. Despite a generally positive perception of ECP's benefits in treating transplant rejection, there is a lack of awareness regarding its efficacy. More clinicians have routine access to ECP for heart and lung transplants than for kidney and liver. The development of standardized protocols could encourage greater use of ECP. While current evidence supports its use, there is a need for further research, including randomized controlled trials, to better understand its full potential and optimize its use across different types of solid organ transplants.

AUTHOR CONTRIBUTIONS

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

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REVIEW
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Immune Monitoring Goes Viral – Torque Teno Virus for Immunologic Risk Stratification After Kidney Transplantation

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Using biomarkers to tailor immunosuppressive therapy after kidney transplantation was proposed to improve clinical care. Timely and individual adaptions of immunosuppression could reduce therapy-related side effects, such as infections, cardiovascular morbidity and malignancy, and further lower the risk of allograft rejection. Despite promising preliminary studies, evidence for implementing such a biomarker in clinical care is insufficient. Prominent candidates for immunologic monitoring after kidney transplantation include donor human leukocyte antigen-specific antibodies, donor-derived cell-free DNA, urinary chemokines and peripheral transcriptomics. In addition, the quantification of Torque Teno virus, a highly prevalent and non-pathogenic virus that was shown to associate with outcomes linked to immunocompetence, has been proposed for immunologic monitoring. This review summarises the prospects and limitations of Torque Teno virus for immunologic risk stratification after kidney transplantation in the context of current state-of-the-art. It will focus on cut-off values of plasma Torque Teno virus load that might be useful to guide immunosuppression in the clinical care of kidney transplant recipients, and highlights recently proposed indications of Torque Teno virus-guided immunosuppression.

Keywords: torque teno virus, immune monitoring, biomarker, kidney transplantation, risk stratification

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INTRODUCTION TO THE CLINICAL PROBLEM

Organ transplantation, which prolongs and improves the lives of patients with end-stage renal disease [1, 2], is complicated by the need to dampen the hosts' immune response. Patients on life-long immunosuppressive drug regimens are at increased risk of infections, cancer and cardiovascular morbidity [3, 4]. In addition, even modern immunosuppressive regimens cannot entirely abrogate alloimmune processes [5, 6]. Therefore, biomarker-guided immunosuppression was proposed to reduce complications caused by extensive or insufficient immunosuppression. Many candidate markers have been studied in recent decades with some very promising results [7, 8]. However, their transition into clinical use is faltering, and scientific evidence for integrating immunologic monitoring markers into routine care remains insufficient. While there are many reasons, they

Abbreviations: ABMR, Antibody-mediated rejection; BKV, BK polyomavirus; c/mL, copies/mL; CMV, Cytomegalovirus; CNI, Calcineurin inhibitor; dd-cfDNA, Donor-derived cell-free DNA; DSA, Donor-specific antibodies; IVDR, *In Vitro* Medical Devices Regulation; MPA, Mycophenolic acid; mTORi, Mammalian target of rapamycin inhibitor; TAC, Tacrolimus; TCMR, T cell-mediated rejection; TTV, Torque Teno virus; qPCR, Quantitative polymerase chain reaction; RCT, Randomised controlled trial.

nearly always come down to a lack of validation in interventional trials, potentially compounded by high costs and a lack of reimbursement. Currently, the most promising candidates for immunologic monitoring after kidney transplantation are donor-specific antibodies (DSAs), donor-derived cell-free DNA (dd-cfDNA), urinary chemokines and peripheral transcriptomics.

Unlike the abovementioned biomarkers, which mainly reflect organ damage or alloreactivity, the Torque Teno virus (TTV) – a highly prevalent and non-pathogenic virus of the family Anelloviridae – was shown to be associated with outcomes linked to both excessive and insufficient immunosuppression. Therefore, TTV may serve as a biomarker indicating the net state of the immune system and thus could complement existing injury and alloreactivity markers. A gradual deviation from an 'optimal' TTV load toward a high or low load was shown to correlate with an increased risk of infections and allograft rejection [9]. More recent data show associations with malignancy and the immune response after vaccination [10]. The introduction of a quantitative polymerase chain reaction (qPCR) assay has made TTV a readily measurable parameter. However, the framework for implementing it in routine clinical care requires further definition. One multicentre interventional trial assessing the clinical value of TTV-guided immunosuppression in kidney transplant recipients was successfully concluded in May 2025 (TTVguideIT, EUCT number: 2022-500024-30-00) [11], and another started recruiting in April 2025 (TAOIST, ClinicalTrails.gov ID: NCT06829719).

This article will reflect on the role of TTV as an immune marker in the clinical care of kidney transplant recipients, focusing on relevant data that have emerged over the last 3 years. Previous relevant studies will only be mentioned briefly, as they have been discussed in detail earlier [9]. The role of TTV from the clinical virologist's perspective has been reviewed by others recently [12, 13]. Biomarkers other than TTV will only be discussed briefly, as current reviews cover peripheral blood gene expression, dd-cfDNA, urinary chemokines and other emerging candidates [8, 14, 15].

CURRENT STATUS OF IMMUNE MONITORING IN CLINICAL CARE OF KIDNEY TRANSPLANT RECIPIENTS

Despite a long history of immune monitoring research in kidney transplantation, no biomarker is supported by sufficient evidence to enter clinical practice. Standardised assays, rigorous validation and interventional trials demonstrating the clinical value of biomarkers when added to the standard of care are prerequisites for broad implementation. Lately, some studies yielded promising results and a recent consensus statement of the European Society of Organ Transplantation cautiously discussed recommendations in favour of biomarker monitoring in certain settings while urgently calling for interventional trials [16]. However, the study design in this context is complicated. Endpoints commonly used in interventional clinical trials, such as allograft rejection or loss, have low incidences, necessitating the inclusion of high-risk patients or large populations. Consequently, a randomised controlled trial (RCT) assessing *de novo* DSA-triggered optimisation of immunosuppression suffered from lower-than-expected rejection and biopsy rates and failed to show improved allograft survival [17]. Similarly, a multicentre RCT evaluating urinary monitoring of C-X-C motif chemokine ligand 10 (CXCL10) in addition to the standard of care could not demonstrate a reduction in rejection rates during the first year post-transplantation, at least partly due to low biopsy and rejection rates [18].

Besides sufficient power, outcome selection is crucial in biomarker trial design. For example, while dd-cfDNA was developed as an injury marker, several studies focused on dd-cfDNA as a tool to rule out rejection and avoid invasive diagnostics. This demands close and longitudinal monitoring in large patient cohorts, which, even with a high negative predictive value, may easily become very resource-demanding. A more effective approach might be ruling in rejection in high-risk patients. Consistent with this approach, the first positive results came from a single-centre RCT demonstrating an accelerated diagnosis of late antibody-mediated rejection (ABMR) in patients with *de novo* DSA if dd-cfDNA was added to the standard of care [19]. Following these first promising results, validation in large and diverse multicentre cohorts is now eagerly awaited.

The nature of the biomarker should also be considered carefully in the study design and outcome selection phase. For example, injury markers might not be useful for predicting potential future adverse events [20]. Biomarkers reflecting the state of immunosuppression could overcome this problem. TTV is a promising candidate due to its link to both extensive and insufficient immunosuppressive burden before adverse events manifest. Quantifying immunocompetence using TTV may serves as a complement to markers of graft injury (e.g. dd-cfDNA) and alloreactivity (e.g. DSA).

Alternative approaches to quantify the net state of the immune system rely on cellular assays. One proposed assay was the ImmuKnow, which did not enter clinical practice despite promising results within a single centre RCT [21]. Recently, another RCT including paediatric patients showed promising data for Tvis [22], an assay that relies on quantifying virus-specific T cells. Because of the complex logistical procedures, most of the patients (86%) where randomised only at one study site. Multicentre validation will be crucial as the complexity of the assay might pose an obstacle to standardisation and implementation.

TORQUE TENO VIRUS – FROM DISCOVERY TO IMMUNE MONITORING

TTV is a small, circular, non-enveloped, single-stranded DNA virus that was first described in 1997. It is characterised by high genetic diversity, and 26 species are currently classified among the genus *Alphatorquevirus* within the family Anelloviridae. To date, no causal association with any disease has been demonstrated. Its high prevalence in the general population [23, 24], replication in almost all studied body tissues and liquids [25], and high positivity rates among infants [26] have given rise to the

hypothesis of TTV being a non-pathogenic, commensal virus. As such, it was attributed to the human virome [27].

Epidemiological analyses revealed higher TTV prevalences in patients with diseases causing reduced immunocompetence or chronic inflammation [10, 28]. As early as 2001, studies linked TTV prevalence to overall immunocompetence [29, 30]. In the same year, Maggi and Bendinelli speculated on the potential healthcare benefits of monitoring TTV in organ transplantation [31]. In 2003, Moen and colleagues observed steep increases in TTV load upon initiation of immunosuppression in kidney transplant recipients [32]. A decade later, associations between TTV and adverse outcomes in transplant patients became evident. In a systems biology approach, De Vlaminck and colleagues analysed the human plasma virome in patients after heart and lung transplantation, and observed not only a marked expansion of TTV after the initiation of immunosuppression but also an overall lower viral load in patients with allograft rejection [33]. Associations between TTV load and the occurrence of infections were demonstrated shortly after [34]. These findings were subsequently reproduced in a variety of different cohorts with broad consistency among studies and across different types of transplanted organs [9, 35].

Evidence for TTV as an immune marker has also emerged from studies involving non-transplant patients [36]. In patients with antineutrophil cytoplasmic antibody vasculitis, a retrospective analysis of the RAVE RCT [37] showed that those who experienced relapses had lower peripheral blood TTV loads at month 4 after therapy start, potentially reflecting insufficient immunosuppression (unpublished data from the Medical University of Innsbruck). In patients with rheumatoid arthritis, TTV loads were lower in those with persistent rheumatoid arthritis activity despite initiation of disease-modifying anti-rheumatic drug therapy, indicating an insufficient immunosuppressive effect [38].

TTV has also been proposed for triage in visits at emergency medicine outpatient clinics. Patients with a SARS-CoV-2-infection were shown to be at particularly increased risk of admission to the intensive care unit or death if TTV loads in nasopharyngeal swabs were high [39]. Promising results of TTV quantification in patients with oncologic disease were reported and recently summarised [40]. In women with ovarian cancer, those with unfavourable outcomes were found to have higher TTV loads [41]. In patients receiving chimeric antigen receptor T-cell therapy for lymphoproliferative disease, TTV dynamics were associated with therapy response and immune effector cell-associated neurotoxicity syndrome [42].

Altogether, a high TTV load has been associated with host factors and clinical conditions linked to compromised immunocompetence across heterogeneous study populations. In patients receiving immunosuppressive therapy, TTV load may be used to identify those with insufficient immune system control and increased risk of adverse outcomes. Therefore, TTV is a promising biomarker to not only quantify the net state of the immune system but also guide clinical decision-making. Ongoing and future interventional RCTs will help define the value of TTV in the clinical care of kidney transplant recipients.

NOVEL DATA ON TORQUE TENO VIRUS QUANTIFICATION TECHNIQUES

In clinical applications, TTV load is most commonly quantified in plasma; however, it can also be quantified in various body fluids, including serum, whole blood, urine, nasopharyngeal swabs and bronchoalveolar lavage. Quantifying TTV in whole blood and serum yields higher loads than in plasma. Recently, Truffot and colleagues systematically quantified this difference, analysing 216 consecutive paired samples from 68 kidney transplant recipients. They observed a mean TTV load difference of 0.4 $\log_{10}$ copies/mL (c/mL) between whole blood and plasma, with a high correlation between paired samples [43]. Unpublished data from the University of Strasbourg shows a mean TTV load difference of 0.18 $\log_{10}$ c/mL between serum and plasma among 40 solid organ transplant recipients with 169 paired samples. It is well established that viral PCRs for viruses such as cytomegalovirus (CMV) or BK polyomavirus (BKV) can show differences of up to one log between whole blood and plasma or serum, with plasma and serum providing comparable results. Future studies should investigate these relationships for TTV. Until then, we recommend quantifying TTV in plasma, as most proposed cut-offs are based on this matrix.

The most extensively reported systems for quantifying TTV load are qPCR-based and use either published primers and probes developed by Maggi and colleagues [44] or a commercially available *In Vitro* Medical Devices Regulation (IVDR)-labelled assay (TTV R-GENE®, bioMérieux, France) [45]. Notably, TTV loads can differ significantly between applied assays. A recent study compared the in-house PCR developed by Maggi and colleagues and the commercially available PCR in 342 samples from 314 patients, revealing a mean difference of 1.38 $\log_{10}$ c/mL (95% confidence interval: 1.30–1.46) [46]. Notably, the assays showed a high and almost linear correlation, allowing one method to be extrapolated to the other. Besides primers and probes, differences in extractors, cyclers, consumables and local standards might also lead to significant differences in TTV load quantification. Indeed, a comparison of TTV loads quantified with the same PCR assay in Fabrizio Maggi's laboratory in Italy and at the Center for Virology at the Medical University of Vienna showed a difference of 1.0 $\log_{10}$ c/mL (unpublished data). Given these findings, it is evident that locally obtained TTV PCR results need to be cross-validated and adapted to proposed TTV load cut-offs accordingly. Such a process can be facilitated by customised quality assessment programmes like those offered by Quality Control for Molecular Diagnostics (Glasgow, UK).

For the clinical implementation of any TTV qPCR assay, a low inter- and intra-centre variability is desirable. A recent analysis by the clinical virologists of the TTVguideTX consortium demonstrated that this can be achieved for the commercial PCR using standard testing platforms [47]. In preparation for the multicentre TTVguideIT trial, the PCR was set up locally in 13 recruiting centres across Europe. Applying an internal quality control demonstrated excellent accuracy, with an inter-laboratory standard deviation of 0.19 $\log_{10}$ c/mL and an intra-laboratory standard deviation of 0.07–0.18 $\log_{10}$ c/mL. External quality assessment and linearity panels similarly showed small variability. Implementation of qPCR assays might be further

TABLE 1 | TTV load cut-offs proposed based on an IVDR-labelled qPCR assay to guide immunosuppression after kidney transplantation.

Clinical setting	Time of TTV quantification	TTV threshold
Clinically overt graft rejection[a] (single centre, cohort) [49]	Month 4–12 post-transplant	<4.6 log_{10} c/mL[b,c]
Subclinical rejection[a] (single centre, cohort) [52]	Month 4–12 post-transplant	<4.6 log_{10} c/mL[b,c]
Underimmunosuppression[d] (single centre, cross-sectional) [53]	Month 12–36 post-transplant	<3.8 log_{10} c/mL[e]
Clinically overt graft rejection[a] (single centre, cross-sectional) [54]	Median of 6 years post-transplant	<3.6 log_{10} c/mL[b,c]
Vaccine response[f] (retrospective analysis of a multicentre RCT) [10]	Median of 7 years post-transplant	<4.6 log_{10} c/mL[b,c]
Infection[g] (single centre, cohort) [49]	Month 4–12 post-transplant	>6.6 log_{10} c/mL[b,c]
Malignant disease[h] (single centre cohort, unpublished)	Month 4–12 post-transplant	>6.6 log_{10} c/mL[b,c]
Overimmunosuppression[i] (single centre, cross-sectional) [53]	Month 12–36 post-transplant	>5.1 log_{10} c/mL[e]
CMV-DNAemia >3.0 log_{10} c/mL (single centre, paediatric cohort) [55]	Year 2 (median) to year 5 (median) post-transplant	>6.3 log_{10} c/mL[b,c]
BKV-DNAemia >3.0 log_{10} c/mL (single centre, paediatric cohort) [55]	Year 2 (median) to year 5 (median) post-transplant	>5.0 log_{10} c/mL[b,c]

Abbreviations: ABMR, antibody-mediated rejection; BKV, BK polyomavirus; CMV, cytomegalovirus; c/mL, copies/mL; RCT, randomised controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] *biopsy-proven borderline, cellular and ABMR, according to the respective Banff meeting report.*

[b] *to facilitate the interpretation, TTV cut-off values obtained using an in-house PCR assay have been recalculated to match the results obtained with the TTV R-GENE® qPCR assay according to the comparative study by Görzer et al. who described a mean difference of 1.38 log_{10} c/mL (95% confidence interval 1.30–1.46) between PCR methods [46].*

[c] *plasma was used for TTV load quantification.*

[d] *based on comparison with a healthy collective and antibody response to vaccination.*

[e] *serum was used for TTV load quantification.*

[f] *humoral and cellular.*

[g] *defined as need for hospitalisation, anti-microbial treatment or reduction of immunosuppression.*

[h] *excluding basalioma and carcinoma* in situ.

[i] *defined by the occurrence of serious infections or malignoma.*

supported by using automated test systems. In this regard, a study by Spezia and colleagues might be of special interest. They compared the conventional in-house PCR with an automated approach in 112 samples and found a high concordance rate [48]. Automated qPCR systems could facilitate shorter turnaround times, reduced workload and higher throughput.

PROPOSED TORQUE TENO VIRUS CUT-OFF VALUES TO GUIDE IMMUNOSUPPRESSION

Most data on TTV in patients receiving immunosuppressive therapy was generated in kidney transplant recipients. Findings from initial retrospective studies have since been validated by non-interventional prospective studies [49, 50]. Today, independent and robust associations have been described between low TTV loads and all types of kidney graft rejection, including clinically overt T cell-mediated rejection (TCMR), ABMR, borderline TCMR and subclinical rejection. Higher TTV loads were found prior to a broad range of infectious events, including opportunistic infections by CMV and BKV, as well as bacterial urinary tract infections. Notably, linear associations showed step-wise increasing risk constellations for both infection and rejection with increasing or decreasing TTV load, respectively, as described in a 2022 review by our group [9] and a 2023 meta-analysis by van Rijn and colleagues [51].

Consequently, quantifying TTV loads was proposed for risk stratification of insufficient or excessive immunosuppression in kidney transplant recipients, and the research focus shifted towards defining clinically relevant TTV load cut-offs. TTV load cut-offs that have been proposed for the care of kidney transplant recipients are presented in **Table 1**; **Figure 1**. To facilitate the interpretation

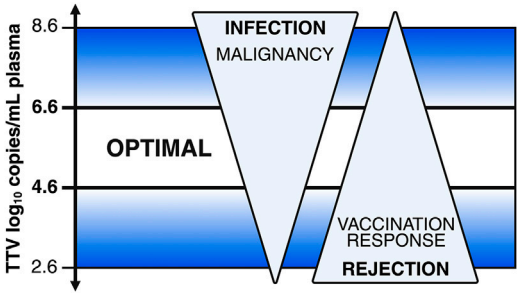

FIGURE 1 | A schematic of using the host's plasma Torque Teno virus (TTV) load for immunologic risk stratification in kidney transplant recipients. A high TTV load indicates a risk of infection and malignancy, and a low TTV load indicates a risk of rejection but associates with a better vaccination response. An optimal TTV plasma load between 4.6 and 6.6 log_{10} c/mL obtained by TTV R-GENE® is proposed.

of these cut-offs, we converted TTV loads obtained by in-house qPCR assays to those of the commercially available qPCR assay. Using data from prospective cohort studies, a plasma TTV load between 4.6 and 6.6 log_{10} c/mL was proposed as an optimal trade-off between the risks of rejection and infection 4–12 months after kidney transplantation [49]. Few studies have investigated TTV loads in patients beyond the first year post-transplantation. Schiemann et al. described an increased risk of rejection in patients with TTV loads <3.6 log_{10} c/mL at a median of 6 years after transplantation in a cross-sectional study (**Table 2**) [54]. Chauvelot and colleagues proposed a range of 3.8–5.1 log_{10} c/mL for patients between one and 4 years after transplantation and validated their findings in a prospective cohort (**Table 1**) [53].

It is important to note, that validation of the proposed cut-off values guiding immunosuppressive therapy in an interventional

TABLE 2 | A selection of studies that have recently expanded the indication of TTV-guided monitoring after kidney transplantation.

Study design	Cohort	TTV monitoring	Main outcome	Main finding
Paediatric cohort				
Retrospective analysis of single centre cohort [55]	71 KTX included 2y after TX; 3y FUP	every 4 to 8w for 3y	10 BKV / 7 CMV infections	High TTV load associates with CMV and BKV DNAemia
SARS-CoV-2 vaccination				
Retrospective analysis of multicentre RCT [10]	100 KTX with mRNA vaccination; 7y after TX	At first vaccination	31 seroconversions post 2 vaccinations	High TTV load associates with impaired vaccine response
Retrospective analysis of single centre cohort [56]	459 KTX with 2 or 3 mRNA vaccination; 6y after TX	At first vaccination	208 seroconversions post 2/ 130 post 3 vaccinations	High TTV load associates with impaired vaccine response
TTV load kinetic				
Retrospective analysis of single centre cohort [57]	48 KTX with isolated CNI dose adjustment; 1 year after TX	0, 30, and 60d after CNI dose adjustment	TTV load	TTV load changes detectable only 2m after CNI adaption
Retrospective analysis of single centre cohort [58]	43 KTX with 5w MPA withdrawal/ 33 continued MPA; 5y after TX	0, 1m after withdrawal, 2m post reintroduction	TTV load	TTV load decreases 1m after MPA withdrawal/ increases 2m after restart
Non-randomised, open label, controlled pilot [59]	18 KTX with 2w MPA withdrawal/ 22 continued MPA; 4y after TX	0, 2w after withdrawal, 1m post reintroduction	TTV load	TTV load decreases 2 w and 1 m after MPA withdrawal
Belatacept-based IS				
Retrospective analysis of single centre cohort [60]	68 KTX converted from TAC to belatacept; 4y after TX	0, 3, 6, and 12m after conversion	TTV load	No significant changes of TTV load post TAC-conversion
Retrospective analysis of 2 RCTs [61]	105 KTX converted from CNI to belatacept; 2y after TX	0, 6, and 12m after conversion	TTV load	No significant changes of TTV load post CNI-conversion
mTORi-based IS				
Cross-sectional, single centre [54]	715 KTX, 30 mTORi-based IS; 6y after TX	at screening	TTV load	Trend towards lower TTV load in mTORi-based IS
post-TX malignancy				
Retrospective analysis of a single centre cohort study [50]	221 KTX; 1 year FUP	0, 7d, 1, 3, 6, and 12m	54 opportunistic infections / 11 malignancies	High TTV load associates with opportunistic infection and malignancy
Retrospective analysis of single centre cohort[a]	428 KTX; 5y FUP	Every 3m for 5y	53 malignancies 2-5y after TX	High TTV load associates with malignancy
RCT				
1:1: TTV-guided TAC trough level vs. SOC [11]	13 EU centres; 260 low risk KTX randomised 4m after TX; 9m FUP	Every 6w for 9m	Death, graft loss, rejection, infection	TTVguideIT: last patient last visit May 2025; results expected 2026
1:1: TTV-guided IS vs. SOC[b]	4 French centres; 300 low risk KTX randomised 1-4y after TX; 3y FUP	Every 3m for 3y	Rejection, infection, cancer, graft loss, DSA	TAOIST: first patient first visit April 2025; results expected 2030

Abbreviations: BKV, BK polyomavirus; CMV, cytomegalovirus; CNI, calcineurin inhibitor; d, days; DSA, donor-specific antibodies; DSMB, data safety monitoring board; FUP, follow-up; IS, immunosuppression; KTX, kidney transplant recipients; MPA, mycophenolic acid; m, month(s); mRNA, messenger RNA; mTORi, mammalian target of rapamycin inhibitor; TX, transplantation; RCT, randomised controlled trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TAC, tacrolimus; SOC, standard of care; w, weeks y, years.

[a]*unpublished data from a retrospective analysis of the prospective TTV-POET study (DRKS ID: DRKS00012335).*

[b]*study protocol published onClinicalTrials.gov(NCT06829719).*

setting is necessary prior to clinical implementation. One completed (TTVguideIT, EUCT number: 2022-500024-30-00) and one ongoing (TAOIST, ClinicalTrials.gov ID: NCT06829719) RCT will help to clarify the clinical value of TTV-guided immunosuppression in post-transplant care. In addition, these multicentre RCTs will allow for the validation of TTV load cut-offs derived from single-centre studies. TTVguideIT was a multicentre, interventional, patient- and assessor-blinded RCT conducted in 13 European centres recruiting stable adult kidney transplant recipients with low immunological risk (**Table 2**). The corresponding study protocol and the statistical analysis plan have been previously published [11, 62]. Between 2022 and 2024, 260 patients were randomised at month four after transplantation to either standard of care or TTV-guided tacrolimus dosing at a 1:1 ratio. TTV load was quantified in both arms every 6 weeks for 9 months. In the interventional arm, the investigators followed a protocol to set tacrolimus target trough levels according to the actual TTV load. In the control arm, TTV load was concealed. The primary endpoint was a composite of the occurrence of infections, biopsy-proven allograft rejection, graft loss and death scored by central assessors blinded to the allocation sequence. The last patient concluded the trial in May 2025.

The TAOIST trial is an interventional, open-label, parallel-group RCT being conducted in four French

centres and recruiting adult kidney transplant recipients (**Table 2**). It aims to include 300 stable, low immunological-risk patients from months 12–48 after transplantation. The patients will be randomised to either standard of care or TTV-guided immunosuppression dosing for 36 months. TTV load will be quantified every 3 months. In the interventional arm, physicians will be free to change the dosing of immunosuppressive drugs to keep the TTV load within a predefined range. The primary outcome is a composite of *de novo* DSA, biopsy-proven rejection, infection, cancer or graft loss. The first patient was recruited in April 2025.

Notably, age, sex, and body mass index, which are associated with TTV load, do not confound or modify the association between TTV load and adverse effects related to over- and under-immunosuppression [23, 24, 63, 64]. Therefore, no adjustments to TTV cut-offs are necessary based on these characteristics. Conversely, it is plausible that patients at high risk for graft rejection - such as recipients with preformed DSA (and thus non-standard induction) or *de novo* DSA, re-transplantation, or a history of ABMR - as well as those at increased risk for infection - like older, frail recipients or individuals with comorbidities - may benefit from tailored immunosuppression. This could be reflected by higher or lower TTV cut-offs. Such a concept should be evaluated in phase three trials once the ongoing phase two studies, which recruit low-risk patients, demonstrate the safety of TTV-guided monitoring.

TIMING OF TORQUE TENO VIRUS-BASED IMMUNE MONITORING

TTV load cut-offs for the guidance of immunosuppression have been proposed to be useful from month 4 post-transplant. In the first 3–4 months after kidney transplantation, TTV load is not in a steady state, and thus the definition of clinically relevant cut-off values to guide immunosuppression is difficult [34, 49]. In contrast to the well-described dynamics of TTV load after initiation of immunosuppression, TTV kinetics following dose changes of immunosuppressive drugs were unknown until recently. Two cohort studies during the COVID-19 pandemic evaluating pausing antimetabolite treatment to enhance responses to SARS-CoV-2 mRNA vaccination produced the first insights (**Table 2**) [58, 59]. Both studies showed a reduction in TTV load between 4 and 6 weeks after pausing antimetabolite treatment, and TTV load reached baseline values within 2 months after reinitiation of antimetabolite therapy. This evidence was recently complemented by a single-centre study by Regele et al. [57], who examined 48 kidney allograft recipients with isolated calcineurin inhibitor (CNI) dosage changes from the TTV-POET study. No significant changes in TTV load were observed 1 month after the CNI dose changes. However, a median CNI dose reduction of 33% translated to a significant decrease in TTV load 2 months after the dosage change, and a 50% increase in CNI dosage caused a trend toward higher TTV loads 2 months later (**Table 2**). Notably, no TTV load measurements were available after 2 months, making it impossible to analyse further changes beyond that time. Integrating the findings of these studies with the consistently described peak of TTV loads at around 3–4 months after initiating immunosuppression following transplantation, the optimal time frame for quantifying the TTV load may be assumed to be every 2–4 months. It is important to note, that assessing the effect of an immunosuppressive dose change on TTV load shortly afterward is not appropriate. Due to the time lag in TTV load changes following dose adjustments in immunosuppressive therapy, measuring TTV load should only be done approximately 2 months later.

TORQUE TENO VIRUS LOAD IN BELATACEPT- AND mTOR INHIBITOR-BASED IMMUNOSUPPRESSION

One question that has come up repeatedly in recent years is how TTV load cut-off values defined in patients treated with CNI-based immunosuppression can be translated to other immunosuppressive regimens. In a single-centre cross-sectional study with a limited number of patients, a higher TTV load was initially observed in those on belatacept-based (n = 23) compared to CNI-based immunosuppression [54]. Therefore, it was hypothesised that co-stimulation blockade might have led to more potent immunosuppression or insufficient formation of TTV-specific T-cells and thus directly influenced viral control. However, two recent studies challenged this earlier finding and did not show significant increases in TTV loads after conversion from CNIs to belatacept (**Table 2**) [60, 61, 65]. In a retrospective study in Grenoble that included 68 patients converted from CNI to belatacept at a median of 4 years after transplantation, TTV loads did not change significantly from baseline [60]. A retrospective analysis of two RCTs examined TTV loads in 105 patients randomised to either CNI continuation or conversion to belatacept at 6 and 12 months after conversion [61]. Those who switched to a belatacept-based regimen showed stable TTV loads and no significant differences in TTV dynamics compared to those who maintained CNI-based therapy at both time points. In both studies, while infection and rejection rates were low, precluding any meaningful analysis, TTV loads tended to be higher in patients with subsequent infections and lower before rejection episodes. These data suggest the potential application of TTV cut-off values defined using CNI-based regimens for risk stratification also in patients on belatacept-based immunosuppression.

Unlike belatacept-based immunosuppression, insufficient data is available for mammalian target of rapamycin inhibitor (mTORi)-based immunosuppression to make recommendations concerning the clinical value of TTV-guided immunosuppression. In only one retrospective cross-sectional single-centre study, the 30 patients receiving mTORi-based immunosuppression showed absolute but not statistically

significant lower TTV loads than those receiving CNI-based immunosuppression (**Table 2**) [54].

TORQUE TENO VIRUS MONITORING IN PAEDIATRIC KIDNEY TRANSPLANT RECIPIENTS

Until recently, cut-off values for TTV-guided immunosuppression were unavailable for paediatric kidney transplant recipients, and data were mainly derived from one cross-sectional study and one single-centre cohort study associating Anelloviridae trajectories with immunosuppression and graft rejection [66, 67]. Recently, a larger retrospective single-centre study by Eibensteiner and colleagues added to these data (**Table 2**). They retrospectively analysed all paediatric kidney transplant recipients followed between 2014 and 2020 at the Medical University of Vienna for TTV load at 4–8 weeks intervals in the context of CMV and BKV infections (n = 71) [55]. They described a higher TTV load in patients with subsequent CMV and BKV infections during a 3-year follow-up and defined cut-offs at 7.7 and 6.4 $\log_{10}$ c/mL, respectively, to predict subsequent clinically relevant viral DNAemia (**Table 2**). Recipients in the cohort showed a wide age range (IQR 3.5–13.2 years at transplantation), and it is well established that TTV load increases with age [24, 68]. Analyses from adult kidney transplant cohorts have demonstrated an association between TTV load and adverse effects related to both over- and under-immunosuppression across all age groups [49]. Future research should explore whether this relationship also applies to the full paediatric recipient population.

NOVEL ENDPOINTS FOR TORQUE TENO VIRUS-BASED MONITORING: MALIGNANCY AND VACCINATION RESPONSE

The consequences of intense immunosuppression go beyond an elevated incidence of infections, as such patients are also at an increased risk of oncologic disease. Until recently, only one single-centre cohort study that included 221 patients indicated higher TTV loads in kidney transplant recipients with subsequent oncologic disease. Notably, oncologic disease was analysed only within a combined endpoint that included mainly opportunistic infections (**Table 2**) [50]. An yet unpublished analysis of data from the prospective TTV-POET study (DRKS ID: DRKS00012335) showed that the cumulative TTV load in 428 patients from months 4–12 after transplantation was predictive for the development of malignoma (53 events) in the subsequent 4 years of follow-up. Using the Vienna in-house PCR, patients with a TTV load >8 $\log_{10}$ c/mL had a significantly higher risk of developing cancer than those with a TTV load <8 $\log_{10}$ c/mL. Notably, this TTV load cut-off is equivalent to the cut-off for defining patients at risk of infection (**Table 1**). Therefore, it can be speculated that targeting the optimal TTV load range proposed to reduce infection might also reduce malignancy rates.

Another clinically relevant side effect of immunosuppression in kidney transplant recipients is a reduced response to vaccination, and recent studies have analysed TTV loads in this context. Graninger and colleagues retrospectively analysed 100 kidney transplant recipients from samples prospectively stored by an interventional German multicentre RCT, demonstrating that TTV loads were lower in serological responders than in non-responders after two doses of the SARS-CoV-2 mRNA vaccine. Those with TTV loads >10^6 c/mL showed no cellular immune response, and only 12% showed a serological response (**Table 2**) [10]. These findings were confirmed by a retrospective single-centre study involving 459 kidney transplant recipients receiving their second dose of the SARS-CoV-2 mRNA vaccine, of which half then received a third dose (**Table 2**) [56]. Notably, during the COVID-19 pandemic, temporal antimetabolite withdrawal was shown to enhance responses to SARS-CoV-2 vaccination in some [58, 69] but not all [59] RCTs. Therefore, a TTV-based approach to individualise both the amount and timing of reducing immunosuppression before planned vaccination could be an interesting design to evaluate in an interventional trial.

SCENARIOS WHERE TORQUE TENO VIRUS LOAD MIGHT NOT REFLECT IMMUNE FUNCTION ACCURATELY

Besides insufficient data on patients receiving mTORi-based immunosuppression, as mentioned above, there are other scenarios where TTV-guided immunosuppression might be challenging. In a few patients, the TTV load does not reach the detection limit of the commonly used qPCRs. In these cases, differentiating between non-infection and DNAemia below the detection limit is difficult, and the TTV load cannot be used for risk stratification of immunosuppression. Quantification of other genera of the Anelloviridae family might help in this situation. Recently, a study involving 168 solid organ transplant recipients showed that quantifying *Betatorquevirus* (formerly the Torque Teno Mini virus) and *Gammatorquevirus* (formerly the Torque Teno Midi virus) improved the prediction of the SARS-CoV-2 vaccination response [70].

TTV was shown to become almost undetectable following myeloablative conditioning regimens in hematopoietic stem cell transplantation patients [71, 72]. Similarly, TTV load significantly decreases during anti-thymocyte globulin treatment in solid organ transplant recipients [73]. In both settings, the TTV load cannot be used to quantify immunosuppression. Notably, TTV loads returned to baseline 1–2 weeks after anti-thymocyte globulin treatment and might reflect immunosuppression accurately again after that time point [73]. In concordance with the above mentioned findings leukocytes were proposed as a replication pool for TTV and it may be speculated upon whether the validity of TTV loads is also

reduced during episodes of significant leukopenia due to, for example, CMV infection or drug toxicity.

SUMMARY AND OUTLOOK

The association between TTV load and adverse outcomes linked to immune function in kidney transplant recipients is increasingly robust, and cut-offs for TTV-guided immunosuppression have been proposed. Recent studies involving paediatric cohorts, patients with belatacept-based immunosuppression and endpoints other than infection and rejection might broaden its potential clinical applications. Future studies must focus on knowledge gaps, including TTV loads in patients at later time points after transplantation and recipients on mTORi-based immunosuppression. Improved quantification methods of TTV load have been proposed to support implementation, which will depend on the results of ongoing interventional trials. Following results of ongoing interventional trials, TTV will have to position itself in the context of other emerging biomarkers for immunologic monitoring.

AUTHOR CONTRIBUTIONS

KD and GB wrote the manuscript, and SK and FH edited and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

GB received fees from bioMérieux for preparing communication material for TTV-R-GENE®, an assay to quantify Torque Teno virus load sold by bioMérieux, and for a talk at a scientific conference. GB is coordinater of the European Commission-funded TTVguideTX project assessing the clinical value of Torque Teno virus-guided immunosuppression (grant agreement ID: 896932; consortium lead: Medical University of Vienna).

The remaining authors declare that the research 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) declare that no Generative AI was used in the creation of this manuscript.

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REVIEW
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Navigating a Quandary in Kidney Exchange Programs: A Review of Donor Travel versus Organ Shipment

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In multicenter kidney exchange programs (KEPs), either the explanted kidney must be shipped, or the donor must travel to the transplanting center. This review describes the available data on these two approaches and formulates recommendations for practice. We searched for studies addressing organ shipment or donor travel in KEPs. Data were categorized into four domains: cold ischemia time (CIT), logistics, donor/recipient perspectives and professional perspectives. From 547 articles screened, 105 were included. Kidneys are shipped in most countries. Prolonged CIT due to shipment may increase the risk of delayed graft function, but does not seem to impact graft survival. Planning the shipment requires a robust logistical framework with guaranteed operating room availability. Donor travel is reported to be both emotionally and financially distressing for donors and exposes them to inconsistencies in donor evaluation and counseling across centers. Reduced willingness to participate in KEP when travelling was reported by 36%–51% of donors. Professionals generally support offering organ shipment to donors not willing to travel. In conclusion, the decision between donor travel or organ shipment should be tailored to local circumstances. Healthcare professionals should prioritize minimizing barriers to KEP participation, either by facilitating organ shipment or reducing the burden of donor travel.

Keywords: organ shipment, donor travel, kidney paired donation, kidney transplantation, living donor

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INTRODUCTION

Living donor kidney transplantation is the optimal treatment for end-stage kidney disease [1, 2]. While desensitization enables incompatible kidney transplantation, it comes with a higher immunosuppressive burden and inferior outcomes [3–5]. Kidney exchange programs (KEPs) provide a viable alternative, allowing recipients to receive a blood-type or Human Leukocyte

Abbreviations: CAD, Canadian Dollars; CIT, Cold Ischemia Time; DGF, Delayed Graft Function; HLA, Human Leukocyte Antigen; KEP, Kidney Exchange Program; NKR, National Kidney Registry; OPO, Organ Procurement Organization; UD, Unspecified Donor.

Antigen (HLA) compatible kidney by making alternative donor-recipient combinations through exchange chains [6, 7].

The success of KEPs depends on the size and HLA diversity of the donor pool [8–10], particularly for highly immunized patients that are currently accumulating in KEPs [11]. Nevertheless, multicenter KEPs can be challenging; matched donors and recipients are often located in distant transplant centers. To overcome this, the donor must travel to the transplanting center, or the kidney must be shipped between centers after procurement in the donor hospital [12]. Recipient surgeries are typically performed at the initial evaluating center, as this safeguards continuous care for the recipient and these patients face travel limitations due to their kidney disease [13–16]. In contrast, donors are generally healthy and therefore expected to be able to travel.

Shipping donor kidneys will likely increase cold ischemia time, potentially affecting graft outcomes [17, 18]. In addition, donor nephrectomy and kidney implantation are performed in different centers, requiring transplant professionals to cooperate and arrange logistics for transport [19]. Donor travel, while logistically simpler, places a greater burden on donors and might create a disincentive for KEP participation [20–22].

The geographical separation of transplant centers poses a dilemma for multicenter KEPs [12, 23–26]: the travel burden could reduce donor participation, while organ shipment introduces medical, logistical, and financial complexities. A review of pros and cons of both modalities is currently lacking. We aim to provide an overview of this dilemma by analyzing the available data on cold ischemia time (CIT), logistics, donor/recipient perspectives and professional perspectives.

METHODS

We performed a systematic search and review [27]. This entails that we did perform a systematic search to identify all the relevant studies. Since the relevant data were often not the primary topic of included studies, it was not deemed appropriate to perform a formal quality and risk of bias assessment. We narratively synthesized the included data and summarized study data in tables. Based on the synthetized data, recommendations were formulated for clinical practice.

Literature Search

We conducted a systematic search of multiple databases up to December 20, 2024. The search strategy incorporated terms for living donor kidney transplantation, kidney exchange, organ shipment and donor travel (**Supplementary Table S1**).

Inclusion and Exclusion Criteria

Studies describing data on pros and cons of organ shipment or donor travel in KEP were included. Articles not published in English and conference abstracts were excluded. We excluded studies not specifically addressing KEP donors or unspecified donors (UDs), except for studies on CIT for which we also included articles describing living donor transplants in general.

Additional Data Collection

To provide context with current KEP practices worldwide, we searched the literature and Internet on the policy (donor travel, organ shipment, or combined) and transplant volume (annual KEP transplants and total living donor kidney transplants) of countries with multicenter KEPs. In case of missing data, we contacted KEP representatives via e-mail.

Screening

Two reviewers (MtK, MrK) independently screened the articles based on title/abstract and full text subsequently. Citation searching of the included studies was performed to find additional, relevant articles. Discrepancies were discussed between the two reviewers. If no consensus was reached, a third reviewer (AW) provided the final decision.

Data Extraction

For each of the four domains, i.e., CIT, logistics, donor/recipient perspectives and professional perspectives, the first author (MtK) grouped the studies and extracted the relevant data. This included study characteristics (study type, year of publication, number and type of participants, and country) and any data on the pros and cons of organ shipment or donor travel. Extracted data were validated by the second author (MrK).

Data Analysis

A narrative synthesis of the included studies was performed, and study data were summarized in tables. To avoid the inclusion of duplicate study data, we identified overlapping cohorts and presented the data accordingly in the tables.

RESULTS

Inclusion

Our initial search identified 530 unique publications, of which 91 were included after full text screening (**Figure 1**; **Supplementary Table S2**). An additional 14 articles were found through citation checking of included studies. The majority of included studies were from the United States (63%) and Canada (13%). Additionally, we searched for the characteristics of 22 multicenter KEPs. For ten KEPs, we found the data on the Internet. Of the twelve KEPs that were contacted, nine provided us with data on their program.

Current KEP Practices

Worldwide, multicenter KEPs vary substantially in size and contribution to the national living donor kidney transplant program (**Table 1**). Organ shipment is the predominant modality in 15 of 22 described programs. India, Saudi Arabia and the Netherlands reported donor travel [32, 46], while Canada reported a recent transition from donor travel to organ shipment after the COVID-19 pandemic [47]. KEPs in the United States

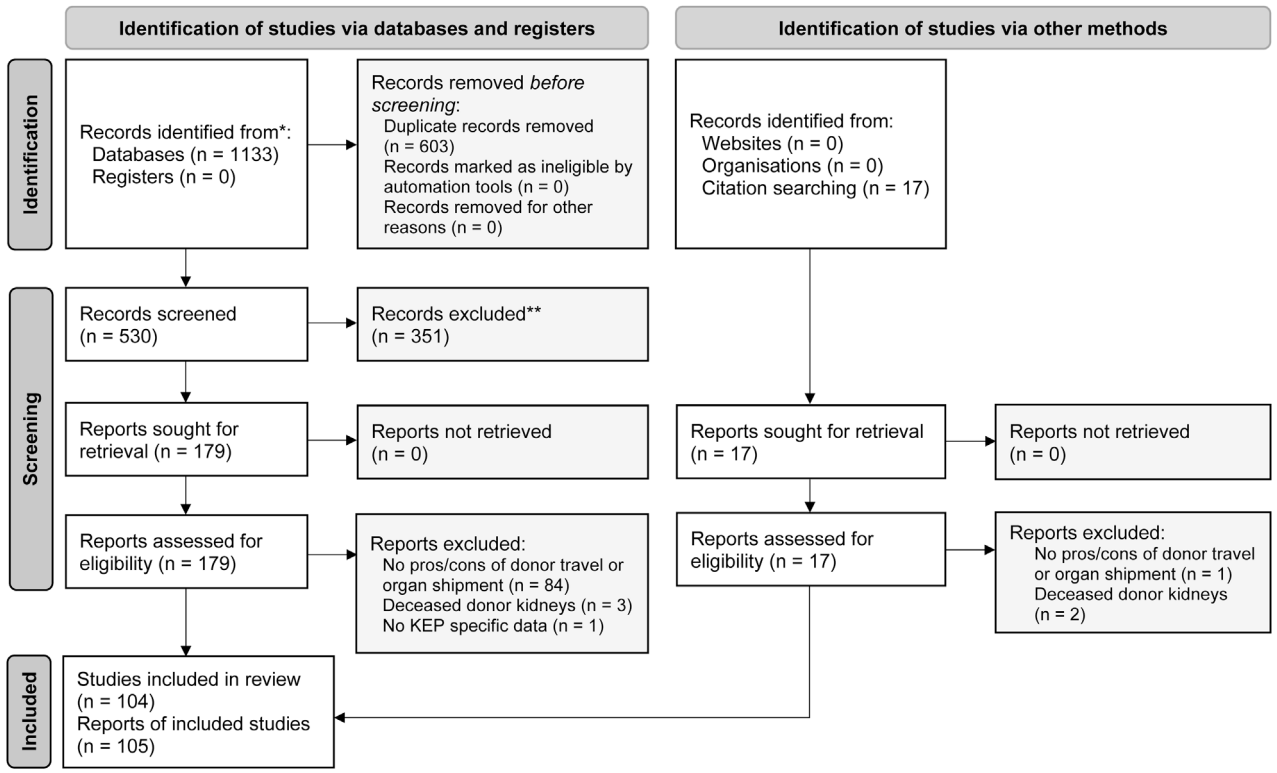

FIGURE 1 | PRISMA flow diagram of the systematic search and review of donor travel and organ shipment in kidney exchange programs, *adapted from Page et al.* [28].

(US) offer a dual modality based on donors' and recipients' preferences. [48–52].

Cold Ischemia Time

Organ shipment has the disadvantage of prolonging CIT [18, 53]. As many studies had overlapping cohorts [44, 48, 54–56], original studies with a head-to-head comparison of shipment versus donor travel in KEP were limited [19, 57–59]. We therefore extrapolated the analysis with circumstantial evidence (e.g., KEP versus non-KEP) and categorized studies per type of comparison.

Shipped Versus Non-Shipped Grafts

Nine studies compared DGF incidence in shipped versus non-shipped grafts, mostly including KEP transplants only, while Serur et al. included non-KEP controls (**Supplementary Table S3**) [19, 44, 48, 51, 54–59]. Four studies reported data on unique cohorts [19, 51, 57–59]. Analysis of the US transplant registry revealed a higher DGF incidence (4.5% vs. 3.3%) in 772 shipped grafts (median CIT 8 h) versus 1,651 non-shipped KEP grafts (CIT not reported), although this did not remain statistically significant in a multivariate model (OR 1.40, 95% CI 0.88–2.40) [59]. Regarding graft survival, no association was found between organ shipment and all-cause (HR 0.89, 95% CI 0.62–1.30) or death-censored graft failure (HR 0.70, 95% CI 0.46–1.08) in a Cox multivariate model [59]. Two case series reported DGF in 2/84 and 1/11 shipped grafts, versus 0/16 and 0/9 in non-shipped KEP grafts, respectively [19, 57, 58]. In contrast, Serur et al. reported comparable DGF incidence for shipped KEP versus non-shipped living donor transplants in the US. [51].

KEP Versus Non-KEP Transplants

Six studies compared KEP to non-KEP transplants, with on average longer CIT in the KEP group, but no reported shipping or travel status (**Supplementary Table S4**) [18, 43, 60–63]. A longer CIT (median 8.8 versus 1.0 h) and higher adjusted DGF incidence (adjusted OR 1.36, 95% CI 1.05–1.75) were reported for National Kidney Registry (NKR) transplants compared to control living donor transplants in the US. A cohort study in the United Kingdom (UK) found longer median CIT (339 versus 182 min) and higher DGF incidence (5.7% versus 2.9%, $p < 0.001$) in 1,362 KEP compared to 7,909 non-KEP transplants [18]. In adjusted logistic regression with KEP transplants only, DGF risk was higher for prolonged CIT (coefficient −0.59 for CIT <339 versus >339 min, $p = 0.04$). All six studies did not find significant differences in patient or graft survival nor in acute rejection rates (**Supplementary Table S4**).

Shipped Transplants Without Control Group

Fifteen studies examined shipped transplants without non-shipped controls (**Supplementary Table S5**) [11, 15, 64–76]. A

TABLE 1 | Characteristics and annual volume of multicenter kidney exchange programs worldwide.

Kidney exchange program	Organ shipment/donor travel	Annual KEP transplants in 2023 (% of living donation)
Australia and New Zealand Kidney Exchange	Organ shipment [29]	74 (22%) [30]
Austria and Czech Republic and Israel	Organ shipment [31]	3 (3%) [30]
Belgium	Organ shipment[a] [32]	9 between 2013–2023[a] [33]
Canada	Both (organ shipment in 72% in 2023) [34]	100 (±25%) [34]
France	Organ shipment[b]	4 (1%) in 2022[b]
India	Donor travel preferred in guideline [35]	198 (2%) total KEP transplants, including single center programs [30]
Italy	Organ shipment [32]	11 (3%) [30]
Netherlands	Donor travel [32]	31 (6%) [36]
Poland	Both shipment, donor travel and recipient travel[c]	1 (1%)[c]
Portugal	Organ shipment [32]	3 (4%) [30]
Saudi Arabia	Donor travel[d]	2 (national KEP started in 2024)[d]
ScandiaTransplant Exchange Program	Organ shipment [32]	17 (6%) [37]
Slovakia	Both[e]	3 (1%) between 2014–2024[e]
South Alliance for Transplants (Portugal, Italy, Spain)	Organ shipment[f]	3[f]
South Korea	*No data available upon request*	*No data available upon request*
Spain	Organ shipment[f]	16 (4%)[f]
Switzerland	Organ shipment[g]	2 (2%) [38]
Turkey and Kirghizia	Donor travel [39]	3 in 2013 [39]
United Kingdom Living Kidney Sharing Scheme	Organ shipment [40]	199 (24%) in 2023–2024 [41]
United States	Both	1282 (19%) [42]
Alliance for Paired Donation	Organ shipment [43]	*No data available upon request*
National Kidney Registry	Both (shipment in 85% from 2008–2017) [44]	19 (excluding 198 voucher and 9 unspecified donations) [45]
United Network for Organ Sharing	Mainly organ shipment[h]	15[h]

KEP, kidney exchange program.
Annual KEP volume is based on cited references or on personal communications:
[a]*Personal communication (Prof. dr. H. de Fijter and N. Mauws, 2024, e-mail).*
[b]*Personal communication (P. Hesky, 2024, e-mail).*
[c]*Personal communication (Dr. D. Kamińska, 2024, e-mail).*
[d]*Personal communication (Dr. A. Al-Abadi, 2024, e-mail).*
[e]*Personal communication (Prof. dr. I. Dedinská, 2024, e-mail).*
[f]*Personal communication (Dr. B. Domínguez-Gil, 2024, e-mail).*
[g]*Personal communication (Prof. dr. P. Ferrari and L. Straumann, 2024, e-mail).*
[h]*Personal communication (A. Paschke, 2024, e-mail).*

US study analyzing 1,698 shipped grafts found a significantly higher mean CIT in grafts with DGF compared to grafts without DGF (9.0 vs. 6.8 h, p = 0.04) [69]. Another US study compared 2,364 functioning grafts and 38 early lost grafts (≤1 year) and reported no difference in CIT (8.8 vs. 8.8 h) [74].

Long Versus Short CIT in Living Donor Transplants

Four studies compared CIT intervals in living donor transplants in general (**Supplementary Table S6**) [54, 77–79]. Van de Laar et al. (2022) [78] pooled five studies [17, 59, 61, 80, 81] in a meta-analysis, comparing CIT <4 h to CIT >4 h regardless of shipping. There was a significantly lower DGF incidence for CIT <4 h (OR 0.61, 95% CI 0.49–0.77) [78]. Survival data showed a significantly lower death-censored graft survival after 1-year (OR 0.72, 95% CI 0.60–0.87) and 5-year (OR 0.88, 95% CI 0.79–0.99) for grafts with CIT >4 h in univariate analysis. Another meta-analysis showed a pooled mean difference of 21 min CIT (95% CI 6–36 min) between living donor transplants with and without DGF [79].

TABLE 2 | Expert and consensus reports about the logistics and billing of care in organ shipment and donor travel.

Study and Country	Study type	Participants	Results
Mast et al, 2011 [84] United States	Consensus report based on multiple phone conferences	N = 9 Representatives from nine medical centers	- The consensus financial model has seven principles - The model is currently used by over fifty transplant centers participating in the National Kidney Registry in the United States. Afterwards, no transplants have been cancelled anymore due to financial reasons
Irwin et al, 2012 [85] United States	Statement and proposal	N = 3 Representatives from three major commercial health payers in the United States	- Donor charges should be billed to the recipient's center by the OPO. Donor costs and evaluation are standardized: standardized laboratory testing, standardized administration fee for the matching program, and standardized organ acquisition charges - Existing OPOs should manage organ acquisition logistics, transportation, and financial transactions in the same way they manage deceased donor organs today
Melcher et al, 2013 [86] United States	Consensus conference report	N = 73 Transplant hospital personnel, transplant recipients and donors, insurance industry and government agency representatives	- A national KEP standard acquisition charge would best achieve the criteria for a financial model - Packaging, labeling and transportation may benefit from OPO support or guidance. A logistical call should confirm the dates, operating room time and details of kidney transportation. Direct surgeon-to-surgeon communication is recommended prior to and immediately after KEP donor nephrectomy. All kidney transports should follow chain-of-custody principles. When traveling by commercial plane, all flights should be designated lifeguard. Kidneys on non-stop routes should be accompanied by a tracking device. Kidneys on routes involving any layovers should be accompanied by a courier
Ellison, 2014 [52] United States	Systematic review and case studies based on interviews	N = 4 Representatives from transplant centers and KEPs in the United States	- The main rationale for transplant centers employing their own KEP program is to avoid the logistical complexities associated with shipping kidneys - Reimbursement for surgical services is an added complexity associated with KEP. Healthcare costs can vary considerably between centers. It is often much less costly to perform matches internally - A streamlined logistical process, led by the transplant program, with strict guidelines, dictated timetables and scheduled conference calls is preferred by transplant coordinators
Tietjen et al, 2019 [87] United States	Consensus report and guidance	N = 7 Experts in transplant administration and clinical care	- For shipment, the donor hospital bills the recipient's hospital for procurement and transportation costs. Donor and recipient's hospital record the acquisition costs on the Medicare Cost Report, specific for the donor hospital offset by received payments from the recipient's hospital - For donor travel, the hospitalization costs should be included on the Medicare Cost Report of the recipient's transplant program

KEP, kidney exchange program; OPO, organ procurement organization.

Notably, one of the included studies reported a significantly longer shipping distance for DGF cases as well (mean 21.8 versus 15.7 miles, p = 0.033) [69].

Logistics

Feasibility of organ shipment depends on the local infrastructure [16, 82]. In most countries, extensive experience exists with shipping deceased donor kidneys [83]. Studies therefore recommend leveraging the existing Organ Procurement Organization (OPO) infrastructure for packaging and transport (**Table 2**) [15, 85, 86, 88–92].

Most studies report the use of commercial airlines and couriers for shipment [15, 19, 44, 48, 54–56, 58, 66, 67, 89, 91]. Mostly, kidneys are unaccompanied during flights [89, 91], but they should be accompanied by couriers during layovers to arrange alternative transportation in case of delays or missed connections

[86]. Direct flights are preferred whenever available [15]. To minimize delays at the airport, some countries use "lifeguard status", i.e., flight control provides priority for take-off, landing and unloading for commercial flights with kidneys on board [55, 86]. Private jets may be used to reduce the risk of delays [15, 44, 55, 67, 68, 72, 91], though at significantly higher costs compared to commercial flights (US$30,000 versus US$300 –US$550, respectively) [55, 65, 88]. Global Positioning System devices have been proven useful in monitoring transport progress and locating misrouted kidneys [46, 51, 55, 65, 84, 89–91, 93, 94].

Due to the complex logistics [13, 15, 44, 48, 55], hospitals rely on experienced transplant coordinators to oversee the process [19, 50, 51, 58, 72]. Some KEPs organize structured conference calls to review standardized checklists, set up guidelines for transport and coordinate the timetable [48, 57, 95]. This "transplant-program-led" approach is preferred by transplant coordinators (**Table 2**) [52, 86]. To ensure good cooperation, studies recommend surgeons to discuss donor anatomy and surgical aspects, packaging and cold storage solution, and surgery times in advance, and to verify recipient's status shortly before nephrectomy [15, 19, 48, 50, 55, 58, 86].

Scheduling the surgeries is challenging: hospitals should take into account the time for donor nephrectomy, organ preparation and packaging, transport, and the expected interval between arrival and implantation [17, 19]. In addition, organ shipment can shift elective transplant procedures to out-off-office hours in case of long shipping distances or unexpected delays [12, 17, 24, 65, 86, 96, 97], especially when shipping across time zones [65]. An advantage of organ shipment is the ease of maintaining anonymity during hospitalization [12, 92, 98].

No logistical, hazardous events have been reported that directly led to transplant cancellation or graft loss, except for a single case of primary non-function possibly linked to packaging issues [99]. In the NKR, some kidneys were mistakenly left off scheduled flights, but were quickly retrieved with tracking devices and flights rescheduled [93]. Nonetheless, transport delays remain a risk in organ shipment [15, 51, 86]. Unforeseen events can extend CIT, for example, travel congestion, flight delays, weather disruptions, intra-operative delays, and after-hours emergencies affecting surgical staff or operating room availability [17, 19, 24]. In Australian KEP, re-scheduling of flights was required in 19 of 100 cases due to variation in the duration of donor nephrectomy, resulting in two delayed shipments and 17 shipments with earlier flights [19].

In recent years, several international exchanges have been performed [15, 32, 68, 70, 72, 100]. However, logistical difficulties have posed a great challenge in these international collaborations [46, 55, 72, 101, 102]. Different languages, protocols, laws, reimbursement policies, and custom clearance must be overcome [68]. Especially, international travel of donors can cause difficulties, due to the complex KEP logistics and unpredictable timeframe [102]. A study describing a transatlantic, global exchange between the Philippines and the US reported challenges with visa and immigration requirements, transmissible diseases, funding for lodging, follow-up care and donor complication insurance [103].

Billing

Donor evaluation and organ procurement costs need to be charged to the matched recipient's center or insurance provider if costs cannot be charged to the intended recipient's payor, such as for UDs, and cannot be reimbursed by the donor insurance [87]. However, variation in these costs between centers led to delayed transplants and hampered kidney exchange in general in the US. [40, 50, 52, 84, 85, 95]. Financial disincentives for centers towards KEP participation also extend to donor travel: when the UD travels to a different center for donation, the referring center incurs evaluation costs but does not receive a donor kidney in return [13].

To overcome these financial barriers, several models have been developed in the US. One approach involves transactions being channeled through OPOs, comparable to deceased donation [57, 85], by using a standardized acquisition charge. This model is preferred by transplant professionals and commercial payers in the US (**Table 2**) [85, 86]. Alternatively, the NKR has developed a model that relies on Medicare cost reports for billing, with the recipient center being financially responsible for the shipment [84, 104].

Donor Care in Different Centers

Donor travel comes with additional evaluation costs [21, 22, 24, 65, 86], as both the referring and transplanting centers assess the donor's suitability to donate [86, 99, 105]. Variations in donor acceptance criteria between centers may result in the decline of proposed matches (**Table 3**) [99]. Furthermore, traveling donors receive care from two different transplant teams [12, 46, 106], which may lead to greater inconsistencies in donor counseling (**Table 3**). In Canadian KEP, proposed surgery at the referring hospital differed from eventual surgery in the transplanting hospital in 31%, of which 50% were significant deviations in surgical approach, such as laparoscopic to open or right to left side [21].

Donor/Recipient Perspectives

Travel to the recipient's center is often described as an inconvenience for donors [12, 13, 15, 21, 22, 24, 47, 51, 89, 93, 95–97, 107–110]: travel to a distant city, surgery in an unfamiliar hospital with unfamiliar staff, being separated from the intended recipient and social support system, incurring costs for travel and lodging, and discontinuity of care and follow-up may reduce a donor's willingness to participate in KEP. For large geographical distances and different language regions, travel may even be a major hindrance [12, 110–112]. Donor travel may be especially inconvenient for compatible pairs, which could have donated directly to their intended recipient without the emotional distress and logistical complexity of travel [65, 113]. However, a US simulation study suggested that most compatible pairs included in a national KEP pool could be matched within their own center, minimizing the need for travel [114].

Multiple studies have stated that organ shipment contributed to the expansion of the KEP donor pool in the US [89, 93, 94, 115–117] and that shipment was preferred by KEP participants [57, 66, 90, 91]. In interviews, travel and additional travel expenses were mentioned by donor candidates as barriers for

TABLE 3 | Discrepancies between centers in donor evaluation when the donor travels for kidney exchange.

Study and country	Inclusion	Results
Cole et al, 2015 [99], Canada	439 KEP candidates and 467 KEP donors	240 transplants were completed, while 58 proposed matches were declined. The transplanting center declined donors that were approved by the referring center due to medical reasons in 19, due to surgical reasons in three, and due to non-medical reasons in 11 donors
Reikie et al, 2017 [21], Canada	51 KEP donors with surgical work-up and nephrectomy in different centers	Performed donor nephrectomy in the transplanting center differed from the initially proposed surgery in the referring center in 16 of 51 cases (31%). For donors with different surgery performed than proposed, three had surgery on the opposite side. Four had an open procedure instead of a laparoscopic procedure. Other conversions included open to laparoscopic (n = 3), and hand assisted to laparoscopic (n = 2) or laparoscopic to hand-assisted nephrectomy (n = 6)

KEP, kidney exchange program.

KEP participation (**Table 4**) [118–120]. Survey studies have found that donor travel to another region decreases willingness for compatible KEP participation (**Table 5**) [20, 119, 121, 122].

In the US, some KEPs take donor travel preferences and restrictions into account when matching [52]. While this approach respects individual preferences, it can significantly impact match rates. Two simulation studies on a national US KEP showed that pairs willing to travel outside of their region had more and better quality matches and shorter waiting times [123, 124], especially for difficult-to-match pairs [123].

Travel Expenses

Traveling donors often pay upfront for transportation, fuel, parking, food and accommodation for themselves and a traveling companion. Although these costs may be reimbursed later, the initial expenses can be of concern. In interviews, UDs and donor-recipient pairs expressed concerns about the costs of travel (**Table 4**) [120]. Donors reported increased willingness to participate in KEP if travel expenses were reimbursed for both themselves and traveling companion (**Table 5**) [20, 119].

Currently, provincial governments reimburse travel expenses in Canada [40, 99]. However, Canadian KEP donors faced high travel expenses and a significant financial gap of 1,677 Canadian dollars despite this reimbursement (**Table 6**) [125, 126]. In the US, recipients are permitted to cover their donor's travel costs [22, 115, 127]. The National Living Donor Assistance Center provides reimbursements if expenses cannot be reasonably covered by governments or insurance providers and the recipient experiences financial hardship. In Iran, reimbursements are funded through charitable donations and contributions from KEP participants within the exchange chain [128]. In Europe, Biro et al. [32] reported that countries with the most developed KEPs have cost neutral reimbursement policies.

Professional Perspectives

Many transplant professionals have expressed concerns about potential negative effects of shipping on graft outcomes [12, 55, 66, 78, 83, 89, 90, 105, 129–131], the complex logistics of multi-center KEPs [26, 52, 53, 94, 106], and the burden of travel for donors (**Table 7**) [49, 105, 107, 132, 133]. Good outcomes after shipment encouraged professionals to start shipping organs [13, 116, 117]. Consensus reports in the US stated that UDs should not be burdened by donor travel [105], living donor kidneys could be shipped safely [86], and that organ shipment would enhance KEP participation [86]. Recently, Canadian transplant surgeons reached consensus on shipping kidneys whenever possible, to eliminate the disincentive of donor travel [47]. Similarly, Australia mandated shipping to ensure consistent donor care and clarity of expectations about the donation process [19].

Some studies have suggested that surgical issues may arise when a kidney is procured and transplanted by different teams in organ shipment. The implanting surgeon cannot customize the donor nephrectomy to the specific needs of the recipient and relies on the donor surgeon to receive a transplantable organ [19, 50, 54]. This requires a high level of trust in the quality of the external donor nephrectomy [66, 74]. Reassuringly, in the Australian KEP, concerns from recipient surgeons about donor procurement quality were uncommon [19].

DISCUSSION

Multicenter KEPs face a fundamental choice: whether to ship the donor kidney or let the donor travel. The decision hinges on balancing the medical safety and logistical challenges of shipment with the burden of travel and potential disruptions to donor care. As KEPs gain prominence in optimizing living donation programs, addressing this dilemma is crucial in all (new) KEPs.

An important, medical argument against organ shipping is the prolongation of CIT. Current studies comparing shipped to non-shipped grafts, KEP to non-KEP transplants or CIT intervals within KEP do not reveal a significant impact of shipment on graft survival. However, a meta-analysis comparing short and prolonged CIT in living donor kidney transplants, irrespective of shipping, found impaired graft survival for prolonged CIT [78]. Graft survival in these type of studies may be biased by prolonged surgery duration: the prolonged CIT group had more markers of transplant complexity, such as re-transplantation and sensitization, and included in-center procedures without organ shipment [81]. These transplant complexity factors have also been associated with DGF [79]. Nonetheless, shipment itself and shipping distance have been associated with DGF in other studies,

TABLE 4 | Donor and recipient perspectives on donor travel and travel expenses.

Study and country	Participants	Results of interview studies
Kranenburg et al, 2006 [118] Netherlands	N = 96 24 directed and 24 KEP donor candidates and their intended recipients	- Most often, emotional reasons were mentioned as reasons not to participate in KEP. Other reasons not to participate were practical objections, for instance, if the donor had to travel to another hospital
Fortin et al, 2021 [119] Canada	N = 35 18 donor and 17 transplant candidates for compatible living kidney transplantation	- Major concerns for KEP expressed during interviews were: no emotional bond with donor/recipient, fear of broken chains or donor reneging, delays in transplantation, additional travel and related costs - Donors were reluctant to travel to the recipient's center, because they want to stay close to family for support and do not want to deal with an unfamiliar medical team with which they have not yet established trust - Reimbursing travel expenses for a traveling companion to have support during organ recovery and offset lost income were cited as facilitating factors for KEP participation
Maghen et al, 2021 [120] United States	N = 31 Secondary analysis of telephone interview and questionnaire in previous non-directed donors	- 20 participants (65%) discussed financial concerns during the interviews, while 11 participants stated they were not concerned about costs (35%). Donors with financial concerns were younger (mean age 44 versus 54, p = 0.01) - Direct costs (travel, lodging, parking) were mentioned by 11 participants, with the majority about travel to and from the transplant center

KEP, kidney exchange program.

TABLE 5 | Impact of donor travel on the willingness of donors and recipients to participate in kidney exchange.

Study and country	Participants	Survey question		Reported willingness		
				Less willing	No change	More willing
Ratner et al, 2010 [119], United States	N = 105 Survey of 53 donor and 52 transplant candidates at initial evaluation visit in the out-patient clinic	Willing to participate in altruistic unbalanced paired kidney exchange?	Donors Recipients	*Mean Likert score[a] 3.1* *Mean Likert score[a] 3.4*		
		Willing to participate if the donor must go to another hospital than the recipient?	Donors Recipients	*Mean Likert score[a] 3.2* *Mean Likert score[a] 3.3*		
Hendren et al, 2015 [20], Canada	N = 116 Survey of 81 previous living directed donors and 35 recipients who responded to be willing to participate in KEP if this option had been provided at the time of donation	The donor was required to travel out of province	Donors Recipients	51% 19%	47% 76%	3% 5%
		Reimbursements of travel expenses for me and traveling companion were provided (currently only donor expenses are reimbursed)	Donors	0%	28%	72%
Kute et al, 2017 [122], India	N = 300 Survey of patients with end-stage kidney disease who consented to KEP transplantation	Willing to travel to other centers in multicenter KEP	Recipients	*50% not willing due to disparity in quality and cost of healthcare*		
Fortin et al, 2021 [119], Canada	N = 116 and N = 111 Survey of 116 donor and 111 transplant candidates undergoing evaluation for compatible living kidney donation	The donor must go to another hospital for surgery but stayed in the same city	Donor Recipient	7.8% 8.1%	83.6% 81.8%	8.6% 10.8%
		The donor must travel to another province to donate	Donor Recipient	36.2% 28.3%	58.6% 62.6%	4.3% 8.1%
		Travel expenses for the donor and one travel partner are covered if they must travel to another province to donate	Donor Recipient	2.6% 0%	31.0% 23.4%	66.4% 76.6%
		Travel expenses for the donor and >1 travel partner are covered if they must travel from another province	Donor Recipient	2.6% 1.8%	57.8% 35.1%	36.7% 63.1%
		Logistics of donor travel as the most important factor that would hinder my decision to participate	Donor Recipient	*6/116 (5%)* *12/111 (11%)*		
		Upfront costs of traveling as the most important factor that would hinder my decision to participate	Donor Recipient	*4/116 (3%)* *12/111 (11%)*		

KEP, kidney exchange program.

[a]*Likert score 1=strongly disagree, 2=disagree, 3=neither agree nor disagree, 4=agree, 5=strongly agree.*

TABLE 6 | Travel costs for kidney exchange donors reported in prospective surveys.

Study and country	Inclusion	Included costs	Results
Przech et al, 2018 [125], Canada	676 living directed donors, 111 KEP donors and 34 UDs	Ground and air travel, parking, accommodation, prescription medications	Median out-of-pocket costs were 1,254 CAD for direct living donors, with mean difference of +205 CAD for KEP donors and –316 for UDs (both not significant)
Barnieh et al, 2019 [126], Canada	137 directed, 14 KEP donors and 8 UDs in Ontario that received reimbursements from a reimbursement program	Ground and air travel, parking, accommodation, prescription medications	Mean out-of-pocket costs were 2,212 CAD and mean amount reimbursed was 925 CAD for all living donors. KEP donors and UDs had a mean gap of, respectively, 1,677 CAD and 2,691 CAD between out-of-pocket costs and reimbursements

CAD, canadian dollars; KEP, kidney exchange program; UD, unspecified donor.

though the absolute increase was small and not significant after adjustment in Gill et al. [59, 69] Limitations in study design, lack of sufficient adjustment of confounding factors, and significant heterogeneity between studies in CIT duration and local care practices, prevent drawing robust conclusions on the safety of CIT extension. Current evidence does not support a specific cut-off for safe CIT prolongation. It is therefore recommended to keep CIT as short as possible, without compromising transplant opportunities. Comprehensive analysis of data on the safety of shipment is warranted, especially for Europe with the current collaboration for European KEP programs.[1]

Next to CIT, certain patient characteristics might influence the medical risks of shipping, such as donor age, recipient' body mass index, or sensitization [79, 134]. This is an important consideration when shipping over long distances: it might benefit highly immunized patients by expanding the donor pool [18, 68, 98, 101], but these immunized patients are likely more susceptible to the adverse effects of prolonged CIT. Continuous hypothermic machine perfusion during transport might be useful in cases with high risk for DGF or graft loss [18, 134, 135], as it has been demonstrated to reduce DGF and improve 1-year graft survival in deceased donor kidneys [136]. KEPs could consider including the expected CIT in the allocation algorithm [16, 18, 78], although this might aggravate disparities between KEP participants [86].

To overcome the logistical challenges of shipment, KEPs could cooperate with OPOs: they have experienced coordinators, agreements with logistical partners, guidelines for transport and support for billing. We recommend scheduling conference calls between both centers with standardized checklists, as is practiced in the NKR [48], to facilitate communication about surgical and logistical issues. To avoid prolongation of CIT due to logistical barriers, centers should ensure operation room and staff availability and track logistical delays [137]. However, waiting for the arrival of a shipped kidney might be a major challenge for centers with tight operation room scheduling. Furthermore, delayed arrival of the kidney requires additional surgical staff during out-of-office hours.

Donor travel eliminates the medical risks and logistical complexity of shipping [24]. In addition, it enables the surgeon to perform both nephrectomy and implantation, which might be preferred by some centers. In countries with limited resources or limited logistical infrastructure, donor travel might be more convenient for transplant professionals and less costly. For the traveling donor, however, a high number of inconsistencies between centers in donor evaluation and counseling has been reported [21, 99]. In case of donor travel, both centers review the safety for the donor and the quality of the kidney, while in organ shipment the transplanting center mainly reviews the quality of the kidney (as in deceased donor allocation). The double donor evaluation in case of door travel increases evaluation costs, is prone for inconsistencies and likely reduces donor convenience. For example, Canadian living kidney donors reported frustration with the duplication of tests and poor information exchange between centers [139].

Disparities in healthcare quality between centers discourage donors to travel to another center [122]. However, this also hampers organ shipment, as the recipient surgeon must rely on the donor surgeon for the kidney procurement. Due to this dependency, transplant surgeons might feel reluctant to accept surgical-technical challenging or extended-criteria kidneys. It is necessary to standardize and disseminate KEP protocols, especially in international KEPs, for donor evaluation, informed consent, surgery and follow-up [139].

Donors reported reduced willingness to participate in KEPs when traveling to another region. Remarkably, willingness was not reduced if they had to travel to another hospital in the same city, suggesting that the unfamiliarity with the other hospital and team might not be a main hurdle [119]. In the Dutch KEP with donor travel, graft outcomes and health-related quality of life were similar for KEP and non-KEP donors [135, 140], although this could be related to the relatively short travel distances.

Most of the logistical and financial distress of donor travel can be addressed by good reimbursement programs and consistent donor evaluation and counseling. Healthcare payors should therefore provide reimbursements for all out-of-pocket costs of KEP donors and traveling companion, including travel, parking, accommodation, meals, and loss of workdays, also in cases where the recipient center declines the traveling donor after evaluation [50, 86, 96, 141]. In addition, centers should manage expectations of traveling KEP donors: the decision for surgery type and side

[1]https://www.hnbts.hu/euro-kep/project

TABLE 7 | Professional perspectives on donor travel and organ shipment in kidney exchange programs.

Study and Country	Study type	Participants	Results
Adams et al, 2002 [105] United States	Report of National Conference	N = 32 American transplant professionals (medical, logistical, government)	- Donor travel is ideal from surgical perspective due to short CIT and low DGF rate - UDs are at risk of non-reimbursed expenses due to limited available financial resources. UDs should not be burdened to travel
Woodle et al, 2005 [132], United States	Survey prior to initiation of multicenter KEP	N = 48 Transplant program personnel from eight transplant programs	- A significant degree of indecisiveness was expressed (mean Likert score 2.7) about the decision to participate in multicenter KEP. - Specific concerns and perceived barriers to multicenter KEPs included: (1) the need for donor travel, (2) financial concerns, (3) privacy and confidentiality maintenance, (4) medical equity assurance of quality of kidneys and (5) potential for medical-legal complications
Woodle et al, 2005 [49] United States	Pre- and post-conference survey	N = 48 Representatives from eight transplant programs	- Mean Likert score[a] (1 = strongly agree, 5=strongly disagree) for being concerned about travel costs for the donor was 1.7 before and 1.49 after the educational conference (no significant difference)
Clark et al, 2010 [107] United States	Web-based survey	N = 78 Directors of 78 different transplant programs	- Donor travel was frequently cited in the open-ended comments by centers that did not want to participate in national KEP. - Logistics of donor travel was the most frequently cited, but not most important, barrier to national KEP participation
Durand et al, 2014 [133] Canada	Semi-structured interview study	N = 19 Transplant personnel from four adult transplant centers	- Traveling companion expenses for compatible pairs should be reimbursed if organ shipment is not possible - Transporting the kidney rather than the donor was one of the four conditions mentioned for compatible pair participation
Melcher et al, 2013 [86] United States	Consensus conference report	N = 73 Transplant hospital personnel, transplant recipients and donors, insurance industry and government agency representatives	- Donors should have the option, but never be required to travel to the recipient's center. KEP centers should be willing to transport kidneys, both from and to the center, as current evidence shows it can be performed safely and it maximizes KEP participation and volume - Priorities for reducing distance between centers and prioritizing same center matches could be incorporated but should be deemphasized, as they represent logistical rather than biological considerations - Payers should cover donor travel and lodging costs when a donor travels for KEP.
Tietjen et al, 2019 [87] United States	Consensus report and guidance	N = 7 Experts in transplant administration and clinical care	- Transplant programs should facilitate reimbursement of travel costs by referring donors to the available services, including insurance providers and the National Living Donor Assistance Center

CIT, cold ischemia time; DGF, delayed graft function; KEP, kidney exchange program; UD, unspecified donor.
[a]Likert score 1=strongly agree, 2=agree, 3=neither agree nor disagree, 4=disagree, 5=strongly disagree.

of nephrectomy should be left to the operating donor surgeon. Counseling of potential donors must be improved, as only half of all donors in the NKR received education about organ transport and reimbursements [142]. Combined policies with both organ shipment and donor travel based on donor/recipient preferences can be considered to optimize donor convenience.

Strengths and Limitations

This review summarizes current evidence on organ shipment and donor travel in KEP, providing actionable recommendations for policymakers and clinicians (**Table 8**). KEPs should weigh these arguments for their specific situation.

Many of the included studies did not investigate our outcomes of interest as primary outcome. The retrospective design brings inherent bias, especially for the studies on CIT. Additionally, long term follow-up data on prolonged CIT in shipped versus non-shipped living donor kidneys was limited, and cost-comparison studies on donor travel versus organ shipment were not found. Furthermore, the external validity of our findings is limited due to a geographic disbalance: studies on CIT, logistics and professional perspectives were mainly performed in the US and studies on

TABLE 8 | Recommendations for clinical practice.

Organ shipment	Donor travel
Keep CIT as short as possible without compromising transplant opportunities, given the potentially higher risk of DGF.	Ensure comprehensive reimbursement of travel-related out-of-pocket costs for the donor and a travel companion, and donor's loss of workdays, with the possibility of payments in advance.
Consider the use of machine perfusion for kidneys with expected CIT >8 h, kidneys from older donors and kidneys for highly immunized recipients.	Offer organ shipment to donors unwilling to travel (especially for unspecified or compatible KEP donors).
Collaborate with organ procurement organizations to streamline the logistics of shipment, and agree on transfer conditions and liability with logistical parties.	Discuss with the donor that evaluation will take place in two different centers and that the final surgical approach will be decided on in the transplanting center.
Organize conference calls with checklists to standardize pre- and post-operative communication between surgeons.	Communicate the KEP match to the donor after both centers reviewed and agreed on medical and immunological test results.
Schedule operation theatre upfront and keep operation theatre available when delays in transport occur.	Consider donor travel in specific situations, such as recipients with high DGF risk or surgical-technical issues, limited operating room availability, or insufficient logistical infrastructure.
Agree on the billing of donor evaluation and procurement costs with payors and insurance providers.	Ship kidneys in international exchange to ensure consistent care, follow-up and convenience for donors.
Consider including expected CIT as variable in the matching algorithm.	Consider allocation based on donor/recipient preferences or preferred travel-distances.
Share protocols for donor evaluation and surgery between the centers.	

CIT, cold ischemia time; DGF, delayed graft function; KEP, kidney exchange program.

donor care and donor perspectives were mainly performed in Canada, while few studies were performed in Europe. Studies of KEPs in developing nations were even more sparse, and ethnic minorities were underrepresented in the qualitative studies [20, 119, 120, 125]. Additionally, while the recommendations were based on the available evidence, they may inherently reflect our interpretations, experiences, and professional opinions.

Conclusion

Multicenter KEPs facilitate a timely and well-matched living donor transplant. However, the involvement of different transplant centers imposes challenges. Either by donor travel, organ shipment or combined policy, programs must guarantee medical and logistical safety, consistent care for donor and recipient and financial justice for all parties.

AUTHOR CONTRIBUTIONS

MtK screened the articles, extracted the data, performed the data analysis, and wrote the manuscript. MrK screened the articles, checked the data extraction, wrote and reviewed the manuscript. FD, SL, RM, SH, and JW reviewed the manuscript. LP participated in research design and reviewed the manuscript. AW drafted the idea, participated in research design, wrote and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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SYSTEMATIC REVIEW AND META-ANALYSIS
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Impact of Islet Transplantation on Type 1 Diabetes-Related Complication: A Systematic Review

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Islet transplantation is a valuable therapy for selected type 1 diabetes mellitus (T1DM) patients, especially those with recurrent severe hypoglycemia, glycemic variability, or impaired hypoglycemia awareness. It improves glycemic control and protects against hypoglycemic episodes. Beyond glucose regulation, islet transplantation may mitigate diabetes-related microvascular and macrovascular complications. We conducted a systematic review to assess its impact on vascular outcomes in T1DM, focusing on islet transplantation alone (ITA) and islet-after-kidney transplantation (IAK). We included studies that quantitatively assessed vascular complications after ITA or IAK in adults with T1DM. Eligible studies compared pre-and post-transplant outcomes or posttransplant outcomes with control groups receiving standard treatment. Twenty-five studies (1,373 patients) evaluated microvascular and macrovascular outcomes using eGFR, ophthalmic e xams, and nerve conduction studies. Islet transplantation was associated with stabilization or improvement in most microvascular complications and longterm renal function preservation. While macrovascular data were less frequent, improvements in vascular health markers such as reduced procoagulant states and atherosclerosis progression were reported, suggesting possible reductions in cardiovascular events and mortality, though data remain limited. Islet transplantation shows clear benefits for microvascular complications and potential advantages for macrovascular outcomes, alongside its established role in improving glycemic stability and quality of life.

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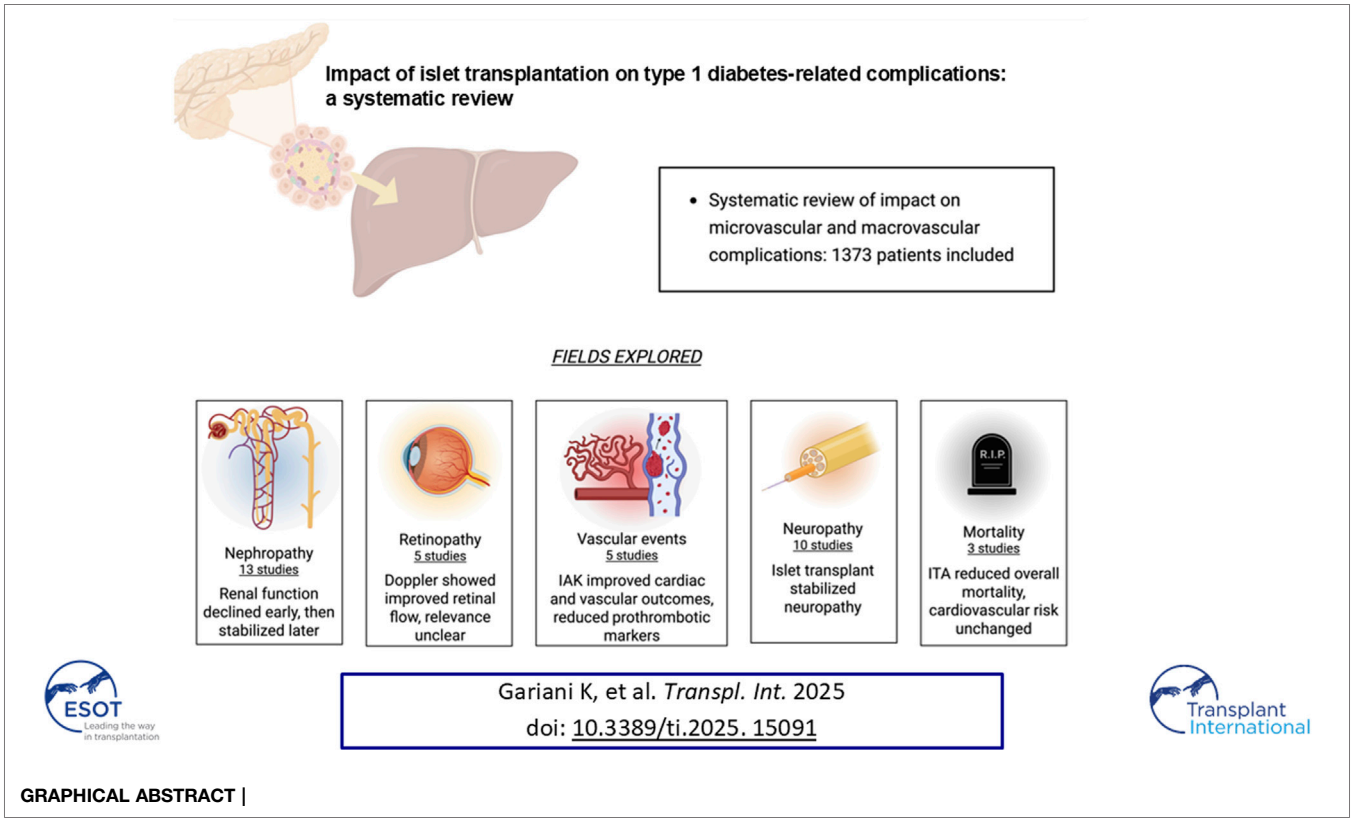

GRAPHICAL ABSTRACT |

INTRODUCTION

The landmark Diabetes Control and Complications Trial (DCCT) established that intensive glucose management in individuals with type 1 diabetes mellitus (T1DM) significantly reduces the incidence of microvascular complications. The subsequent Epidemiology of Diabetes Interventions and Complications (EDIC) study, which extended the follow-up of DCCT participants, further demonstrated that sustained glycaemic control confers long-term protection not only against microvascular complications but also against macrovascular complication events, including myocardial infarction, stroke, and cardiovascular (CV) mortality [1].

Islet transplantation (ITx) has emerged as a valuable treatment option for patients with unstable T1DM. Over the past three decades, substantial progresses have been made in elucidating the mechanisms underlying the loss of functional islet mass, as well as in developing strategies to preserve and enhance islet survival [2–5]. ITx provides significant benefits, particularly for patients with problematic glycaemic profile instability [6, 7]. Recent long-term outcome data have yielded encouraging results. At 1-year post-transplantation, approximately 60% of recipients achieved insulin independence. This proportion declined to around 30% at 5 years and to approximately 20% by 10 years [8]. Nevertheless, even partial islet function may have beneficial effects on diabetes-related complications compared to complete loss of graft function.

In the Edmonton single-centre cohort of 255 patients followed for up to 20 years after ITx [8], 70% achieved sustained graft survival, with a median graft survival of 5.9 years and insulin independence rates of 61% at 1 year and 8% at 20 years. Prolonged graft survival was significantly associated with older recipient age, longer diabetes duration, lower baseline insulin requirements, the combined use of anakinra and etanercept (adjusted odds ratio 7.5), and a BETA-2 score of 15 or higher at 6–12 months after transplantation (adjusted odds ratio 4.1).

Nevertheless, a considerable number of patients who resumed insulin therapy retained partial graft function, resulting in improved glycaemic control and a marked reduction in the frequency and severity of hypoglycaemic episodes. These findings underscore the potential of ITx to provide durable metabolic benefits and to the long-term potential of ITx to enhance metabolic stability and quality of life for patients with T1DM.

T1DM is associated with a range of long-term complications, including microvascular diseases such as diabetic retinopathy, neuropathy, and nephropathy, as well as cardiovascular diseases (CVD). After approximately a decade of disease progression, microvascular complications are observed in around 50% of individuals, while approximately 6% experience macrovascular involvement [9]. Although hyperglycaemia may be managed through exogenous insulin therapy, this does not fully replicate the endogenous, finely tuned regulation of blood glucose. ITx provides an established therapeutic approach

aimed at restoring insulin secretion, thereby facilitating improved glycaemic control. This approach holds the potential not only to mitigate, but in some cases to prevent, the progression of diabetes-related complications.

Considering this, we undertook a systematic review of the literature to assess the impact of ITx on both micro- and macrovascular complications associated with T1DM.

METHODS

Data Sources and Searches

The approach for search strategy, study selection, and data extraction and analysis was guided by a pre-defined protocol registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD420251036400). This systematic review adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [10].

We systematically identified all studies providing a quantitative assessment of diabetes-related complications after islet transplant alone (ITA) or islet-after-kidney (IAK). The literature search encompasses Medline records from 1966 to April 2025. A comprehensive search strategy was conducted using the following combination of keywords and MeSH terms: (islet OR IAK OR ITA) AND (graft OR allograft OR transplant*) AND (microvascular OR macrovascular OR microvascular complication* OR macrovascular complication* OR chronic complication* diabet* complication* OR diabetic nephropathy OR nephropathy OR albuminuria OR microalbuminuria OR macroalbuminuria OR diabetic kidney disease OR kidney disease OR renal disease OR maculopathy OR retinopathy OR diabetic retinopathy OR neuropathy OR diabetic peripheral neuropathy OR diabetic neuropathy OR peripheral neuropathy OR sensory neuropathy OR peripheral arterial disease OR Peripheral Vascular Diseases OR diabetic foot OR foot ulcer OR amputation OR atherothrombo* OR stroke OR CVD OR myocardial infarction OR ischaemic heart disease).

No restriction was placed on publication date or language during the literature search. In addition, the reference lists of all retrieved articles were manually screened to identify further relevant studies. Two investigators (KG and AP) independently assessed titles, abstracts, and full-text articles. Discrepancy regarding study inclusion were resolved through discussion between the two reviewers, with the involvement of a third author (TB) when consensus could not be reached.

Eligibility Criteria

We included observational, prospective studies that investigated the progression of diabetes-related complications after transplantation in adults with T1DM who had undergone IAK or ITA. Diabetes-related complications were defined as the occurrence of nephropathy, retinopathy, neuropathy, peripheral arterial disease, lower-limb amputations, foot ulcers, stroke and myocardial infarction. Studies were excluded if they were case reports, letters to the editor, or investigations conducted on animal models.

Data Extraction

Data extraction was performed by KG in accordance with predefined criteria and independently verified for accuracy by AP. Extracted data included demographic and clinical characteristics of the study population (such as mean age, sex, study design, and time elapsed since transplantation), study characteristics (including country of origin, study design, sample size, and duration of follow-up. Outcomes of interest were defined as diabetes-related complications.

Data Synthesis and Methodological Quality Rating

Owing to substantial heterogeneity in the methodologies employed to assess diabetes-related complications—ranging from generic to disease-specific measures—as well as marked variability in study designs and the limited number of studies evaluating certain complications, neither meta-analysis nor direct comparison of outcomes was undertaken.

The methodological quality of the included studies was appraised using the Newcastle–Ottawa Scale (NOS) [11]. This scale evaluates three key domains: selection of study participants (up to four points), comparability of study groups (up to two points), and ascertainment and reporting of outcomes (up to three points), with a maximum total score of nine. Based on total score, studies were classified as poor (0–3), fair (4–6), or good (7–9). Studies scoring ≤3, indicating significant methodological limitations were excluded from further analysis. Scoring was performed by KG and independently verified for accuracy by AP. The findings were therefore synthesised narratively, without the generation of pooled estimates for diabetes-related complications.

RESULTS

Characteristics of Included Studies, Methodological Quality

Our search strategy yielded 2,034 unique records, of which 1,968 following title and abstracts screening. A total of 66 full-text articles were assessed for eligibility. Upon detailed evaluation, 30 studies met the predefined inclusion criteria. Five articles were excluded due to overlapping patient populations and smaller sample sizes relative to included studies. Finally, 25 studies, encompassing a cumulative total of 1,373 patients, were included in this systematic review. [12–34]. The study selection process is summarized in **Figure 1**.

Among the included studies, 13 were conducted in Europe, 10 in North America and 3 in Oceania. In terms of study design, 14 were prospective cohort studies, 8 were retrospective analyses, and 2 were cross-sectional studies. Detailed characteristics of the included studies, along with the diagnostic methodologies employed, are described in **Table 1**.

Study Quality

According to the NOS scale performed for a critical appraisal, the overall methodological quality of the studies was deemed to be satisfactory, with an average NOS score of 7.0 out of a maximum

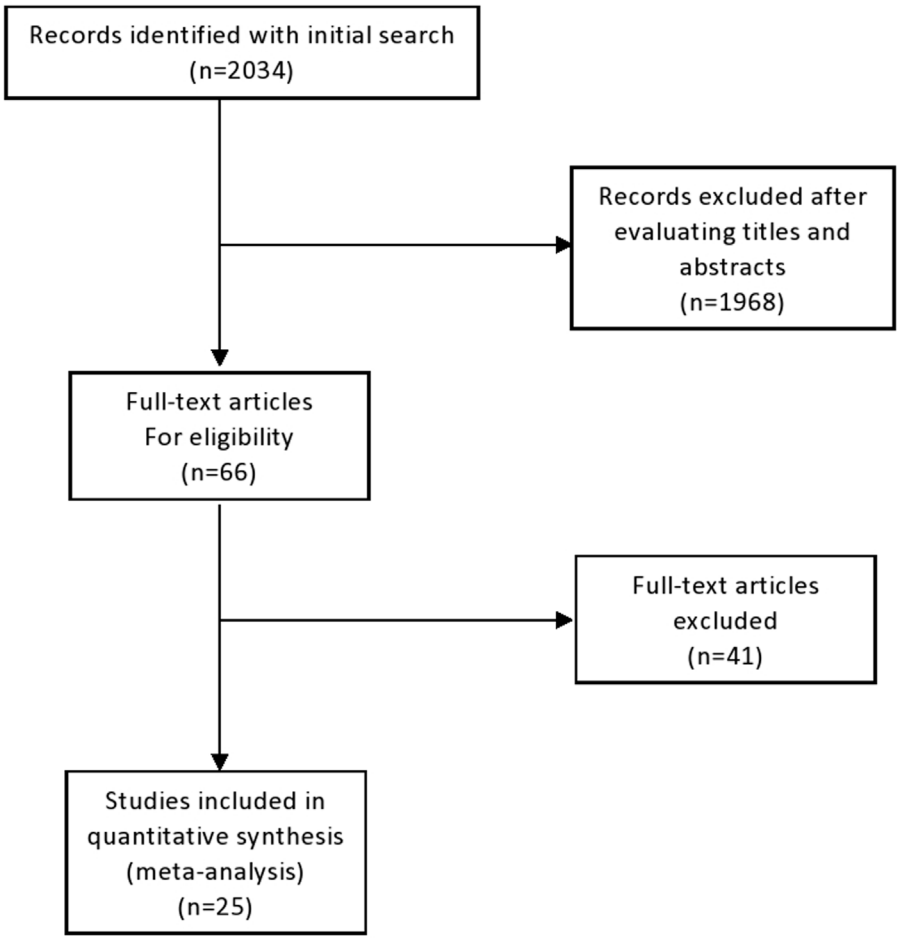

FIGURE 1 | Flow-chart of study selection.

of 9, indicating a generally robust standard of reporting and design across the included literature. Specifically, 7 study achieved a score of 8, reflecting a high level of methodological rigour, 11 studies received a score of 7, denoting good quality with minor limitations, while 7 studies scored 6, suggesting moderate quality with some potential risk of bias in one or more domains. Importantly, no study was excluded on the basis of methodological weakness, as none score below the exclusion threshold of 2 points. This overall quality distribution supports the reliability of the findings synthesised in the review and lends confidence to the narrative interpretation of the reported outcomes (**Table 1**).

Impact on Microvascular Complications

Diabetic Nephropathy

13 studies evaluating the progression of renal function and diabetic nephropathy following ITx were identified. The sample size across studies varied substantially, ranging from 4 to 677 participants, as did the duration of follow-up, which spanned from 1 to 13 years (**Table 1**). Renal function at the end of the follow-up assessed either in comparison to the pre-transplant baseline measurements or to various control groups, including individuals managed with intensive insulin therapy (basal-bolus regimens), recipients of kidney transplantation alone (KTA), recipients of pancreas transplantation, or individuals in whom ITx was unsuccessful. Among studies comparing renal function before and after transplantation, with follow-up periods ranging from 1 to over 9 years, a decline in renal function was consistently observed (**Figure 2**). This decline appeared to be more pronounced during the first post-transplant year, with reductions in eGFR reaching up to 10 mL/min, followed by stabilization in the subsequent years [26, 28, 35].

To reduce the potential confounding impact of immunosuppressive therapy on renal outcomes, one study compared 40 T1D transplant recipients who received IAK with 80 individuals who underwent kidney transplant alone (KTA). The IAK group demonstrated a significantly slower rate of renal function decline relative to the KTA group [25].

Furthermore, a separate study comparing 45 IAK and 61 ITA recipients reported a significant lower incidence of dialysis initiation among the IAK cohort, thereby reinforcing the evidence of the renal protective effect of IAK over ITA [27].

TABLE 1 | Main characteristics of the included studies.

Author, year	Design	Country	Type of transplantation	Time assessmeent after tx	Transplanted individuals (N)	Age (years)	Female (%)	Diabetes duration before (tx)	Complication assessed	Comparison group	NOS score
Alhaidar [12]	P	USA	ITA	75 months	13	44.5	69	NA	Diabetic neuropathy	Before ITA	6
Andres [13]	R	Switzerland	ITA and IAK	12 months	5 ITA and 5 IAK	43	50	NA	Diabetic nephropathy	Combined groups (ITA and IAK) before transplantation	6
Barton [14]	P	USA, Canada, France, Switzerland, Italy, Australia	ITA (85%) and IAK/SIK (15%)	5 years	677	44.3	59.2	28.8	Diabetic nephropathy	Combined groups (ITA, IAK, SIK) before transplantation	8
D'Addio [15]	P	Italy	ITA	15 months	12	36.9	67	23.3	Prothrombotic factors, platelet function and ultrastructure	Type 1 diabetic patients and healthy control individuals	7
Danielson [16]	P	USA	IAK	12 months	15	49	87	30.1	Carotid intima-media thickness	Before IAK	7
Del Carro [17]	P	Italy	IAK	53 months	18	41.8	56	26.3	Diabetic neuropathy	Kidney transplantation alone and before IAK	7
Deshmukh [18]	R	Australia	ITA	4 years	8	NA	NA	NA	Cardiac autonomic neuropathy (CAN)	Type 1 diabetes individuals	7
Fensom [19]	Crossectional	Canada	ITA	74 months	30	44		29	Diabetic neuropathy	Medical therapy	8
Fiorina [20]	P	Italy	ITA	7 years	24	41.9	NA	27.2	Diabetic nephropathy	T1D individuals with unsuccessful islet transplantation	7
Fiorina [21]	P	Italy	IAK	7 years	37	41.8	NA	27.1	Cardiovascular death, endothelial injury and atherothrombotic profile	T1D patients still on hemodialysis	7
Fiorina [22]	P	Italy	IAK	3 years	17 IAK 25 KTA	48.6	45.2	31	Carotid intima-media thickness Left ventricular function	Before IAK	7
Hering [35]	P	Canada and USA	ITA	24 months	48	48.4	60	28.5	Diabetic nephropathy	Before ITA	8
Lee [23]	P	USA	ITA	12 months	8	NA	NA	NA	Diabetic neuropathy and diabetic retinopathy	Before ITA	6
Lehmann [24]	P	Switzerland	SIK/IAK	13 years	38	51.8	50	37	Diabetic nephropathy	Combined SPK/PAK after transplantation	7
Maanaoui [25]	R	France	IAK	10 years	40	46.1	43	NA	Diabetic nephropathy	Kidney transplantation alone	8
Nijhoff [34]	R	Netherlands	IAK	24 months	13	50.9	38	35,5	Diabetic nephropathy	Before ITx	7
O'Connell [26]	P	Australia	ITA	12 months	17	49.8	82		Diabetic nephropathy	Before ITA	6
Palmer [36]	R	Australia	ITA	4.7 years	16	NA	NA	NA	Cardiovascular autonomic neuropathy	Before ITA	6
Perrier [27]	R	France	ITA, IAK	11.7 years	61 ITA and 45 IAK	48	44.3	32	First occurrence of a composite criterion composed of mortality, transient ischemic stroke, nonfatal stroke, nonfatal	T1D control patients for ITA and T1D + KTA for IAK.	8

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TABLE 1 | (*Continued*) Main characteristics of the included studies.

Author, year	Design	Country	Type of transplantation	Time assessmeent after tx	Transplanted individuals (N)	Age (years)	Female (%)	Diabetes duration before (tx)	Complication assessed	Comparison group	NOS score
									myocardial infarction, amputation or dialysis.		
Rickels [28]	R	USA, Canada	ITA and IAK	4.55 years of follow-up in the ITA group and 3.43 years of follow-up in the ITA group	48 ITA and 24 IAK	48.6	55.6	33	Diabetic nephropathy	Before ITA for individuals with ITA and before IAK for individuals with IAK	8
Ryan [29]	R	Canada	ITA	5 years	65	42.9	57	27.1	Diabetic nephropathy, diabetic neuropathy and diabetic retinopathy	Before ITA	8
Tekin [30]	R	USA	ITA	9.2 years	4	44.3	75	30	Diabetic nephropathy, diabetic neuropathy, and diabetic retinopathy	Before ITA	6
Thompson [31]	Crossectinal	Canada	ITA	66 months	29	NA	NA	NA	Diabetic nephropathy, diabetic neuropathy and diabetic retinopathy	DT1 individuals intensively medically treated	7
Vantyghem [32]	P	France	ITA, IAK	5 years	21	NA	NA	NA	Diabetic neuropathy and CAN	Combined groups (ITA,IAK) before transplantation	6
Venturini [33]	P	Italy	ITA	12 months	10	38	NA	24.9	Diabetic retinopathy	Before ITA and DT1 patients on waiting list for transplantation	7

C, cross-sectional study; CAN, cardiac autonomic neuropathy; IAK, islet after kidney; ITA, islet transplant alone; NA, non-available; P, prospective study; PAK, pancreas after kidney transplant; R, retrospective study; SIK, simultaneous islet-kidney transplantation; SPK, simultaneous pancreas-kidney transplant.

Patients with unsuccessful ITx exhibited a higher incidence of renal graft loss and a more pronounced increase in the microalbuminuria index compared to individuals in the IAK group who maintained functioning grafts [20]. Finally, when compared with a cohort of 8 T1DM patients treated with intensive insulin therapy, 29 recipients of IT showed an attenuated decline in eGFR [31].

Diabetic Retinopathy

Data on diabetic retinopathy progression was reported in 5 studies, including a total of 116 patients (**Figure 3**). All studies exclusively included patient who had undergone ITA, with baseline prevalence of diabetic retinopathy ranging from 50% to 80%. Retinopathy assessment methods included fundoscopic examination or colour Doppler imaging of the central retinal arteries and veins. In longitudinal analyses comparing retinopathy status before and after ITA, 2 studies reported no progression of diabetic retinopathy, indicating clinical stability over follow-up periods ranging from 1 to 9 years [23, 30]. Another study, with a 5-year follow-up, showed that, among 65 patients, 4 required treatments with laser photocoagulation or vitrectomy [29]. A comparative study involving a cohort of 29 individuals evaluated retinopathy progression in ITA recipients versus those receiving medical treatment alone and demonstrated a significantly greater progression of retinopathy in the medically treated group ($p < 0.01$) [31]. In a separate study using colour Doppler imaging to assess retinal vasculature, a significant improvement in blood flow velocities both in the central retinal artery and vein was observed at 12 months post-ITA in 10 recipients. This finding suggests a potential stabilising or protective effect of ITA on the progression of diabetic retinopathy. In contrast, among patients with T1DM followed for 1 year, no change was observed in the central retinal artery, while a trend towards reduced flow velocity was noted in the central retinal vein, possibly indicative of disease progression [33]. The precise clinical significance of these haemodynamic changes, however, remains to be determined.

Diabetic Neuropathy

A total of 10 studies assessing the progression of diabetic neuropathy after ITx were identified. Of these, 8 focused specifically on peripheral diabetic neuropathy, 2 addressed cardiac autonomic neuropathy (CAN), and 1 investigated both conditions. Follow-up duration ranged from 12 months to over 9 years. Assessment of diabetic peripheral polyneuropathy employed a variety of methodologies including clinical scoring systems, neurothesiometry, and nerve conduction studies (NCS) (**Figure 4**). Across these studies, a general trend towards stabilization of diabetic peripheral neuropathy after transplantation was observed, with some patients showing improvements in conduction parameters.

Notably, two studies comparing the progression of neuropathy in T1DM patients undergoing ITx versus those receiving intensive insulin therapy (IIT) reported differing outcomes: while neuropathy tended to improve in the IIT group, a worsening was observed in the non-transplanted T1DM controls [19, 31].

In the study comparing the progression of diabetic neuropathy between 18 ITx patients and 9 undergoing KTA, the aim was to mitigate the potential confounding influence of immunosuppressive therapy, known for its possible neurotoxic effects. Diabetic neuropathy was present in all participants at baseline, prior to transplantation. Neuropathy progression was assessed using NCS scores, sensory action potentials (SAP), and compound motor action potential (CMAP) amplitudes. The ITx group showed an improvement in the NCS score over time, whereas no significant change was observed in the KTA group after 53 months of follow-up.

Furthermore, improvements in SAP and CMAP amplitudes were observed in the ITx group, while both parameters declined in the group undergoing KTA [17].

Regarding the type of neuropathic involvement, sensory neuropathy showed a tendency to improve relative to the pre-transplant baseline values, while motor function remained stable [12, 32]. Moreover, when compared with control groups consisting of patients receiving either medical treatment or KTA, patients undergoing ITx demonstrated significantly more favorable outcomes [17, 19].

CAN was assessed in three studies. In a study evaluating heart rate variability via a 24-h Holter monitor, no significant difference was observed between a group of patients 4 years after ITA and a control group of T1DM patients [18].

Two additional studies examined CAN in patients both before and after ITx. In a cohort of 16 subjects, a significant reduction in resting heart rate was observed nearly 5 years following ITA, compared to baseline values prior to transplantation, thus suggesting an improvement in CAN [36]. In contrast, another study involving 21 subjects, no significant difference in CAN was observed 5 years post-transplantation [32].

Macrovascular and Coagulation Parameters

Five studies have explored the impact of ITx on outcomes related to mortality, CVD, atherosclerosis development, left ventricular function, prothrombotic status, and endothelial injury. A multicentre study comparing 61 ITA recipients with propensity score-matched 610 T1DM patients reported no significant differences in the incidence of major macrovascular events, such as myocardial infarction, stroke, transient ischemic attack, or lower-limb amputation. Interestingly, data from the same study suggested a higher risk of myocardial infarction in the 45 IAK individuals (**Figure 5**) [27].

In another study involving 15 patients, a reduction in carotid intima-media thickness (CIMT) was observed 12 months post-transplantation, as assessed by arterial ultrasound, compared to pre-transplant measurements. Among the seven patients re-evaluated at 50 months, both common and internal CIMT remained significantly lower than at baseline [16]. A separate study compared changes in CIMT and left ventricular function between patients undergoing 17 IAK and 25 KTA recipients, from baseline to 3 years post-transplant. Results indicated that CIMT remained stable over the 3-year period in the IAK group, whereas the KTA group experienced a significant progression in CIMT. From a cardiological perspective, patients in the IAK

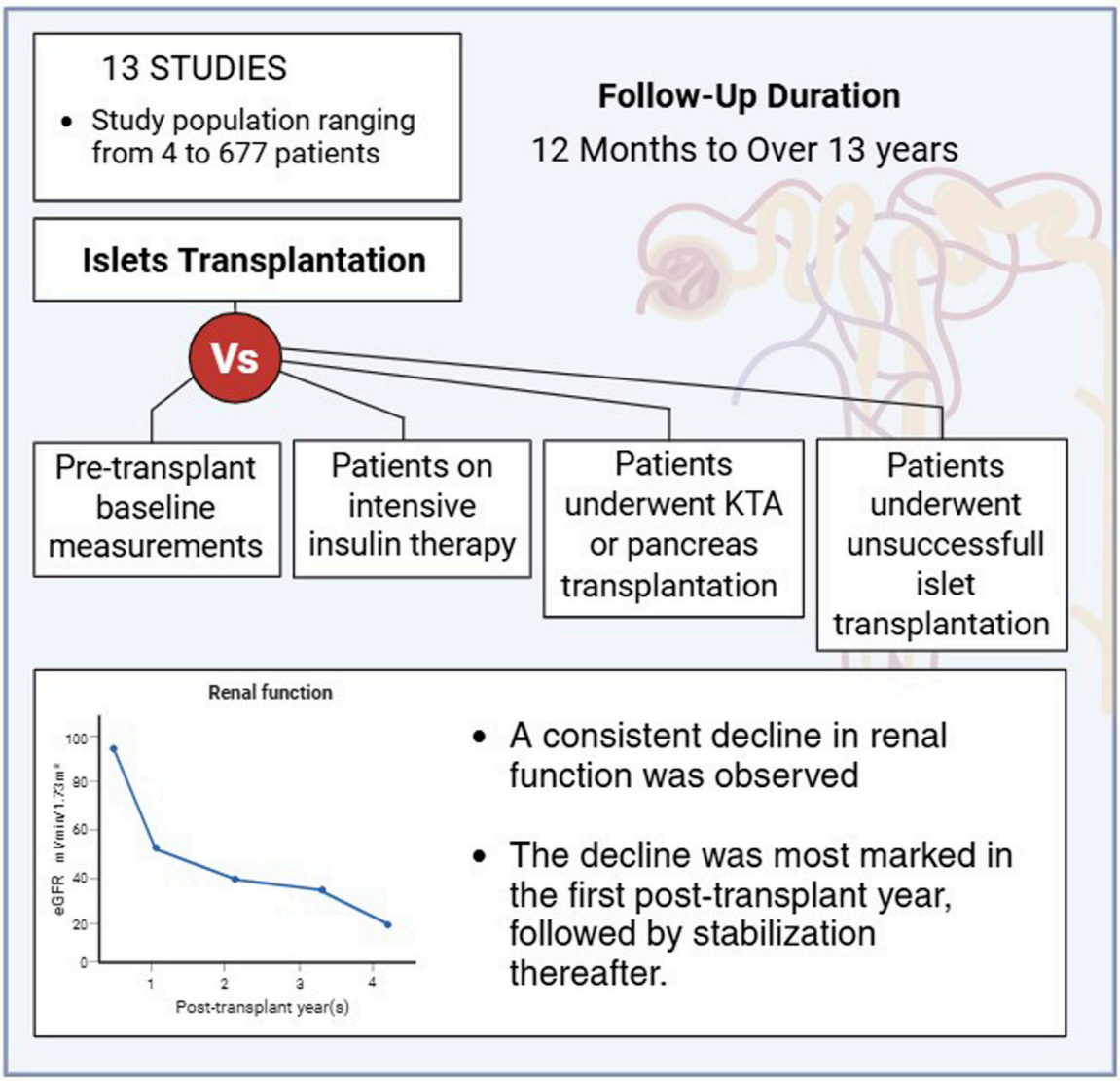

FIGURE 2 | Summary of 13 studies with follow-up durations ranging from 12 months to 13 years, showing an initial decline in renal function during the first year post-transplantation, followed by stabilization in subsequent years.

group showed significant improvements in left ventricular function, as evidenced by an increased left ventricular ejection fraction, an enhanced mean peak filling rate, and a reduction in B-type natriuretic peptide (BNP) levels. In contrast, no significant changes were observed in the KTA group, indicating that both systolic and diastolic ventricular function improved in the IAK cohort, while remaining stable in the KTA group [22].

Two studies assessed the evolution of plasma prothrombotic markers following ITx. Compared to 196 T1DM subjects on haemodialysis, 37 patients with IAK showed a reduction in various atherothrombotic plasma markers, such as XDP levels or F1 and F2 fragments. Additionally, an increase in antigenic activity of protein C and ATIII levels was observed, indicating an improvement in natural coagulation activity. A significant reduction in CV mortality was also observed in the group of patients with IAK [37].

Another study, also focusing on atherothrombosis parameters, highlighted that 12 patients undergoing ITA showed near-complete normalization of platelet morphology and function. Moreover, levels of prothrombotic markers such as fibrinogen and D-dimer approached normal values, in contrast to T1DM subjects who had not undergone transplantation [15].

Mortality

To date, data concerning mortality following ITA or IAK remain very limited, with only three studies available. In one of these investigations, 61 ITA recipients were matched with 610 T1DM control patients and followed for over a decade. A significant

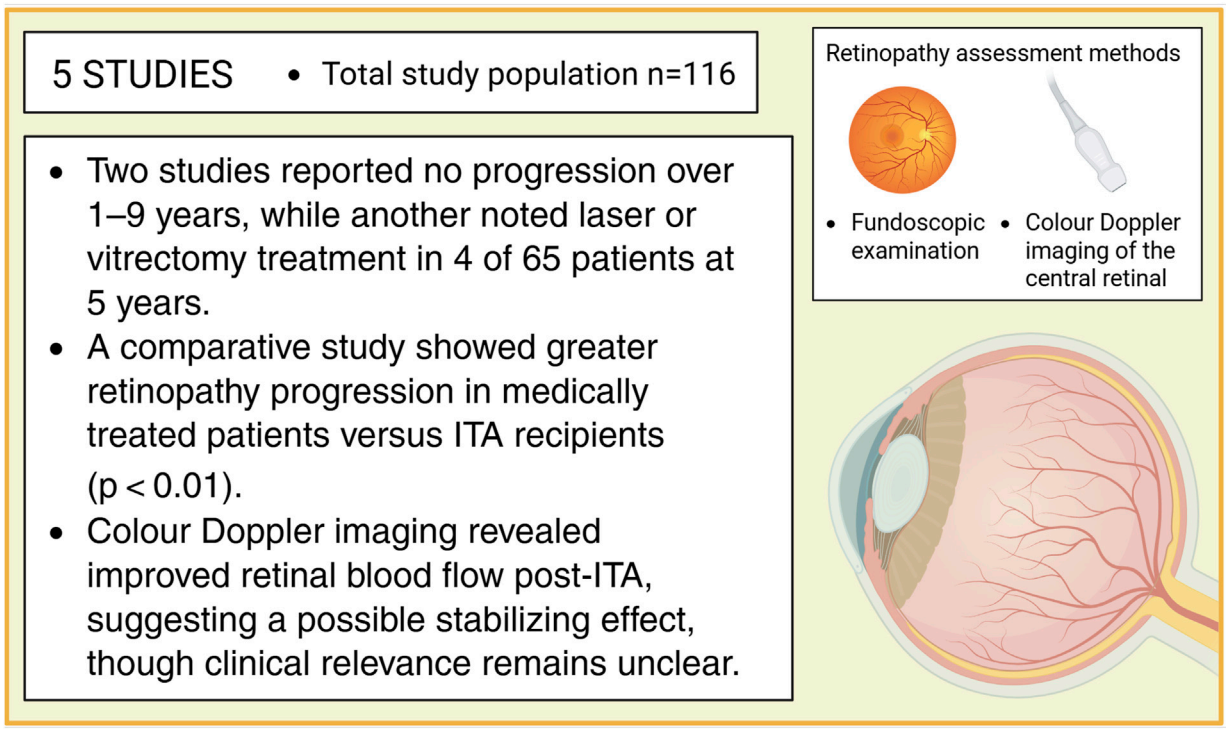

FIGURE 3 | Impact of islet transplantation on the progression of diabetic retinopathy, showing a tendency toward stabilization and more favorable outcomes compared to patients treated with medical therapy alone.

reduction in all-cause mortality was observed among ITA recipients compared to their T1DM counterparts [27]. This observation should be interpreted cautiously because of the small number of events; nonetheless, it might reflect a decrease in CV incidents, as suggested by the trend of fewer myocardial infarction and strokes in the ITA group.

In the study by Maanaoui et al. [25], 40 kidney transplant recipients with type 1 diabetes who underwent IAK transplantation demonstrated significantly improved patient–graft survival compared with those who received KTA. Notably, this benefit was primarily driven by a reduction in mortality risk, rather than by an improvement in death-censored graft survival or a slower decline in renal function. Specifically, no significant association was found between IAK and death-censored graft survival (HR 0.73, 95% CI 0.30–1.89; p = 0.36), indicating that the protective effect was attributable to a reduced risk of death rather than improved renal outcomes *per se*. Importantly, CV causes and sudden death at home were the main causes of mortality (**Figure 6**).

The third study evaluating mortality after ITx, reported that the rate of CV death among the 37 individuals of the IAK group (18%) was comparable to that observed among the 42 patients from the KTA group (19%) and in the 196 people with T1DM undergoing haemodialysis (16%).

A lower CV mortality rate was found in the group underwent simultaneous islet and kidney transplantation (5%), comparable to the rate observed in the uremic T1DM patients who received SPK transplantation (8%). Moreover, within the ITA group, CV outcomes varied according to the success of ITx, underscoring the potential additional benefit of achieving successful and sustained islet function [37]. Of note, mortality was not considered a primary outcome in the included studies, and any interpretation should therefore be regarded as exploratory analysis.

CONCLUSION

This systematic review highlights a consistent improvement in microvascular complications (and possibly in macrovascular outcomes) following ITx, whether ITA or IAK. These benefits were observed in comparison with the pre-transplant state, standard medical therapy in T1DM, and KTA. IT was found to promote stabilization and, in some cases, potential improvement, of several diabetes-related complications relative to baseline. Such improvements are particularly important for T1DM patients who suffer from several complications that impact significantly the quality of life, induce morbidity and potentially impact their life-expectancy.

These findings may, in part, be attributed to the improvement in post-transplant glycaemic control, a relationship previously observed in the DCCT. For instance, regarding diabetic neuropathy, it was present at baseline in 5.6% of patients in the conventional group and 6.8% in the intensive group. After 6.5 years of follow-up, the prevalence increased to 17.5% in the

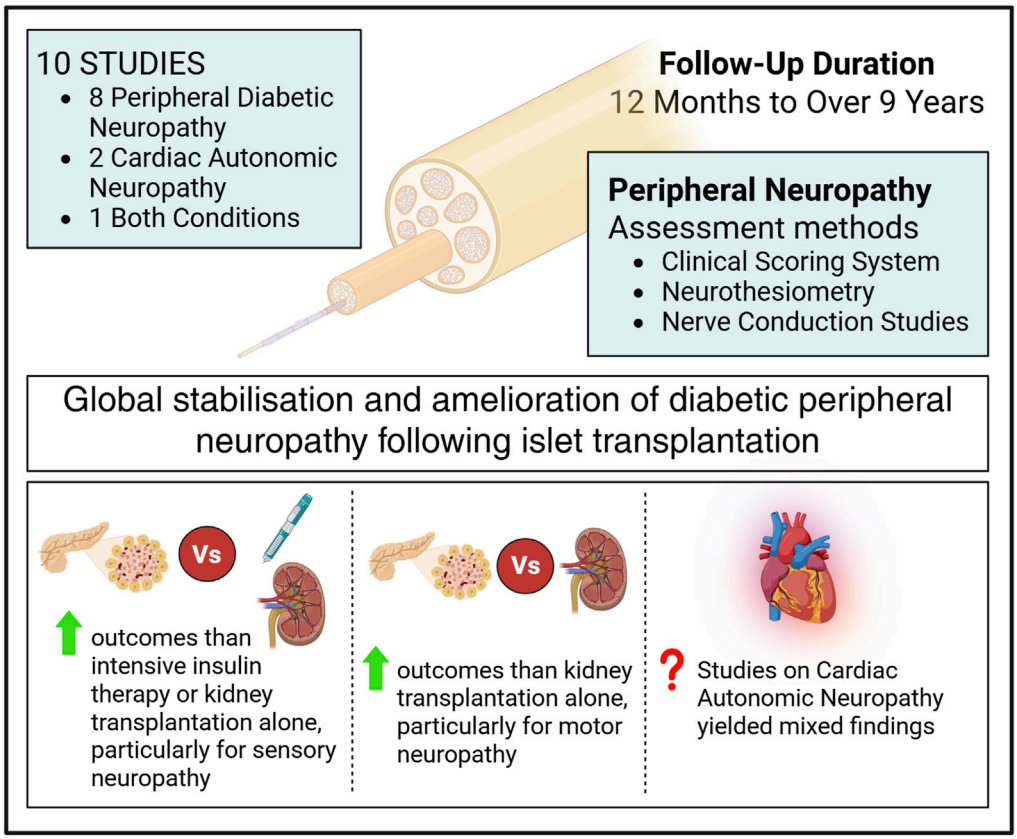

FIGURE 4 | Effect of islet transplantation on diabetic neuropathy, based on 10 studies with follow-up durations ranging from 12 months to 9 years, showing a general trend toward stabilization.

conventional group, compared to only 9.3% in the intensive group [1].

A decline in renal function is frequently observed during the initial years following transplantation, likely because of immunosuppression nephrotoxicity, followed by a stabilization of renal function [20, 26]. In particular, IAK leads to a significant improvement in clinical outcomes in the context of chronic kidney disease (CKD), including a reduction in the need for dialysis and lower mortality rates. These outcomes underscore the value of islet transplantation, beyond the observed biological impact on renal function [25]. Severe biological mechanisms may contribute to the observed improvement, or reduction, in renal function decline after transplantation. These include sustained intensive glycaemic management in some patients, improved overall glycaemic control, and the potential nephroprotective effect of C-peptide [31, 38]. Current evidence indicates that C-peptide interacts with a G-protein-coupled receptor sensitive to pertussis toxin, triggering several intracellular signalling cascades that promote the expression of genes involved in kidney protection. Additionally, studies conducted in both animals and humans have demonstrated the beneficial effects of C-peptide administration [39]. In animal models, treatment with C-peptide has been shown to significantly reduce glomerular hyperfiltration, glomerular enlargement, expansion of the mesangial matrix, and proteinuria [40]. In human subjects, C-peptide infusions have been associated with decreased hyperfiltration and lower levels of microalbuminuria. These results suggest that C-peptide exerts a protective effect on the kidneys, potentially offering benefits from islet function restoration beyond merely improving blood glucose control [41]. Nevertheless, accurately delineating the impact of ITx on renal function remains inherently challenging. Heterogeneity in baseline renal function, variations in study design, and the potential nephrotoxicity effects of immunosuppressive regimens, may confound the interpretation of post-transplant renal outcomes across available studies.

ITx has been shown to promote the stabilization of diabetic neuropathy over the medium and long term, with follow-up extending beyond 10 years. Improvements have been observed particularly in sensory neuropathy, although similar benefits have not been reported for motor neuropathy. Since hyperglycaemia is a key driver in the development and progression of diabetic neuropathy, the achievement of euglycemia, often obtained following islet transplantation, likely plays a central role in mediating the observed neurological benefits [42].

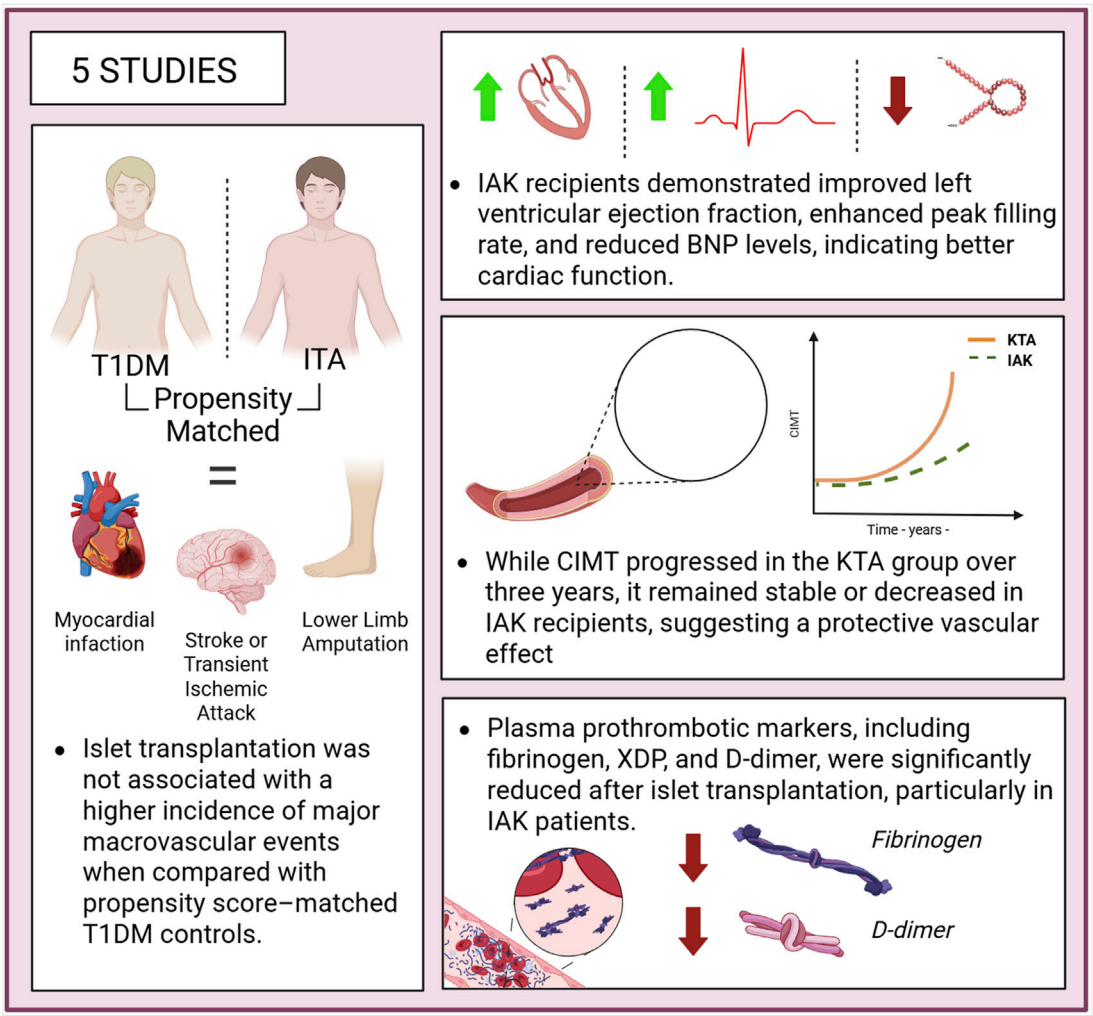

FIGURE 5 | Cardiovascular outcomes following islet transplantation, showing improved myocardial function, stabilization or regression of carotid intima-media thickness (CIMT), reduced pro-thrombotic markers, and no increase in macrovascular events compared to matched patients with type 1 diabetes managed with medical therapy.

At the mechanistic level, a reduction in the expression of receptor for advanced glycation end products (RAGE) within the *vasa nervorum* was documented 4 years post-transplantation [17, 43]. This finding is of relevance, as RAGE is implicated in the pathophysiology of diabetic neuropathy. Additionally, the elevated levels of C-peptide observed after transplantation have been linked with potential improvement in nerve function [44]. C-peptide has bioactive properties, as demonstrated by preclinical studies, which have shown that its administration in animal models of diabetic neuropathy can lead to structural and functional improvements in peripheral nerves [45, 46]. Finally, the positive impact of ITx on renal function may confer an indirect benefit on neuropathy, by reducing the neuropathic damage associated with chronic kidney disease [47].

The evidence gathered in this systematic review suggests that, akin to its effects on diabetic neuropathy, ITx contributes to stabilize diabetic retinopathy. This is likely related to the improvement in glycaemic control, which may reverse endothelial dysfunction and thus enhance retinal microvascular perfusion [48]. Clinically, it has been observed that a 10% reduction in HbA1c value results in an approximate 40% reduction in the risk of diabetic retinopathy progression [49]. The post-transplant rise in circulating C-peptide levels may exert a direct beneficial effect on the retina. Experimental evidence has shown that C-peptide administration can reduce fluorescein leakage across the blood–retinal barrier, supporting a potential role in limiting vascular permeability [41]. In a small number of cases, a transient worsening of diabetic retinopathy following ITx has been observed [29, 31]. This phenomenon is likely attributable to the rapid normalisation of glycaemia, rather than being a direct consequence of the transplant itself. Such early deterioration, typically occurring within the first post-transplant year, has also been reported with other treatments that intensify glycaemic control in patients with existing diabetic retinopathy

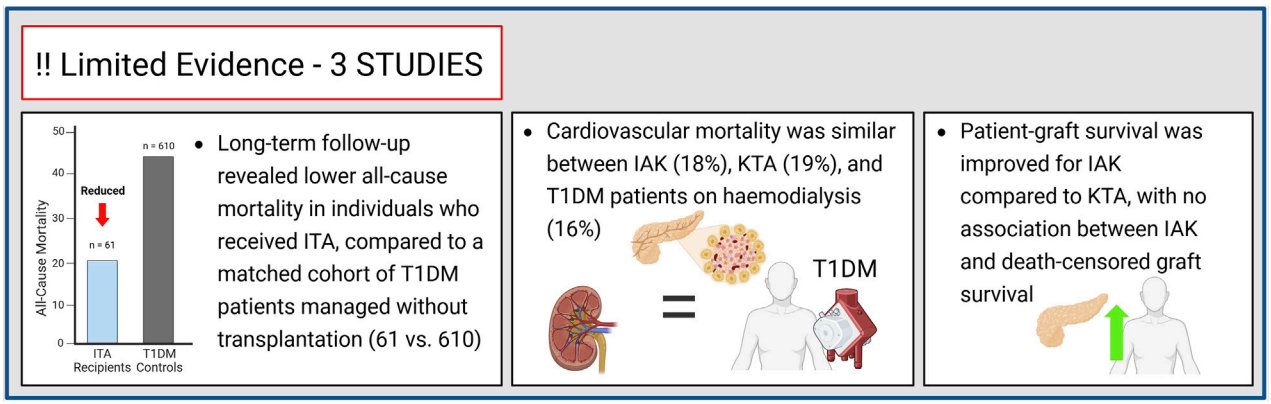

FIGURE 6 | Reduced all-cause mortality following islet transplantation, compared to a matched cohort of patients with type 1 diabetes, with similar mortality rates observed between patients undergoing IAK or KTA and those receiving hemodialysis.

[50]. It is therefore not necessarily specific to ITx. Furthermore, this worsening was observed in a limited number of cases (<10%), and it is difficult to determine whether islet transplantation exacerbated retinopathy or simply failed to slow its natural progression, leading to the occurrence of complications. Lastly, the precise role of immunosuppressive therapy in the progression of diabetic retinopathy remains unclear even is, based on current evidence, does not appear to exert a direct detrimental effect on the course of retinopathy.

Partial preservation of islet graft function, as opposed to complete loss of function, most likely plays a beneficial role in the progression of various diabetes-related complications. However, subgroup analyses based on the degree of graft function preservation were not available in the included studies and should therefore be further investigated in future research.

Current evidence on the impact of ITx on macrovascular diseases remain limited. Interestingly, one study suggests a higher risk of myocardial infarction in the IAK population compared to matched T1D controls. This result contrasts with other studies, which have shown improvements in cardiovascular (CV) function and reductions in CIMT. The observed increase in myocardial infarction risk should be interpreted with caution, as it may stem from limitations in the propensity score matching process. In particular, the IAK group was disadvantaged in relation to two critical CV risk factors (age and history of myocardial infarction) which may have introduced bias into the analysis [27]. Moreover, the small sample size and limited number of CV events further constrain the robustness of this association, raising the possibility of a statistically significant yet clinical uncertain finding. Two studies reported that ITx stabilizes carotid artery plaque, a key marker of cardiovascular disease [16, 22]. Improvements in left ventricular function and normalization of coagulation markers after transplantation further support its cardioprotective benefits [15].

The restoration of euglycemia after ITx is likely to play a central role, much as it does in other diabetes-related complications, in mitigating key pathophysiological processes implicated in CVD. These include chronic low-grade inflammation, oxidative stress, and endothelial dysfunction. Findings from the DCCT/EDIC study underscore this association, showing that the individuals in the intensive therapy arm experienced over a 50% reduction in strokes, non-fatal myocardial infarctions, and CV mortality, in addition to a slower CIMT progression, when compared with those receiving conventional treatment [51, 52].

Nonethless, this remains a pressing need for the future studies to explore CV outcomes in greater depth: especially concerning diabetes-related complications that have not yet been evaluated after transplantation, such as peripheral arterial disease or coronary artery disease. The application of non-invasive imaging modalities to monitor atherosclerosis progression in these contexts would be highly beneficial. Furthermore, prospective trials comparing post-transplant CV event rate (e.g., myocardial infarction, stroke) with those observed in appropriately matched T1DM controls, such as patients on the transplant waiting list, could provide more definite insights into the cardioprotective potential of ITx.

In this study, we opted for a systematic review instead of a meta-analysis due to clinical, methodological, and statistical heterogeneity. Despite this limitation, our findings clearly demonstrate the benefits of ITx in stabilizing or even reducing diabetes-related complications in individuals with T1DM.

This work has several limitations. The included studies have considerable heterogeneity, particularly regarding the prevalence and severity of each diabetes-related complication prior to transplantation. Variability is also evident in how each complication if defined and assessed, which may limit the comparability of outcomes across studies. Additionally, differences in study design further complicate interpretation. Control groups range from patients receiving intensive medical treatment to those who have undergone KTA, with considerable variation in baseline characteristics between comparator cohorts. Such methodological diversity inevitably introduces bias and complicates pooled analysis. Another relevant source of heterogeneity lies in the temporal distribution of the studies. The transplantation periods covered differ significantly, as do the immunosuppressive protocols employed. Given that

TABLE 2 | Main findings of diabetes-related complication evolution after islets transplantation.

Author, year	Proportion of complications before tx	Baseline rate of complications	Main findings
Alhaidar [12]	Diabetic neuropathy was assessed with Utah Neuropathy Scale (UNS) and Nerve conduction study (NCV)	38.5% based on the UNS	There was no significant difference between UNS and nerve conduction study parameters at baseline and at the end of follow-up. However, a significant decrease was observed in the F-wave latencies of the peroneal nerve (50.34 ± 6.12 ms vs. 52.42 ± 6.47 ms, P = 0.005) and the ulnar nerve (27.5 ± 2.15 ms vs. 29.45 ± 2.10 ms, P = 0.009), along with an increase in ulnar sensory nerve conduction velocity (49.98 ± 6.27 m/s vs. 47.19 ± 5.36 m/s, P = 0.04)
Andres [13]	Kidney function assessed using creatinine clearance using the Cockroft-Gault formula	Basal creatinin clearance at 72 mL/min 10% with microalbuminuria and 20% with macroalbminuria	Significant decrease of ClCr from 72 mL/min to 57 mL/min
Barton [14]	Diabetic nephropathy assessed with eGFR estimated by the CKD-EPI	NA	No significant decline of eGFR
D'Addio [15]	Prothrombotic factors were assessed using thromboplastin time, prothrombin time, protein C, and protein S activated partial fibrinogen (Fg), antithrombin, fasting homocysteine d-dimer fragments (D-dimer), levels of prothrombin fragments 1 + 2 and platelet intracellular calcium using fresh plasma samples Platelet function and ultrastructure were assessed using platelet size, morphology, and granule content, and platelet areas were measured	NA	Near-normalization of platelet morphology, size, calcium platelet homeostasis and aggregation Platelets size after ITA vs. DT1 (3.199 ± 0.287 × 10^6 nm [2] vs. 3.860 ± 0.288 × 10^6 nm [2], p < 0.05) Levels of resting [Ca2+]I after ITA vs. DT1 (87.6 ± 18.8 nmol vs. 107.7 ± 40.0, p < 0.05) Haemostatic abnormalities with a prothrombotic state before ITA was near-normalized after islets transplantation Levels of Fg after ITA vs. DT1 (367.0 ± 26.0 mg/dL vs. 328.5 ± 35.0, p < 0.05) Levels of D-dimer after ITA vs. DT1 (0.24 ± 0.02 μg/mL vs. 1.07 ± 0.80 μg/mL)
Danielson [16]	CIMT was assessed using high-resolution B-mode carotid arteries ultrasound	Absence of cardiovascular disease	Significant reduction of CIMT at 12 months (–0.058 mm, p < 0.05) and at 50 months continued reduction of CIMT but of smaller magnitude (–0.026 mm)
Del Carro [17]	Diabetic neuropathy was assessed using NCV score, CMAP and SAP	100% of diabetic neuropathy at baseline	NCV score improved significantly in the IAK group and did not change significantly in the kidney transplant alone group Both SAP and CMAP amplitude recovered in the IAK group and worsened in the kidney transplant alone group
Deshmukh [18]	CAN was assessed using 24-h Holter monitor to evaluate Heart rate variability (HRV)	NA	No significant difference in HRV parameters at a median of 4 years between subjects post-islet transplantation and T1D individuals
Fensom [19]	NCV	66%	Subjects with diabetic neuropathy at baseline displayed significant improvement post-transplant while it worsened significantly in medically treated patients
Fiorina [20]	Kidney graft survival rate, kidney function with eGFR and urinary albumin excretion	Basal eGFR at 56.3 mL/min in the ITA group	Significant better kidney graft survival rates à 7 years in the successful IAK group 83% vs. 51%, no difference in eGFR between both group at 4 years follow-up Significant increase of microalbuminuria index in the unsuccessful IAK group (92.0 ± 64.9 to 183.8 ± 83.8, p = 0.05) and trend of reduction of microalbuminuria in the successful group (108.5 ± 53.6 to 85.0 ± 39.0)
Fiorina [21]	Hemostatic activity was assessed using prothrombin time (PT) and partial thromboplastin time (PTT), D-dimer fragments (XDP), fibrinogen (Fg), F1 2 fragments (F1 2), antithrombin III (ATIII), and protein C and S activity Patient survival and cardiovascular death were assessed	NA	In the islet transplantation group, markers of atherothrombotic risk factors were reduced. Notably, there was a significant decrease in F1.2 and XDP levels. Additionally, an improvement in natural anticoagulant activity was observed, as evidenced by increased protein C antigen activity and ATIII levels Patient survival was significantly higher in the islet

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TABLE 2 | (*Continued*) Main findings of diabetes-related complication evolution after islets transplantation.

Author, year	Proportion of complications before tx	Baseline rate of complications	Main findings
			transplantation group than T1D patients still on hemodialysis group ($p = 0.05$) The cardiovascular mortality rate was comparable with 18% in the islet transplantations, and 16% in the T1D patients still on hemodialysis group
Fiorina [22]	CIMT was assessed with high-resolution carotid arteries ultrasound Left ventricular function was measured with radionuclide left ventriculagraphy	NA	In patients who received a kidney-islet transplant, IMT remained unchanged over the 3-year follow-up period. In contrast, those in the kidney-only group experienced a significant increase in mean IMT after 3 years ($p < 0.05$) Significant increase in mean ejection fraction, as a marker of left ventricular systolic function, from baseline in IAK group ($p < 0.05$), whereas it remained unchanged in the KTA group Significant improvement in the mean peak filling rate, as a marker of left ventricular diastolic function in the IAK group ($p < 0.05$), while it remained unchanged in the KTA group Significant reduction of BNP from baseline in the IAK groupe and stability of BNP level in the KTA group
Hering [35]	Renal function was assessed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula	The median eGFR at baseline was 102 mL/min/1.73m^2	20% decline of eGFR at 2 years 102 mL/min/1.73m^2 vs. 82 mL/min/1.73m^2
Lee [23]	Diabetic retinopathy assessed by slit-lamp eye exam Diabetic neuropathy was assessed by electromyelogram	62.5% with diabetic retinopathy 62.5% with diabetic neuropathy	No progression of retinopathy, with one patient improving from very mild retinopathy to no retinopathy 25% showed significant improvement in conduction studies, while 75% had no notable changes in diabetic neuropathy
Lehmann [24]	Renal function was assessed by measuring serum creatinine and estimating the glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula	100%	There was no significant difference in the rate of decline in renal function between islet transplant recipients and pancreas transplant recipients −13.3 mL/min decline of eGFR during a follow-up of 13 years in the SIK group and 8.1% of the patients change in CKD stage during the 13 years follow-up in the SIK group
Maanoui [25]	Composite outcome, is defined as the occurrence of death, re-transplantation, or return to dialysis	Mean serum creatinine of 1.3 mg/dL eGFR (MDRD) 64.6	13 (33%) of 40 patients in the IAK transplantation group returned to dialysis or died vs. 36 (45%) in the kidney transplantation alone group
Nijhoff [34]	eGFR	NA	There was no significant change in estimated creatinine clearance, with an eGFR of 43.5 mL/min before ITx and 48.2 mL/min after ITx
O'Connell [26]	eGFR and albuminuria	0%	A 13% reduction in eGFR at 1 year (77 mL/min at baseline compared to 67 mL/min at 12 months, $p = 0.051$ One patient experienced an increase in their microalbuminuria level, while another developed microalbuminuria after switching to tacrolimus
Palmer [36]	CAN was assessed using resting heart rate measurements obtained from pre and post-transplant myocardial perfusionscans	NA	Significant reduction in RHR suggesting a reverse cardiovascular autonomic neuropathy after ITA
Perrier [27]	Composite criterion including, dialysis, amputation, nonfatal stroke, nonfatal myocardial infarction, transient ischemic attack and death	1.64% with amputation, 4.92% with stroke and 9.84% with myocardial infarction in the ITA group 55.6% with dialysis, 11.1% with amputation, 6.67% with stroke, 4.44% Transient ischemic attack and 13.3% with myocardial infarction in the IAK group	Compared to T1D control patients, ITA and IAK recipients had a lower risk of the composite outcome ($P = 0.002$ and $P = 0.014$, respectively), which seemed to result from lower mortality in ITA recipients ($P < 0.001$) and a decreased need for dialysis in IAK recipients ($P < 0.001$)
Rickels [28]	Kidney function was assessed with the estimated glomerular filtration rate (eGFR) derived from serum creatinine with the (CKD-EPI equation	eGFR before transplantation 100.28 mL/min/1.73m^2 in the ITA group and 75.80 in the IAK group mL/min/	eGFR from 100.28 to 89.23 after 4.55 years of follow-up in the ITA group eGFR from 75.8 to 72.06 after 3.43 years of follow-up in the ITA group Mean UCAR was 5.6 µgm/mgm in the ITA at

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TABLE 2 | (*Continued*) Main findings of diabetes-related complication evolution after islets transplantation.

Author, year	Proportion of complications before tx	Baseline rate of complications	Main findings
			baseline and was 9.8 µgm/mgm after the follow-up There was a highly significant ($p < 0.0001$) but clinically marginal increase in UACR Mean UCAR was 26 µgm/mgm in the IAK at baseline and was 13 µgm/mgm after the follow-up There was no significant change in UCAR before in after transplantation
Ryan [29]	Renal function assessed with albuminuria Diabetic retinopathy assessed with fundoscopic examination by ophtalmologist Diabetic neuropathy was assessed with a neurothesiometer	35% with microalbuminuria 74% with diabetic retinopathy 32% with peripheral neuropathy	4 patients required retinal laser photocoagulation or vitrectomy 5 patients with microalbuminuria developed macroproteinuria Absence of progression of peripheral neuropathy
Tekin [30]	Diabetic nephropathy was assessed with eGFR and albuminuria DR was assessed with fundoscopic examination by ophtalmologist DN was assessed with NCV and clinical evaluation	None with diabetic nephropathy 50% with diabetic retinopathy 50% with diabetic neuropathy	Kidney function remained stable except in on patient who developed transient and reversible microalbuminuria No progression of diabetic retinopathy One subject developed mild axonal neuropathy within 2 years, which remained stable. Another showed no neuropathy, while two others partially improved in scores and nerve conduction
Thompson [31]	Renal assessement: eGFR assessed using MDR formula and ^{99m}Tc-DTPA Retinopathy assessment: fundoscopic examination by ophtalmologist Neuropathy assessment: NCV	NA	The rate of decline of renal function is reduced in the ITA compared to the intensiveylly medical treated group Significant progression of diabetic retinopathy in the medical treated group compared to the ITA A non-significant trend toward enhanced nerve conduction velocity was observed in the ITA group
Vantyghem [32]	Diabetic neuropathy was assessed using NCV and CAN was assessed using electrophysiological and cardiovascular autonomic	NA	Significant improvement in sensory neuropathy, with no substantial changes in motor or cardiac autonomic neuropathy
Venturini [33]	DR was assessed using color Doppler imaging of the central retinal arteries and veins	80% with RD	Significant increase of blood velocities of central retinal arteries and veins in ITA patients compared to baseline before and transplantation No statistical difference at in T1D patients compared to the same group a year before Blood flow velocities of central retinal artery (psv: 6.09 ± 0.46 vs. 10.12 ± 1.20 cm/s, $P < 0.01$/edv: 1.65 ± 0.07 vs. 2.99 ± 0.48 cm/s, $P < 0.05$) Blood flow velocities of central retinal vein (maxv: 3.12 ± 0.28 vs. 6.12 ± 1.00 cm/s, $P < 0.01$/minv: 1.86 ± 0.22 vs. 4.14 ± 0.56 cm/s, $P < 0.05$)

BNP, brain natriuretic peptide; CIMT, carotid intima-media thickness test; CKD-EPI, chronic kidney disease epidemiology collaboration; CMAP, compound muscle action potential; EDV, end diastolic velocity; ESRD, end-stage renal disease; MAXV, maximum velocity; MINV, minimum velocity; NCV, nerve conduction velocyty; SAP, sensory action potential; PSV, peak systolic velocity; UTS, utah neuropathy scal.

immunosuppressive agents can influence the progression of certain complications, particularly nephropathy and diabetic neuropathy, this variation is of particular concern. Baseline treatment data, including nephroprotective therapies such as renin-angiotensin-aldosterone system (RAAS) inhibitors or sodium-glucose co-transporter 2 (SGLT2) inhibitors, as well as CV treatments were reported in only a very limited number of studies. Although these data are highly relevant for evaluating micro- and macrovascular complications, they were largely missing. It would therefore be beneficial for future studies reporting on the evolution of complications after ITx to include this information. Of note, the definition of each diabetes-related complication was not precisely specified in the included studies. In most cases, the focus was on the evolution of specific parameters related to the complication before and after treatment, without the use of clearly defined thresholds or cut-off values. Finally, while the available data provide a relatively robust picture of the impact of ITx on microvascular complications, the evidence concerning macrovascular outcomes remains sparse. Future research studies should prioritise targeted investigation on atherosclerosis-related conditions in transplanted patients using standardised endpoints and longitudinal follow-up to clarify the CV benefits of ITx.

This systematic review highlights a consistent improvement in microvascular complications (and possibly in macrovascular outcomes) following ITx, whether ITA or IAK (**Table 2**), in patients with T1DM, particularly in relation to the prevention and management of microvascular complications, and with promising indications for macrovascular outcomes. By promoting stabilisation and, in some cases, partial reversal or attenuation of disease progression, ITx emerges as a valuable therapeutic option. These findings lend further support but already strengthen the broader application of ITA or IAK for T1DM treatment not only for patients already burdened by diabetes-related complications, but also as a proactive strategy to reduce long-term morbidity and enhance quality of life in this population.

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

KG and AP conceived the study, designed the research strategy, and supervised the project. FH, RK, C-HW, MM, and NK collected and curated the clinical data and contributed to formal analysis. PC and TB provided clinical oversight, contributed to data interpretation, and ensured critical revision of the manuscript. EB contributed to the study concept, methodological supervision, and interpretation of translational aspects. AP and KG drafted the initial manuscript. All authors critically revised the manuscript for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors declare that the research 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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Death and Graft Loss in Simultaneous Pancreas-Kidney Recipients by Donor-Recipient Cytomegalovirus Serostatus in the United States

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Cytomegalovirus (CMV) serologic discordance is a known risk factor for adverse outcomes after solid-organ transplantation. This study evaluated outcomes of simultaneous pancreas–kidney (SPK) recipients based on donor and recipient CMV serostatus. Using the Scientific Registry of Transplant Recipients, we identified adult SPK recipients between 2014 and 2024 and categorized them as donor/recipient negative (D–/R–), recipient positive (R+), or donor positive/recipient negative (D+/R–). Patients with missing data, nonstandard immunosuppression, or positive crossmatch were excluded. Among 4,744 recipients (831 D–/R–, 2,671 R+, 1,242 D+/R–), the D+/R– group had the highest 1-year rates of graft rejection (16.6%, p = 0.02) and hospitalization (67.2%, p = 0.005), whereas the D–/R– group had the lowest (11.8% and 60.0%, respectively). In multivariable models, D+/R– recipients had higher risks of death (HR 1.28; 95% CI, 1 .01–1.62; p = 0.045), pancreas graft-loss (HR 1.25; 95% CI, 1.06–1.48; p = 0.009), and death-censored kidney graft-loss (HR 1.31; 95% CI, 1.01–1.69; p = 0.04) compared with R+. Conversely, D–/R– recipients had a lower risk of kidney graft-loss (HR 0.66; 95% CI, 0.46–0.96; p = 0.03). CMV D+/R– serostatus is independently associated with increased mortality and graft-loss after SPK transplantation. Matching CMV-seronegative donors with seronegative recipients may improve outcomes, warranting further study of the feasibility and broader impact of CMV serostatus–based-matching.

Keywords: simultaneous kidney pancreas transplantation, CMV serostatus, D+/R-, donor cytomegalovirus positive, recipient negative

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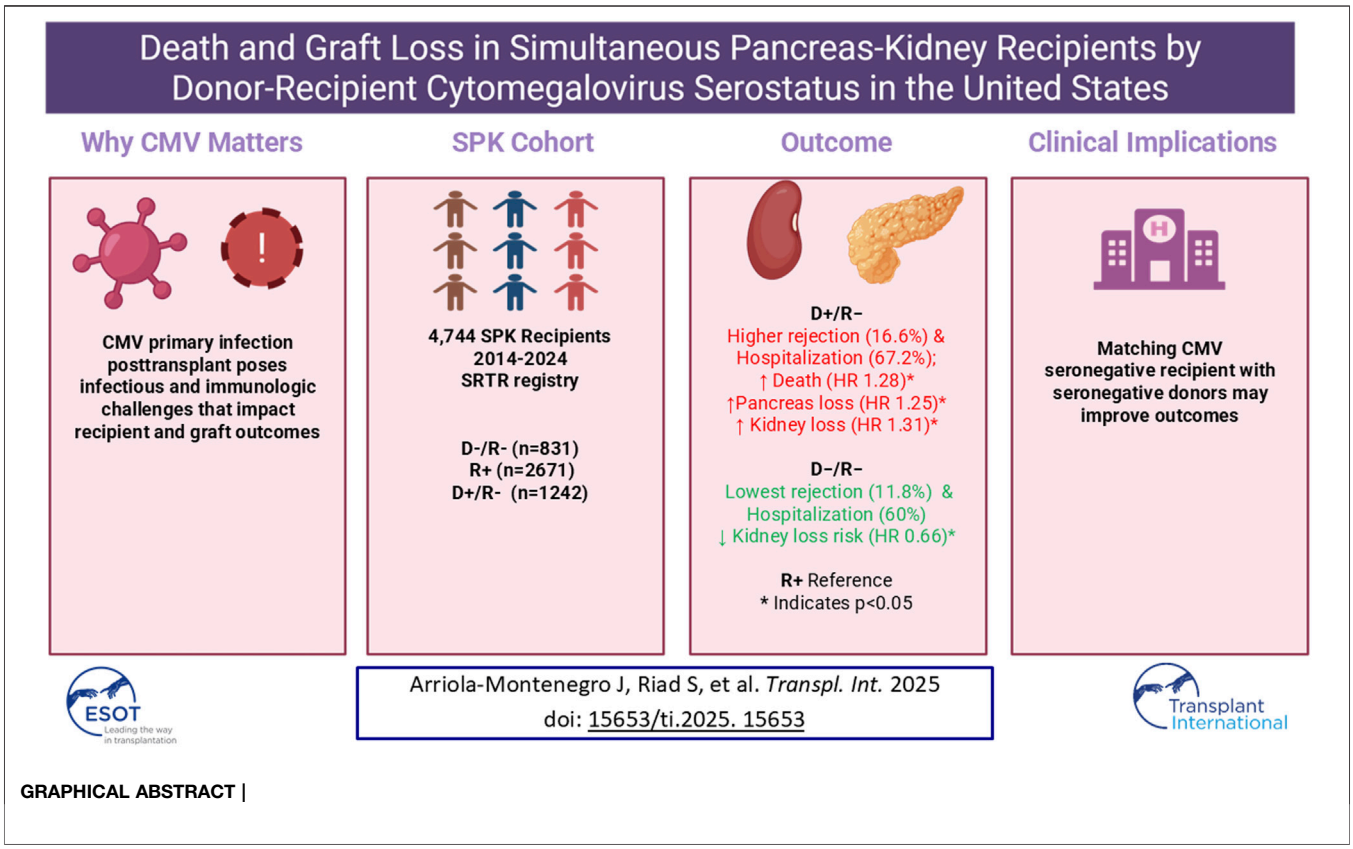
Abbreviations: CMV, cytomegalovirus; D+/R–, donor positive and recipient negative; D–/R–, donor negative and recipient negative; R+, recipient positive; SPK, simultaneous pancreas-kidney; SRTR, Scientific Registry of Transplant Recipients.



GRAPHICAL ABSTRACT |

INTRODUCTION

Simultaneous pancreas-kidney (SPK) transplant offers persons with diabetes-related uremia freedom from both dialysis and insulin dependence [1], with the additional potential to reverse microvascular disease [2] over time. Moreover, compared with kidney-alone transplant [3–7], SPK transplant offers substantial survival and quality-of-life benefits and is the most cost-effective option when considering patient and graft survival probabilities [8]. Despite these advantages, SPK transplant presents several challenges related to immunologic and infectious complications [9, 10].

One challenge for SPK transplant recipients is the pancreas graft's high immunogenicity [11–14], which requires augmented immunosuppression to mitigate the risk of rejection [15, 16] and makes SPK recipients more susceptible than kidney-only recipients to complications such as cytomegalovirus (CMV) infection, especially in cases involving a donor who is CMV positive and a recipient who is CMV negative (D+/R–) [17–22]. CMV infection, a common and serious complication in solid-organ transplant recipients, increases the incidence of hospitalization, graft loss, and death among kidney transplant recipients, particularly among those who underwent SPK transplant [23, 24]. CMV infection is most prevalent in recipients who do not receive antiviral prophylaxis or who are exposed to high doses of immunosuppressive therapy [17, 24]. The risk of primary CMV infection is particularly elevated for D+/R− cases [19, 25, 26], which occur frequently with SPK transplant [27, 28].

Prophylactic administration of valganciclovir is the standard of care for all SPK patients who are at risk for CMV primary infection or reactivation (recipient positive, R+, or donor positive and recipient negative, D+/R–) and has proved beneficial in reducing rates of CMV infection after SPK transplant [29]. This preventive intervention has been shown to improve both short- and long-term allograft outcomes in SPK recipients by reducing the incidence of CMV-related complications [17, 29, 30]. However, valganciclovir does not entirely prevent CMV infection; in one study, up to 38% of kidney transplant recipients had delayed-onset primary CMV infection after completing 6 months of valganciclovir prophylaxis [31].

Given these considerations, the current analysis aimed to assess the long-term outcomes of SPK transplant recipients on the basis of donor-recipient CMV risk profiles and shed light on the potential effect of CMV serostatus discordance on recipient and graft survival. We analyzed the outcomes of a contemporary cohort of SPK recipients, who were of average immunologic risk, by donor-recipient CMV serostatus.

MATERIALS AND METHODS

Data Source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. The study was deemed exempt by the Mayo Clinic Institutional Review Board (INC8014532).

Study Population

In the SRTR standard analysis file we identified all patients who received an SPK transplant between 1 January 2014, and 31 March 2024. During the study period, valganciclovir prophylaxis was routinely administered to SPK recipients for 3 months for R+ cases or up to 6 months for D+/R− cases. CMV-naïve recipients with a CMV-negative donor (D−/R−) did not receive valganciclovir prophylaxis [17, 23]. We excluded recipients on the basis of induction regimen (missing; mixed; or other than rabbit anti-thymocyte globulin, alemtuzumab, and interleukin-2 receptor agonist), maintenance regimen (missing, or other than tacrolimus and mycophenolate mofetil with or without corticosteroids), crossmatch data (missing, positive, or weakly positive), and CMV serostatus (missing). We categorized recipients into three risk groups on the basis of recipient and donor CMV serostatus: low-risk, D−/R−; intermediate-risk, R+; and high-risk, D+/R−, consistent with the risk stratification endorsed by major transplant and infectious diseases societies.

Outcomes of Interest

The primary outcomes of interest were recipient and overall allograft survival by donor-recipient CMV serostatus risk category. Death-censored allograft survival was also evaluated. Short-term outcomes included 1-year rates of hospitalization, rejection of kidney alone, rejection of pancreas alone, and rejection of either organ.

Statistical Analyses

Continuous variables were summarized as means and SDs and compared by using analysis of variance or pooled *t* tests. Categorical variables were summarized as counts and percentages and compared with the χ^2 test.

Time-to-event data were summarized with Kaplan-Meier estimates of incidence through 7.5 years post transplant. The log-rank test was used to compare groups. Cox proportional hazards models (referred to as *multivariable models*) were used to evaluate the effect of CMV serostatus risk category on outcomes of interest, with adjustment for the following possible confounding variables: age, sex, ethnicity, diabetes type, preemptive transplant, dialysis duration, induction type, corticosteroid maintenance, HLA antigen mismatch, calculated panel reactive antibody, local vs. imported organs, pancreas donor risk index, transplant year, and donor-recipient Epstein-Barr virus status. The center was entered as a random effect in the multivariable models. Linearity in all tests was evaluated by using splines for continuous variables. We used Schoenfeld residuals plots to test the assumption of proportionality.

All analyses were performed with R version 4.2.2 (R Foundation for Statistical Computing). Statistical significance was defined as $P < 0.05$.

RESULTS

Baseline Characteristics

We identified 7,847 patients who underwent SPK transplant during the study period. The final analysis cohort consisted of 4,744 SPK recipients with complete data: 831 low-risk (D−/R−), 2,671 intermediate-risk (R+), and 1,242 high-risk (D+/R−) (**Figure 1**).

Table 1 details the demographic characteristics of recipients and donors by CMV serostatus. Recipients had a mean (SD) age of 42.3 (9.2) years and body mass index (calculated as weight in kilograms divided by height in meters squared) of 25.7 (4.2); these features were similarly distributed across risk groups. Overall, 61.6% of recipients were men, but the R+ group had a significantly lower share of men than the other groups ($P < 0.001$). Black and Hispanic recipients were significantly more represented in the R+ group ($P < 0.001$).

Recipients in the R+ group were significantly less likely than those in the D−/R−and D+/R−groups to receive a preemptive transplant (15.1% vs. 18.2% vs. 19.4%, respectively) ($P = 0.002$) and were on dialysis for significantly longer than recipients in the other groups (mean, 2.1 vs. 1.8 vs. 1.8 years; $P < 0.001$). The pancreas donor risk index and proportion of locally procured organs did not differ between groups. The proportion of organs procured after circulatory death was significantly higher in the D−/R−group than in the R+ and D+/R−groups (3.9% vs. 2.7% vs. 1.5%, respectively; $P = 0.004$). The groups also differed significantly in terms of diabetes type, preemptive transplant, calculated panel reactive antibody, induction type, Epstein-Barr virus status, and donor age and ethnicity (**Table 1**).

Univariable Outcomes

One-year outcomes post transplant are shown in **Table 2**. Kidney rejection rates and pancreas rejection rates did not differ significantly between risk groups, but the combined kidney or pancreas rejection rate did. The combined rejection rate was significantly higher in the D+/R− group than in the D−/R−and R+ groups (16.6% vs. 11.8% vs. 14.4%, respectively; $P = 0.02$). The D+/R− group was also hospitalized significantly more frequently than the D−/R−and R+ groups (67.2% vs. 60.0% vs. 63.0%, respectively; $P = 0.005$).

In the Kaplan-Meier analysis of recipient survival (**Figure 2**), the D+/R− group had the lowest overall survival (log-rank $P = 0.03$). The 7.5-year survival probabilities were 82.1%, 82.9%, and 76.4% in the D−/R−, R+, and D+/R−groups.

The overall kidney survival probability (**Figure 3**) was significantly lower in the D+/R− group than in other groups (log-rank $P = 0.01$). The 7.5-year overall kidney survival

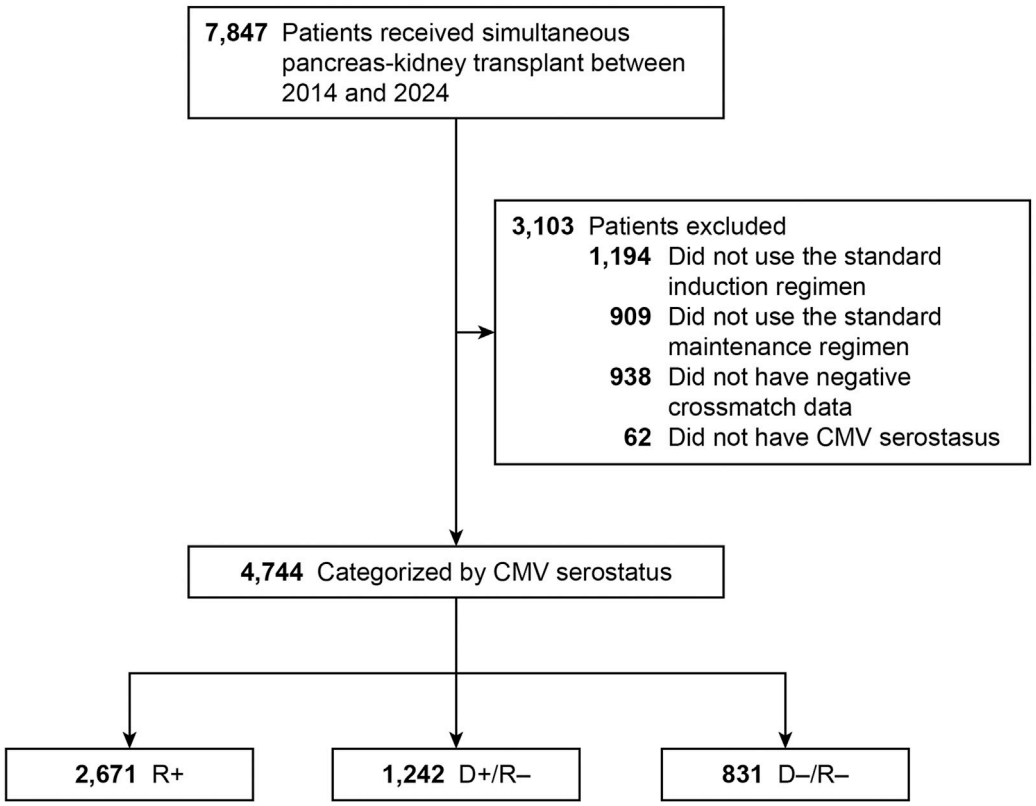


FIGURE 1 | Flowchart of Study Design. Flowchart of study design showing inclusion and exclusion criteria for simultaneous pancreas–kidney (SPK) transplant recipients categorized by donor–recipient cytomegalovirus (CMV) serostatus. CMV indicates cytomegalovirus; R+, CMV-positive transplant recipients; D+/R–, CMV-positive donors and CMV-negative recipients; D–/R–, CMV-negative donors and recipients.

probabilities were 77.1%, 73.8%, and 68.1% in the D–/R–, R+, and D+/R–groups. **Figure 4** shows the death-censored survival of kidney allografts. The D–/R– group had a significantly higher probability of graft survival than the other groups (log-rank P = 0.001). The 7.5-year death-censored kidney graft survival probabilities were 90.8%, 84.6%, and 81.5% in the D–/R–, R+, and D+/R–groups.

The overall pancreas allograft survival probability (**Figure 5**) was significantly lower in the D+/R– group (log-rank $P < 0.001$). The 7.5-year overall pancreas survival probabilities were 73.8%, 71.0%, and 62.8% in the D–/R–, R+, and D+/R–groups. **Figure 6** shows the death-censored pancreas graft survival probabilities. The D–/R– group had a significantly higher probability of graft survival than the other groups (log-rank P = 0.002). The 7.5-year death-censored pancreas allograft survival probabilities were 87.3%, 82.5%, and 78.4% in the D–/R–, R+, and D+/R–groups.

Multivariable Outcomes

In the multivariable model for recipient death and graft loss, compared with R+ serostatus, D+/R– serostatus was significantly associated with a 28% higher risk of death (P = 0.045) and a 25% higher risk of pancreas graft loss (P = 0.009) (**Table 3**). It was also associated with a 20% higher risk of kidney graft loss, but the effect was not significant (P = 0.06). CMV D–/R– serostatus was not associated with altered risks of death or pancreas or kidney graft loss. However, in the death-censored graft loss model, D–/R– serostatus was significantly associated with a 25% lower risk of pancreas graft loss (P = 0.04), and a 34% lower risk of kidney graft loss (P = 0.03), compared with R+ serostatus. In the death-censored model, D+/R–serostatus was significantly associated with a 31% higher risk of kidney graft loss (P = 0.04) compared with R+ serostatus.

Causes of Death and Graft Failure

The causes of death and kidney and pancreas allograft failure are detailed in **Supplementary Tables S1–S3**. Notably, the specific cause of death was not reported for most recipients. Cancer as a cause of death was reported more frequently in the D+/R–group than in the other groups (**Supplementary Table S1**).

The causes of kidney and pancreas graft failure were not reported for approximately half of the recipients. Kidney graft rejection was the leading documented cause of kidney graft loss in the D+/R– group (**Supplementary Table S2**). Primary nonfunction was the most common documented cause of pancreas graft loss (**Supplementary Table S3**). Pancreas rejection was the cause of graft loss more frequently in the D+/R– group than in the other groups.

TABLE 1 | Baseline characteristics of recipients, donors, and transplants[a].

Characteristic	D−/R− (N = 831)	R+ (N = 2,671)	D+/R− (N = 1,242)	*P* value
Recipients				
Age, y	42.0 (9.1)	42.3 (9.1)	42.4 (9.5)	0.58
Sex				<0.001
Female	259 (31.2)	1,166 (43.7)	398 (32.0)	
Male	572 (68.8)	1,505 (56.3)	844 (68.0)	
Ethnicity				<0.001
White	530 (63.8)	1,104 (41.3)	797 (64.2)	
Black	202 (24.3)	890 (33.3)	290 (23.3)	
Hispanic	72 (8.7)	505 (18.9)	117 (9.4)	
Other	27 (3.2)	172 (6.4)	38 (3.1)	
BMI	25.60 (4.40)	25.79 (4.18)	25.65 (4.10)	0.43
Dialysis duration, y	1.8 (1.9)	2.1 (2.0)	1.8 (1.8)	<0.001
EBV status	n = 760	n = 2,349	n = 1,124	<0.001
R+	655 (86.2)	2,164 (92.1)	1,007 (89.6)	
R−/D+	76 (10.0)	163 (6.9)	107 (9.5)	
R−/D−	29 (3.8)	22 (0.9)	10 (0.9)	
Diabetes type	n = 828	n = 2,640	n = 1,234	<0.001
Type 1	709 (85.6)	2,023 (76.6)	1,022 (82.8)	
Type 2	119 (14.4)	617 (23.4)	212 (17.2)	
Preemptive transplant	151 (18.2)	402 (15.1)	240 (19.4)	0.002
Peripheral vascular disease	125 (15.1)	319 (11.9)	172 (13.9)	0.07
Donors				
Age, y	23.4 (8.1)	24.3 (7.9)	24.6 (7.7)	0.002
Ethnicity				<0.001
White	608 (73.2)	1,579 (59.1)	712 (57.3)	
Black	135 (16.2)	593 (22.2)	267 (21.5)	
Hispanic	62 (7.5)	401 (15.0)	219 (17.6)	
Other	26 (3.1)	98 (3.7)	44 (3.5)	
Sex				0.76
Female	242 (29.1)	799 (29.9)	358 (28.8)	
Male	589 (70.9)	1,872 (70.1)	884 (71.2)	
PDRI	0.98 (0.24)	0.99 (0.25)	0.98 (0.24)	0.97
Local organs	579 (69.7)	1,801 (67.4)	829 (66.7)	0.35
Non–heart-beating donor	32 (3.9)	73 (2.7)	19 (1.5)	0.004
Transplants				
Calculated PRA, %	11.3 (22.8) (n = 792)	15.6 (26.9) (n = 2,487)	11.9 (23.7) (n = 1,170)	<0.001
No. of HLA antigen mismatches	4.57 (1.12)	4.66 (1.09)	4.58 (1.10)	0.05
Induction type				0.01
r-ATG	636 (76.5)	2,083 (78.0)	970 (78.1)	
Alemtuzumab	145 (17.4)	497 (18.6)	211 (17.0)	
IL-2RA	50 (6.0)	91 (3.4)	61 (4.9)	
Corticosteroid maintenance	583 (70.2)	1,848 (69.2)	902 (72.6)	0.09
Length of hospitalization, d	9.9 (10.1) (n = 831)	9.9 (11.7) (n = 2,666)	9.8 (8.4) (n = 1,242)	0.95

Abbreviations: BMI, body mass index; D−/R−, CMV-negative donors and recipients; D+/R−, CMV-positive donors and CMV-negative recipients; EBV, Epstein-Barr virus; IL-2RA, interleukin-2 receptor agonist; PDRI, pancreas donor risk index; PRA, panel reactive antibody; r-ATG, rabbit anti-thymocyte globulin; R+, CMV-positive recipients.

[a]*Values are mean (SD) or No. of patients (%).*

DISCUSSION

Our analysis of the SRTR database represents the most contemporary report on the outcomes of SPK transplant recipients stratified by donor-recipient CMV serostatus. Our results highlight significant differences in clinically meaningful short- and long-term outcomes for CMV-naïve patients, depending on whether they received allografts from a CMV-seropositive or CMV-seronegative donor. CMV D+/R− serostatus was associated with higher risks of death and overall graft loss, and CMV D−/R− status was associated with lower risks of death-censored kidney and pancreas graft loss. The rates of hospitalization and combined kidney or pancreas rejection were significantly higher in the CMV D+/R− group and lower in the CMV D−/R− group.

CMV is known to confer worse outcomes after solid-organ transplant, both directly by invading the organ allograft and indirectly by increasing the risk of rejection, promoting immune suppression, and predisposing the recipient to other infections and complications. Conversely, the absence of CMV infection in transplant recipients (D−/R−) may confer several clinical benefits. First, it eliminates the many indirect viral effects

TABLE 2 | One-year outcomes post transplant[a].

Outcome	D–/R–	R+	D+/R–	*P* value
Kidney rejection	45 (6.4) (n = 700)	163 (7.3) (n = 2,244)	96 (9.2) (n = 1,040)	0.06
Pancreas rejection	51 (7.6) (n = 668)	192 (9.0) (n = 2,134)	103 (10.4) (n = 986)	0.14
Kidney or pancreas rejection	79 (11.8) (n = 669)	308 (14.4) (n = 2,144)	163 (16.6) (n = 980)	0.02
Hospitalization	437 (60.0) (n = 728)	1,470 (63.0) (n = 2,334)	737 (67.2) (n = 1,097)	0.005

Abbreviations: D–/R–, CMV-negative donors and recipients; D+/R–, CMV-positive donors and CMV-negative recipients; R+, CMV-positive recipients.
[a]*Values are No. of patients (%) or mean (SD).*

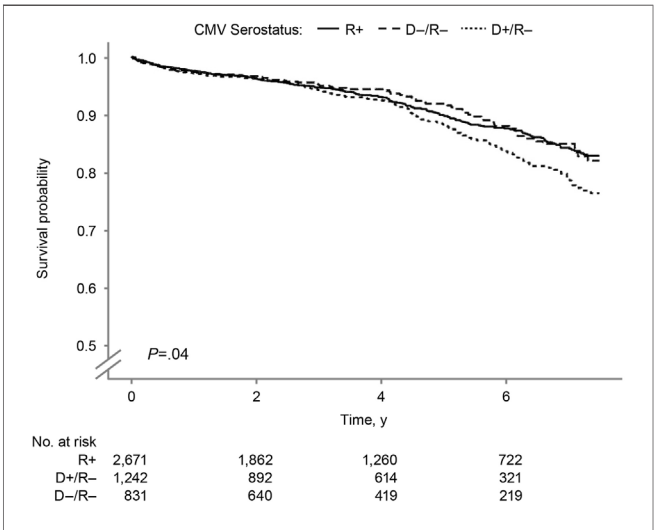


FIGURE 2 | Recipient Survival by Donor-Recipient CMV Serostatus. Kaplan–Meier curves showing recipient survival after SPK transplantation according to donor–recipient CMV serostatus. CMV indicates cytomegalovirus; R+, CMV-positive transplant recipients; D+/R–, CMV-positive donors and CMV-negative recipients; D–/R–, CMV-negative donors and recipients.

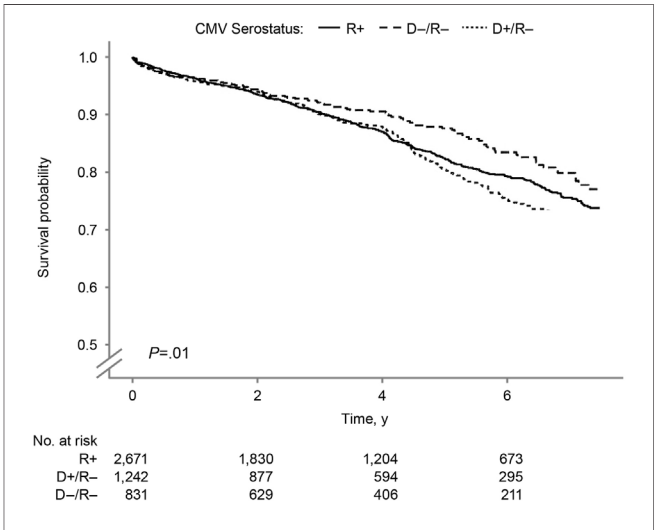


FIGURE 3 | Overall Kidney Graft Survival by Donor-Recipient CMV Serostatus. Kaplan–Meier curves for overall kidney graft survival by donor–recipient CMV serostatus among SPK transplant recipients. CMV indicates cytomegalovirus; R+, CMV-positive transplant recipients; D+/R–, CMV-positive donors and CMV-negative recipients; D–/R–, CMV-negative donors and recipients.

(including CMV-associated rejection, secondary opportunistic infections, and virus-induced inflammation) that can contribute to long-term allograft dysfunction [17, 32]. Second, it obviates the need to reduce immunosuppression, thereby minimizing the risk of rejection, which is often exacerbated when immunosuppression must be tapered to control CMV infection [24]. Third, recipients with CMV D–/R–serostatus do not need prolonged antiviral prophylaxis or therapy and thus avoid the adverse hematologic effects associated with valganciclovir (such as leukopenia, neutropenia, and bone marrow suppression), which can predispose them to secondary infections and graft complications [33]. Our findings showed that CMV D–/R– serostatus was associated with better graft survival, reduced morbidity, and better long-term patient outcomes in SPK transplant recipients.

To reduce the risk of adverse outcomes associated with CMV, prophylaxis with valganciclovir is recommended as the standard of care for high-risk CMV D+/R– solid-organ transplant recipients, as well as those with augmented immunosuppression after organ transplant (such as all at-risk lung and pancreas transplant recipients) [17]. During the study period, valganciclovir prophylaxis was routinely administered to R+ recipients for 3 months and to D+/R–recipients for up to 6 months [17, 23]. However, valganciclovir prophylaxis is often associated with leukopenia, which may require 1) an adjustment in immunosuppression (e.g., reduction in dose of mycophenolate mofetil) which can then increase the risk of rejection or 2) discontinuation of either trimethoprim-sulfamethoxazole prophylaxis or valganciclovir prophylaxis which can then increase the risk of infections. The magnitude of these adverse events is not negligible. In one study, 53% of D+/R–SPK recipients had leukopenia during valganciclovir prophylaxis, resulting in reduced immunosuppression in most recipients and discontinuation of the valganciclovir prophylaxis in more than 28% of recipients [19].

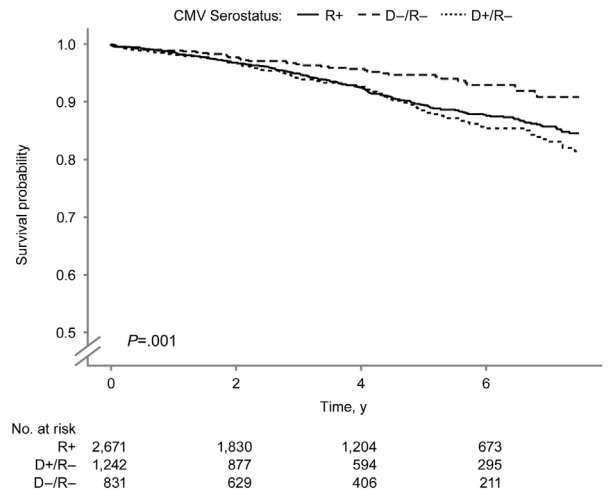


FIGURE 4 | Death-censored Kidney Graft Survival by Donor-Recipient CMV Serostatus. Death-censored kidney graft survival after SPK transplantation by donor–recipient CMV serostatus. CMV indicates cytomegalovirus; R+, CMV-positive transplant recipients; D+/R–, CMV-positive donors and CMV-negative recipients; D–/R–, CMV-negative donors and recipients.

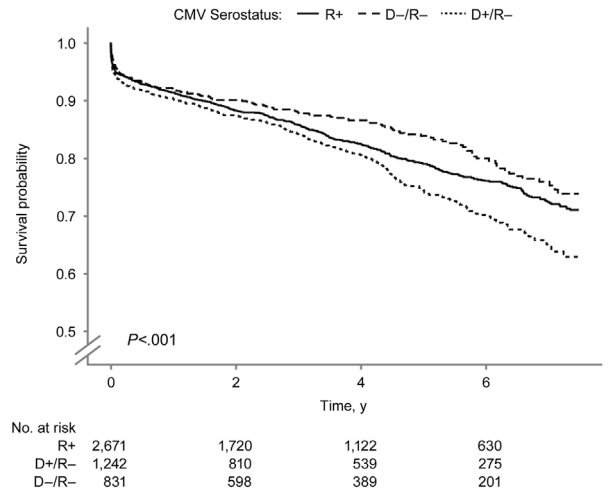


FIGURE 5 | Overall Pancreas Graft Survival by Donor-Recipient CMV Serostatus. Overall pancreas graft survival after SPK transplantation by donor–recipient CMV serostatus. CMV indicates cytomegalovirus; R+, CMV-positive transplant recipients; D+/R–, CMV-positive donors and CMV-negative recipients; D–/R–, CMV-negative donors and recipients.

Individualization of immunosuppressive protocols has been explored as a strategy to reduce infectious complications, including CMV infection, particularly through selective use of non-depleting induction agents [34, 35] or mTOR inhibitors [36, 37]. Our group had previously examined the outcomes of SPK recipient by induction type [38] and non-depletions induction had similar results to r-ATG in terms of recipient and grafts

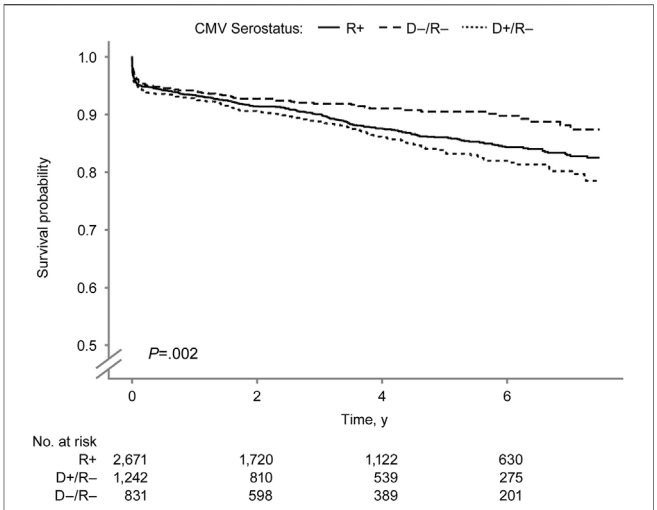


FIGURE 6 | Death-censored Pancreas Graft Survival by Donor-Recipient CMV Serostatus. Death-censored pancreas graft survival by donor–recipient CMV serostatus among SPK transplant recipients. CMV indicates cytomegalovirus; R+, CMV-positive transplant recipients; D+/R–, CMV-positive donors and CMV-negative recipients; D–/R–, CMV-negative donors and recipients.

survival. Although tailored approaches may decrease the incidence of CMV and other posttransplant infections, existing evidence suggests that these modifications have not translated into improved recipient or graft survival after SPK transplantation. In our cohort, outcomes did not differ significantly by induction type, and CMV donor–recipient serostatus discordance (D+/R–) remained the primary determinant of adverse outcomes. This persistent disparity despite efforts to personalize immunosuppression underscores the substantial, independent impact of CMV serostatus on long-term outcomes and highlights the need for national and global initiatives aimed at mitigating the risks associated with high-risk CMV mismatches.

Another challenge for SPK recipients is the risk of delayed-onset CMV infection after discontinuing valganciclovir prophylaxis [22]. Ahopelto et al [19] reported a 68% rate of primary CMV infection among CMV D+/R– SPK transplant recipients in Finland, mainly after the conclusion of 6 months of valganciclovir prophylaxis. In contrast, 36% of CMV R+ recipients had CMV infection after completing 3 months of valganciclovir prophylaxis. The rates of hospitalization and recurrent, refractory, and resistant cases were 2- to 4-fold higher in CMV D+/R– patients than in CMV R+ patients. Our results complement these findings and underscore the current challenges involved in treating SPK transplant recipients. Even in an era of prolonged prophylaxis (up to 6 months for high-risk patients), the negative effects of CMV on short- and long-term allograft and patient survival remain a substantial challenge.

The association between CMV serostatus and posttransplant allograft and patient outcomes has been shown for other organ

TABLE 3 | Multivariable cox proportional hazard models for recipient, pancreas, and kidney outcomes[a,b].

Outcome	D+/R–		D–/R–	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Overall outcomes				
Death	1.28 (1.01–1.62)	0.045	0.98 (0.73–1.32)	0.89
Pancreas graft loss	1.25 (1.06–1.48)	0.009	0.86 (0.70–1.07)	0.17
Kidney graft loss	1.20 (1.00–1.46)	0.06	0.85 (0.66–1.09)	0.19
Death-censored outcomes				
Pancreas graft loss	1.19 (0.96–1.47)	0.11	0.75 (0.56–0.99)	0.04
Kidney graft loss	1.31 (1.01–1.69)	0.04	0.66 (0.46–0.96)	0.03

Abbreviations: D–/R–, CMV-negative donors and recipients; D+/R–, CMV-positive donors and CMV-negative recipients.

[a]*Models were adjusted for recipient age, sex, ethnicity, diabetes type, preemptive transplant, years on dialysis, induction type, corticosteroid maintenance, HLA, antigen mismatch, calculated panel reactive antibody, local vs. imported organs, pancreas donor risk index, and donor-recipient Epstein-Barr virus status.*

[b]*D+/R– and D–/R– groups were each compared with the R+ group (CMV-positive recipients) using the same model.*

transplant types. In a study of kidney-alone transplants, Leeaphorn et al [39] reported that D+/R– serostatus was associated with a 17% higher risk of kidney graft loss and an 18% higher risk of death. Lockridge and colleagues [40] adopted an innovative policy change in an Oregon organ procurement organization that allowed for matching on the basis of donor-recipient CMV status, with some exceptions. This policy change aimed to reduce the number of high-risk D+/R– transplants and increase the number of low-risk D–/R– transplants. The resulting variance in allocation was not associated with changes in transplant rates in either group. However, the national kidney and pancreas allocation systems do not consider CMV matching. Axelrod et al [41] found that D–/R–serostatus was associated with better kidney graft survival, more quality-adjusted life years, and lower costs than D+/R–serostatus. Moreover, they modeled the outcomes of recipients who had to wait for a CMV-negative donor and found survival benefits of up to 30 months. Our results support the findings of these other groups and expand the potential benefits of CMV matching to SPK recipients. However, further studies are needed to assess the practicality and the broader impact of allocation changes.

Strengths and Limitations

To our knowledge, this study represents the largest and most comprehensive to date in documenting the long-term outcomes of SPK transplant recipients on the basis of donor-recipient CMV risk profiles. It was designed to isolate the effects of donor-recipient CMV risk profiles by including only conventional-risk recipients with crossmatch-negative transplants and by using a standardized maintenance regimen. Primary outcomes were based on well-documented metrics from the SRTR.

However, the study has limitations. First, the retrospective design prevents full adjustment for unmeasured confounders. Second, the SRTR standard analysis file has substantial variability in center reporting practices. For example, although the cohort was limited to recipients discharged on a standard maintenance regimen of tacrolimus and mycophenolate mofetil, the standard analysis file lacks consistent data on postdischarge changes to immunosuppressive regimens. This restricts the ability of researchers to analyze variances in immunosuppression exposure, or to assess tolerability of SPK transplant recipients to immunosuppression. Third, the SRTR does not capture granular longitudinal data on the duration of CMV prophylaxis, the magnitude of CMV infection (e.g., viral load) or disease, antiviral drug resistance or management, donor-specific antibody formation, or late rejection episodes. Therefore, it is difficult to determine whether the outcomes observed in this study were primarily influenced by active CMV infection, given that delayed-onset CMV infection remains a common phenomenon in SPK transplant [19, 22]. Finally, the lack of access to a biorepository or T-cell profiling limits the ability of researchers to examine the relationship between primary CMV infection and the immune system in SPK transplant recipients.

Conclusion

In this large cohort of SPK transplant recipients, having a high-risk donor-recipient CMV serostatus discordance (D+/R–) was associated with a significantly higher risk of death and overall graft loss. In contrast, concordant-negative CMV serostatus (D–/R–) was associated with significantly higher death-censored survival of both kidney and pancreas grafts. The high-risk group also had the highest rates of complications, including rejection and hospitalization, whereas the low-risk group had significantly lower rates of these outcomes.

These findings underscore the potential benefit of matching CMV-seronegative transplant recipients with organs from CMV-seronegative donors. Implementing such matching strategies could improve overall survival rates for recipients and allografts and help with CMV prevention. However, further research is needed to evaluate the potential effects of extending wait times for seronegative organs and to explore the feasibility of revising the allocation policies.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: All relevant data supporting the findings of this study are reported within the article or available from the SRTR database, subject to the data use agreement. Requests to access these datasets should be directed to SR, riad.samy@mayo.edu.

ETHICS STATEMENT

The studies involving humans were approved by Mayo Clinic Institutional Review Board (INC8014532). 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

Resident in the Division of Nephrology and Hypertension (JA-M), Mayo Clinic School of Graduate Medical Education, Mayo Clinic College of Medicine and Science, Rochester, Minnesota; and Division of Clinical Trials & Biostatistics (BS), Division of Nephrology and Hypertension (NI, AK, and SR), Division of Endocrinology, Diabetes, Metabolism, and Nutrition (YK), Division of Infectious Diseases (RR), and Mayo Clinic William J. von Liebig Center for Transplantation and Clinical Regeneration (PD and MP) Mayo Clinic, Rochester, Minnesota.

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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.2025.15653/full#supplementary-material

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ORIGINAL RESEARCH
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Living Donation and Pre-Emptive Transplantation Are More Important Than HLA Matching in Pediatric Kidney Transplantation: Results From a 33-Year Comparative OPTN Study

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Poorly HLA matched transplants have poorer long-term outcomes, however it is unclear whether living donation or pre-emptive transplantation can counteract the effects of HLA mismatches. We reviewed the long-term outcomes of paediatric kidney transplants with different HLA matches and aimed to identify other factors which may contribute significantly to long-term outcomes. We conducted a retrospective registry analysis of all pediatric kidney transplants from 1987–2020 in the USA from the OPTN Registry. These were analysed by HLA mismatches and compared by pre-transplant dialysis status and donor type. 21,500 patients were included for analysis. Overall, patients with unfavourable HLA matches had higher rates of delayed allograft function and lower allograft survival. However, patients with unfavourable HLA matched transplants from living donors had better allograft survival than patients with favourable HLA matched transplants from deceased donors (79% at 5 years vs. 71%, p < 0·01). Patients with pre-emptive unfavourable HLA matched transplants had better allograft and patient survival than patients with non-pre-emptive favourable HLA matched transplants (83% at 5 years vs. 78%, p = 0·02% and 98% vs. 96%, p < 0·01 respectively). In conclusion, living donation and pre-emptive transplantation have a more significant impact on clinical outcomes and lead to better allograft and patient survival than HLA matching.

Keywords: pediatric, kidney transplant, HLA mismatch, registry, survival analysis

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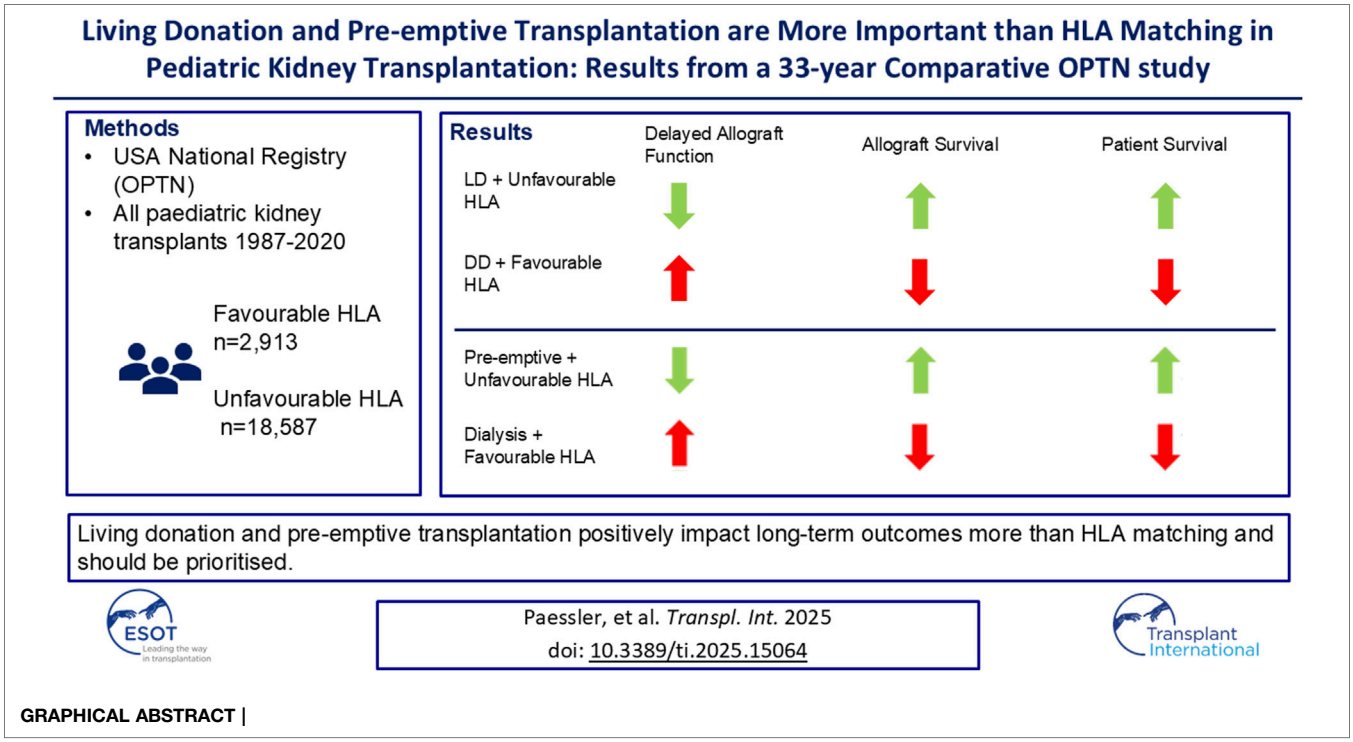
Abbreviations: ANOVA, Analysis of Variance; DGF, Delayed Graft Function; HLA, Human Leucocyte Antigen; SPSS, IBM Statistical Package for Social Sciences; OPTN, Organ Procurement and Transplantation Network; PTLD, Post-Transplant Lymphoproliferative Disorder; UNOS, United Network of Organ Sharing.



GRAPHICAL ABSTRACT |

INTRODUCTION

Due to advances in modern medicine, there is an increasing number of children with complex conditions surviving outside childhood, many with conditions affecting the kidneys. This brings up an increasing number of pediatric kidney transplant candidates. Unfortunately, organ donation rates have not increased in the same proportions. There are currently over 1,200 children waiting for a kidney transplant from a deceased donor in the United States of America (USA), however in 2023, only 548 pediatric kidney transplants took place from deceased donors (based on the Organ Procurement and Transplantation Network (OPTN) data as of November 2024).

Human Leucocyte Antigen (HLA) mismatches is one of the many variables considered when matching kidney donors and recipients [1, 2]. However, over the years its importance has diminished [3, 4]. The Share 35 policy [5], brought many changes, one of which that prioritised kidneys from deceased donors under 35 years old for pediatric recipients, and reduced the importance of HLA mismatch with the exemption of cases with 000 mismatches (no mismatches at HLA-A, -B and -DR). Furthermore, these changes were compounded in the 2014 kidney allocation scheme, which prioritized the highest-quality organs to candidates with the longest predicted survival. Some of the changes meant that that pediatric, highly sensitised and long-term dialysis patients were prioritized over other candidates regardless of HLA mismatch. This meant that for non-highly-sensitised pediatric recipients, HLA mismatch had little importance in kidney allocation [1, 6].

Patients with increasing number of HLA mismatches, have been shown to have shorter allograft survival, possible higher prevalence of post-transplant lymphoproliferative disorder (PTLD) [7] and fewer chances to have a second transplant in the future due to higher sensitisation rate [8]. These factors are particularly important to consider when transplanting children, who have a longer expected lifespan compared to adults and are more likely to require further transplants and therefore have a higher lifetime risk of being affected by potentially negative outcomes.

On the other hand, HLA matching is not the only predictor of long-term outcomes. Evidence shows that receiving transplants from living donors have superior outcomes to transplant from deceased donors [9]. Furthermore, pre-emptive transplants also

TABLE 1 | Number of transplants with each number of HLA mismatches and at each HLA Mismatch Level, proportions for each number of HLA mismatches/ level of HLA mismatches of total number of transplants.

Number of HLA mismatches	Number	Proportion
0	687	3.2%
1	1,107	5.2%
2	3,447	16.0%
3	5,547	25.8%
4	3,881	18.0%
5	4,515	21.0%
6	2,316	10.8%
HLA mismatch level		
1	687	3.2%
2	2,226	10.4%
3	8,634	40.2%
4	9,953	46.2%
Total	21,500	100%

TABLE 2 | Number and proportions of favourable vs. unfavourable HLA matches for different ethnicities, sex, underlying renal disease and eras. Patients with no data on ethnicity, sex, renal disease or era were excluded from analysis for their respective category.

Characteristic		Favourable HLA match number	Favourable HLA match proportion	Unfavourable HLA match Number	Unfavourable HLA match proportion	p-value
Ethnicity	White	1977	67.9%	9,787	52.7%	<0.01
	Black	272	9.3%	3,644	19.6%	<0.01
	Hispanic	550	18·9%	4,071	21·9%	<0.01
	Asian	61	2·1%	605	3.3%	<0.01
	Other/Mixed	53	1·8%	480	2.6%	<0.01
Sex	Male	1718	59.0%	18,587	58·7%	<0.01
	Female	1,194	41.0%	7,654	41.2%	
Renal Disease	Cystic	85	7.8%	891	7·6%	0.79
	Obstructive/Reflux	269	24·8%	2,735	23·4%	0.29
	Glomerulo-nephritis	357	32.9%	3,819	32.7%	0.85
	Hypertension/ Vascular	42	3.9%	556	4·8%	0.18
	Hereditary/ Metabolic	56	5·2%	722	6·2%	0.18
	Hypoplasia/ Dysplasia	177	16·3%	2,130	18.2%	0.12
	Other	98	9.0%	838	7·2%	0.02
Era	<1990	279	21.5%	1,018	78.5%	<0.01
	1990–1999	1,131	19.1%	4,807	80.9%	<0.01
	2000–2009	891	12.6%	6,199	87.4%	<0.01
	2010–2019	580	8.6%	6,197	91.4%	<0.01
	2020>	32	8.0%	366	92.0%	<0.01

TABLE 3 | Overall estimated Kaplan-Meier allograft and patient survival for favourable and unfavourable HLA matches at 1, 3, 5, 10, 20 and 30 years post-transplant, 95% confidence intervals given in (), p-value is the result of the Log-Rank Test.

Survival	Group	1 year	3 years	5 years	10 years	20 years	30 years	p-value
Allograft survival	Favourable HLA Match	94.1 (93.2–94.8) %	88.0 (86.8–89.1) %	80.7 (79.2–82.1) %	65.3 (63.3–67.2) %	31.7 (29.1–34.2) %	9.9 (7.1–13.2) %	**<0.01**
	Number at risk	*2,863*	*2,452*	*2,045*	*1,202*	250	16	
	Unfavourable HLA Match	93.1 (92.7–93.4) %	84.9 (84.4–85.5) %	76.6 (76.0–77.3) %	56.6 (55.7–57.5) %	21.6 (20.5–22.8) %	4.6 (3.4–6.0) %	
	Number at risk	*15,960*	*12,821*	*9,972*	*4,857*	682	15	
Patient survival	Favourable HLA Match	98.4 (97.9–98.8) %	97.4 (96.7–97.9) %	96.0 (95.2–96.7) %	92.5 (91.3–93.5) %	77.6 (74.8 0 89.2) %	50.7 (41.9–59.0) %	**<0.01**
	Number at risk	*2,976*	*2,651*	*2,298*	*1,442*	325	18	
	Unfavourable HLA Match	98.5 (98.3–98.7) %	97.3 (97.0–97.5) %	95.8 (95.5–96.1) %	90.1 (89.6–90.7) %	69.4 (67.8–71.1) %	42.4 (36.5–48.3) %	
	Number at risk	*16,785*	*14,210*	*11,606*	*6,203*	967	18	

Bold values indicate statistical significance.

lead to improved outcomes with less delayed allograft function, better allograft survival time, fewer episodes of acute rejection and a lower risk of death [10].

Due to the many possible variables that can impact outcomes for pediatric kidney transplants, it is unclear which factors should be prioritized when allocating organs. There is also emergencing evidence that other aspects of HLA matching, such as HLA-DQ or eplet mismatch load may be more important than the overall number of HLA mismatches [11–14]. However, globally, allocation systems still use HLA mismatches at HLA-A, -B and -DR in their algorithms. For many countries, particularly middle and low-income countries, the use of eplet mismatch load in day-to-day clinical practice is still a long way off and so it is important to understand HLA-A, -B and -DR better as that is the basis upon which most organs are allocated.

The primary aim of this study was to compare the outcomes of transplants with favourable and unfavourable HLA matches, and more importantly to identify whether living donation or pre-emptive transplantation contribute more significantly to allograft outcomes than HLA matching.

MATERIALS AND METHODS

The OPTN database is an online registry developed by United Network of Organ Sharing (UNOS) that contains all data

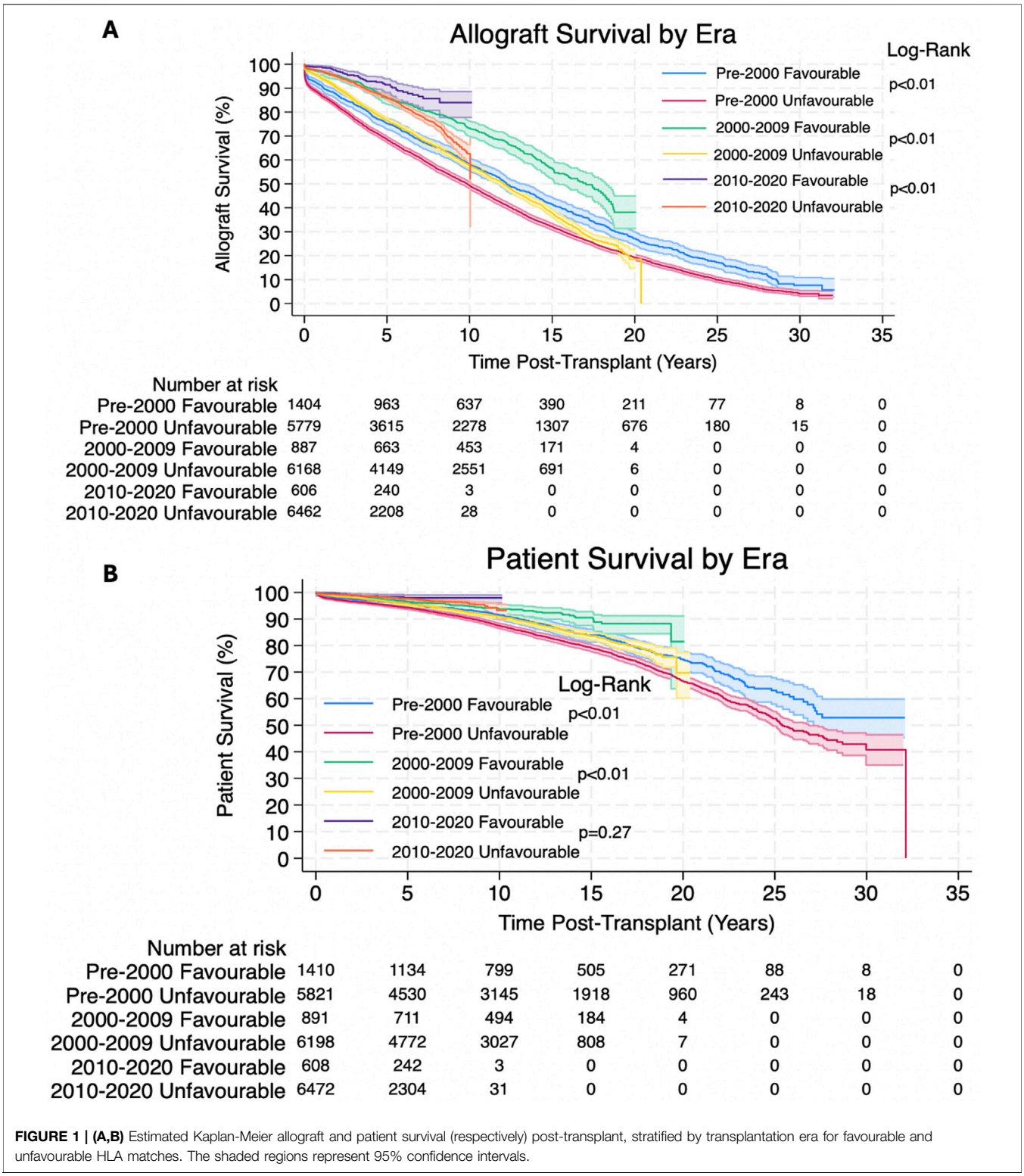


FIGURE 1 | (A,B) Estimated Kaplan-Meier allograft and patient survival (respectively) post-transplant, stratified by transplantation era for favourable and unfavourable HLA matches. The shaded regions represent 95% confidence intervals.

pertaining to patient waiting lists, living and deceased organ donation, organ matching and organ transplants that have taken place in the U.S. since 1st October 1987 [15]. Data are added to the database at the point of listing a patient for transplant, at the point of donation and is updated at 6 months, 1-year and annually post-transplant with recipient outcome data. This database is the largest registry containing data on paediatric kidney transplants.

TABLE 4 | Sensitivity analysis with Multivariate cox proportional hazards regression models for allograft failure for favourable and unfavourable HLA matches.

Variable	Hazard ratio	p-value	95% CI
Model 1			
Unfavourable Match	1.31	<**0.01**	1.25–1.39
Model 2			
Unfavourable Match	1.21	<**0.01**	1.07–1.38
Dialysis Prior to Transplant	1.25	<**0.01**	1.15–1.37
Non-White Recipient Ethnicity	0.98	0.05	0.96–1.00
Male	0.83	<**0.01**	0.78–0.89
Decade of Transplantation	0.74	<**0.01**	0.70–0.78
Deceased Donor	0.92	0.45	0.74–1.14
Donor Creatinine	1.02	**0.03**	1.00–1.05
Recipient Age (Years)	1.04	<**0.01**	1.04–1.06
Cold Ischaemia Time (Hours)	1.00	<**0.01**	1.00–1.01
Model 3			
Unfavourable Match	1.25	<**0.01**	1.18–1.33
Dialysis Prior to Transplant	1.24	<**0.01**	1.17–1.30
Decade of Transplantation	0.73	<**0.01**	0.71–0.75
Deceased Donor	1.37	<**0.01**	1.31–1.42
Model 4			
Unfavourable Match	1.25	<**0.01**	1.18–1.33
Dialysis Prior to Transplant	1.23	<**0.01**	1.17–1.30
Non-White Recipient Ethnicity	1.00	0.66	0.99–1.01
Decade of Transplantation	0.73	<**0.01**	0.71–0.75
Deceased Donor	1.36	<**0.01**	1.31–1.42

Bold values indicate statistical significance.

TABLE 5 | Sensitivity analysis with Multivariate cox proportional hazards regression models for death for favourable and unfavourable HLA matches.

Variable	Hazard ratio	p-value	95% CI
Model 1			
Unfavourable Match	1.29	<**0.01**	1.15–1.43
Model 2			
Unfavourable Match	1.18	1.28	0.92–1.52
Dialysis Prior to Transplant	1.44	<**0.01**	1.20–1.75
Non-White Recipient Ethnicity	0.95	<**0.01**	0.91–0.98
Male	0.78	<**0.01**	0.69–0.89
Decade of Transplantation	0.70	<**0.01**	0.63–0.78
Deceased Donor	1.03	0.88	0.65–1.66
Donor Creatinine	1.04	0.08	0.99–1.09
Recipient Age (Years)	1.04	<**0.01**	1.03–1.07
Cold Ischaemia Time (Hours)	1.01	**0.01**	1.00–1.02
Model 3			
Unfavourable Match	1.6	**0.01**	1.03–1.30
Dialysis Prior to Transplant	1.44	<**0.01**	1.28–1.62
Decade of Transplantation	0.72	<**0.01**	0.68–0.76
Deceased Donor	1.56	<**0.01**	1.44–1.69
Model 4			
Unfavourable Match	1.16	**0.01**	1.03–1.30
Dialysis Prior to Transplant	1.45	<**0.01**	1.29–1.63
Non-White Recipient Ethnicity	0.97	<**0.01**	0.94–0.99
Decade of Transplantation	0.72	<**0.01**	0.69–0.76
Deceased Donor	1.58	<**0.01**	1.45–1.72

Bold values indicate statistical significance.

It was chosen for this study as it would be able to provide us with the largest sample size.

OPTN registry data for all kidney transplants performed for recipients under the age of 18 years in the U.S. from October 1987 until September 2020 were requested. Data retrieved from the registry included donor and recipient demographics, number of prior transplants, dialysis status at transplantation, number of HLA mismatches at HLA-A, -B and -DR, primary allograft non-function, delayed allograft function, allograft survival and patient survival time. HLA-locus specific mismatches for each patient were not included, however mismatch level was included. HLA mismatch levels are referred to as follows:

- Mismatch level 1–000
- Mismatch level 2–0 DR and 0/1 B (100, 010, 110, 200, 210)
- Mismatch level 3–0 DR and 2B, or 1 DR and 0/1 B (020, 120, 220, 001, 101, 201, 011, 111, 211)
- Mismatch level 4–1 DR and 2B or 2 DR (021, 121, 221, 002, 102, 202, 012, 112, 212, 022, 122, 222)

All patients' post-transplant follow up data that were used for analysis were based on their latest data submitted to the registry in January 2021. Patients with no data recorded on the level of HLA mismatches were excluded. Other missing data was assumed to be missing completely at random. For each patient we only analysed data for the first kidney transplant unless otherwise specified.

HLA Mismatch is defined in the OPTN database as occurring when the donor has at least one HLA-A, HLA-B or HLA-DR antigen that is not present in the recipient [15]. The number of HLA mismatches describes the number of antigens in the donor that are not present in the recipient and level of mismatches are described as above. This accounts for the increased immunogenicity of class 2 mismatches and accounts for the evidence that class 2 mismatches are more likely to lead to rejection than class 1 mismatches [16–18]. For the purposes of this study we defined Favourable HLA match as transplants with HLA Mismatch level 1 or 2. Unfavourable HLA matches were defined as transplants with HLA Mismatch level 3 or 4.

All statistical analysis was carried out with IBM Statistical Package for Social Sciences (SPSS) Version 28 [19]. Demographics and post-transplant outcomes including allograft and patient survival were compared between patients with different levels of HLA Mismatches. Means, standard deviations and 95% confidence intervals were reported to describe all numerical data, frequencies and percentages were used to describe categorical data. Independent T-test and Analysis of Variance (ANOVA) was used for significance testing to compare groups of patients. Patient and allograft survival at 1, 3, 5,10, 20, and 30 years post-transplant was estimated using Kaplan-Meier analysis and log-rank testing was used to assess comparisons. Multivariate cox proportional hazard regression analysis to estimate the effect of the level of HLA mismatches on allograft and patient survival while accounting for dialysis status at time of transplantation, recipient ethnicity, recipient sex, recipient age, donor type, decade of transplantation, donor creatinine and cold ischaemia time was also carried out after ruling out colinearity with variance inflation factors. Sensitivity analysis was carried out by running several different models. Hazard ratios for allograft failure and for death over time post-transplant were also presented to display how some determinants of graft failure and death are time-varying; these were presented using piece-wise exponential additive mixed models [20]. P-values, with a

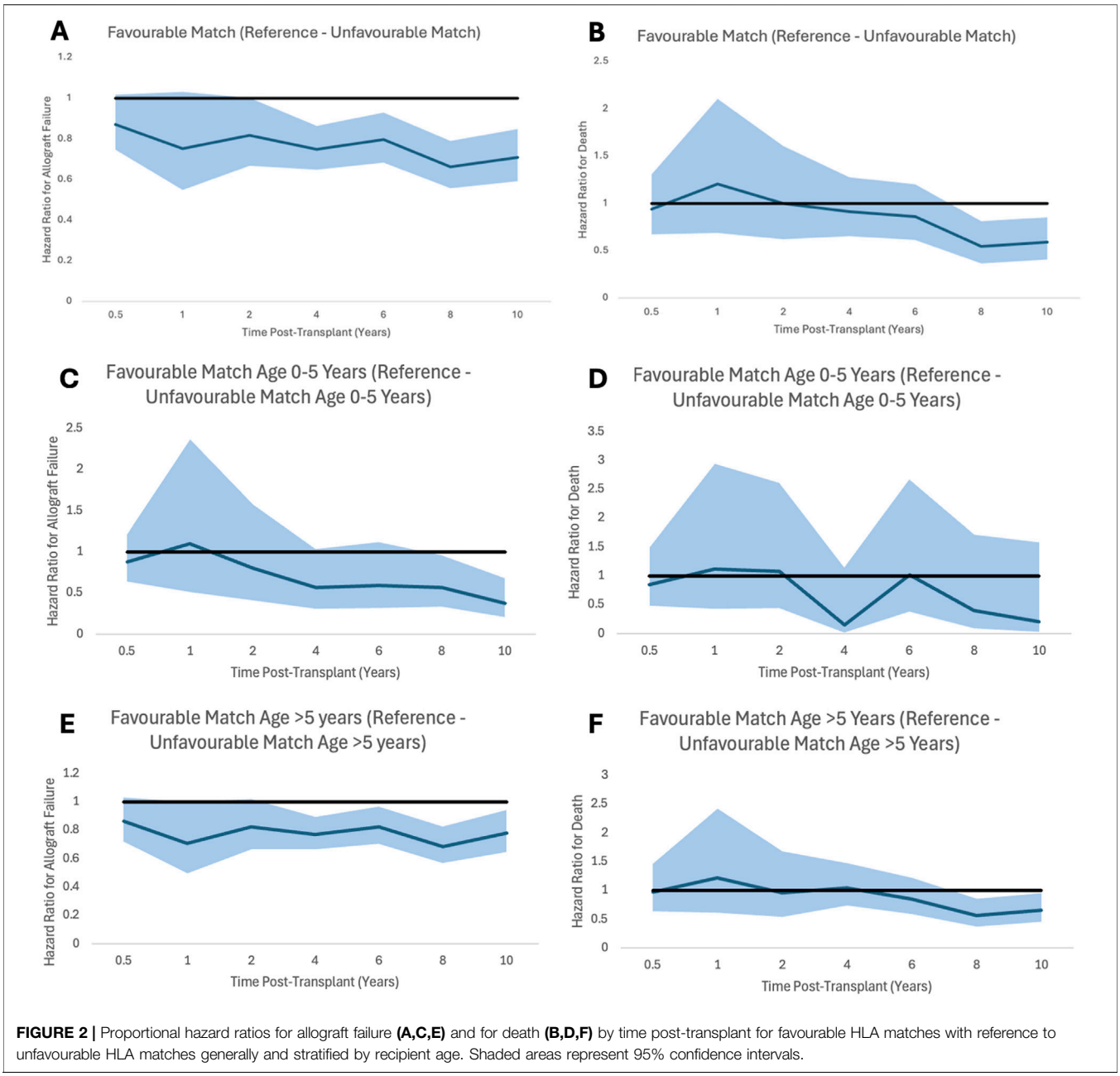


FIGURE 2 | Proportional hazard ratios for allograft failure **(A,C,E)** and for death **(B,D,F)** by time post-transplant for favourable HLA matches with reference to unfavourable HLA matches generally and stratified by recipient age. Shaded areas represent 95% confidence intervals.

threshold of significance of $p < 0{\cdot}05$ are displayed as a measure of significance. When data were used for multiple comparisons Bonferroni corrections were implemented.

RESULTS

Demographics and Background Information

Overall, 21,500 patients met the inclusion criteria. Their distribution across the number of HLA mismatches and HLA mismatch levels can be seen in **Table 1**.

The mean recipient age was 10·77 (10·63–10·90) years with patients with unfavourable HLA matches being significantly older – 10·82(10·75–10.89) vs. 10·61 (10·42–10·80) years ($p < 0{\cdot}02$). Patient ethnicity, sex, underlying renal disease and era data can be seen in **Table 2**. White patients were more likely to have a favourable HLA match than any other ethnicity ($p < 0{\cdot}01$). Over time, as the number of deceased donor transplants increased and the number of living donor transplants decreased, an increasing proportion of transplants were performed with an unfavourable HLA match ($p < 0{\cdot}01$). For example, prior to 1990 21.5% of transplants had a favourable HLA match, and since 2020 this has decreased to just 8.0%.

TABLE 6 | Estimated Kaplan-Meier allograft and patient survival for patients receiving transplants with favourable HLA matches from deceased donors and unfavourable HLA matches from living donors at 1, 3, 5, 10, 20 and 30 years post-transplant, 95% confidence intervals given in (), p-value is the result of the Log-Rank Test.

Survival	Group	1 year	3 years	5 years	10 years	20 years	30 years	p-value
Allograft survival	Favourable HLA Match – Deceased Donor	88.8 (86.6–90.7) %	79.4 (76.5–82.0) %	67.5 (64.2–70.7) %	51.2 (47.4–55.0) %	21.4 (17.4–25.6) %	6.6 (3.0–12.3) %	**<0.01**
	Number at risk	*758*	*614*	*464*	*265*	51	2	
	Unfavourable HLA Match – Living Donor	94.7 (94.2–95.2) %	88.7 (88.0–89.4) %	81.4 (80.5–82.3) %	62.0 (60.7–63.2) %	24.1 (22.5–25.7) %	5.5 (3.7–7.8) %	
	Number at risk	*7,098*	*6,086*	*5,006*	*2,745*	421	9	
Patient survival	Favourable HLA Match – Deceased Donor	96.8 (95.4–97.7) %	94.5 (92.8–95.9) %	91.6 (89.4–93.3) %	85.5 (82.4–88.0) %	65.5 (59.3–71.1) %	37.9 (16.5–59.5)	**<0.01**
	Number at risk	*821*	*712*	*578*	*345*	68	2	
	Unfavourable HLA Match – Living Donor	98.6 (98.3–98.8) %	97.6 (97.3–97.9) %	96.4 (95.9–96.8) %	92 (91.3–92.7) %	74.8 (72.6–76.8) %	55.8 (49.4–61.7) %	
	Number at risk	*7,362*	*6,521*	*5,607*	*3,307*	529	9	

Bold values indicate statistical significance.

The majority of transplants with favourable HLA matches where from living donors (77·0% living donors vs. 23·0% deceased donors), this was a significantly higher proportion than transplants with unfavourable HLA matches (13·8% living donors vs. 86·2% deceased donors) ($p < 0·01$). Patients with favourable HLA matches were more likely to have received their transplants pre-emptively than patients with unfavourable HLA matches (26·5% vs. 23·3%, $p < 0·01$).

Post-Transplant Outcomes

Overall, transplants with favourable HLA matches were significantly less likely to have delayed allograft function (DGF) than transplants with unfavourable HLA matches (n = 204, 7.0% vs. n = 1,571, 8.5%, $p < 0·01$). However, this trend was not seen in relation to primary allograft non-function (n = 23, 0·8% vs. n = 194, 1·0%, $p = 0·20$).

Both allograft survival and patient survival were significantly better in patients with favourable HLA matches. 1, 3, 5, 10, 20 and 30 years allograft and patient survival for these patients is summarized in **Table 3** and survival curves stratified by transplantation era can be seen in **Figures 1A,B**.

Multivariate Cox Proportional Hazards Regression Model of allograft failure and death was carried out to understand the impact of the HLA mismatch level, dialysis status, recipient ethnicity, recipient sex, recipient age, donor type, decade of transplantation, donor creatinine, and cold ischaemia time. Decades of transplantation are described in ascending order from <1990 to 1990–1999, 2000–2009, etc. starting with 1.00 = <1990. All the above variables have variance inflation factors of <1.15 and so colinearity was ruled out. Sensitivity analysis, Hazard ratios with 95% confidence intervals and p-values can be seen in **Tables 4**, **5**. Graphs to show how these risks changed over time and for different age groups can be seen in **Figure 2**.

Impact of Donor Type

Results were also compared between patients who received favourable HLA matched allografts from deceased donors and those who received unfavourable HLA matched grafts from living donors.

Transplants from living donors with unfavourable HLA matches were significantly less likely to have DGF than transplants from deceased donors with favourable HLA matches (n = 396, 5.0% vs. n = 154, 16.7%, $p < 0·01$). However, this trend was not seen in relation to primary allograft non-function (n = 69, 0·9% vs. n = 10, 1·1%, $p = 0·49$).

Analysis showed that patients receiving allografts with unfavourable HLA matches from living donors had significantly better allograft and patient survival. 1, 3, 5, 10, 20 and 30 years allograft and patient survival for these patients is summarized in **Table 6** and survival curves can be seen in **Figures 3A,B**. Graphs to show proportional hazard ratios for allograft failure and death over time by donor type can be seen in **Figure 4**.

Impact of Pre-Emptive Transplantation

Results were also compared between patients who were transplanted after a period of being on dialysis with favourable HLA matched grafts and those who were transplanted pre-emptively with unfavourable HLA matched grafts.

Pre-emptive transplants with unfavourable HLA matches were significantly less likely to have DGF than transplants with favourable HLA matches on dialysis (n = 118, 2.6% vs. n = 245, 10.3%, $p < 0·01$). This trend was not seen in relation to primary allograft non-function (n = 33, 0·7% vs. n = 20, 0.8%, $p = 0·56$).

Analysis showed that patients receiving allografts pre-emptively with unfavourable HLA matches had significantly better allograft survival and patient survival. 1, 3, 5,10, 20 and 30 years allograft and patient survival for these patients is summarized in **Table 7** and survival curves can be seen in **Figures 5A,B**. Graphs to show proportional hazard ratios for allograft failure and death over time by dialysis status can be seen in **Figure 6**.

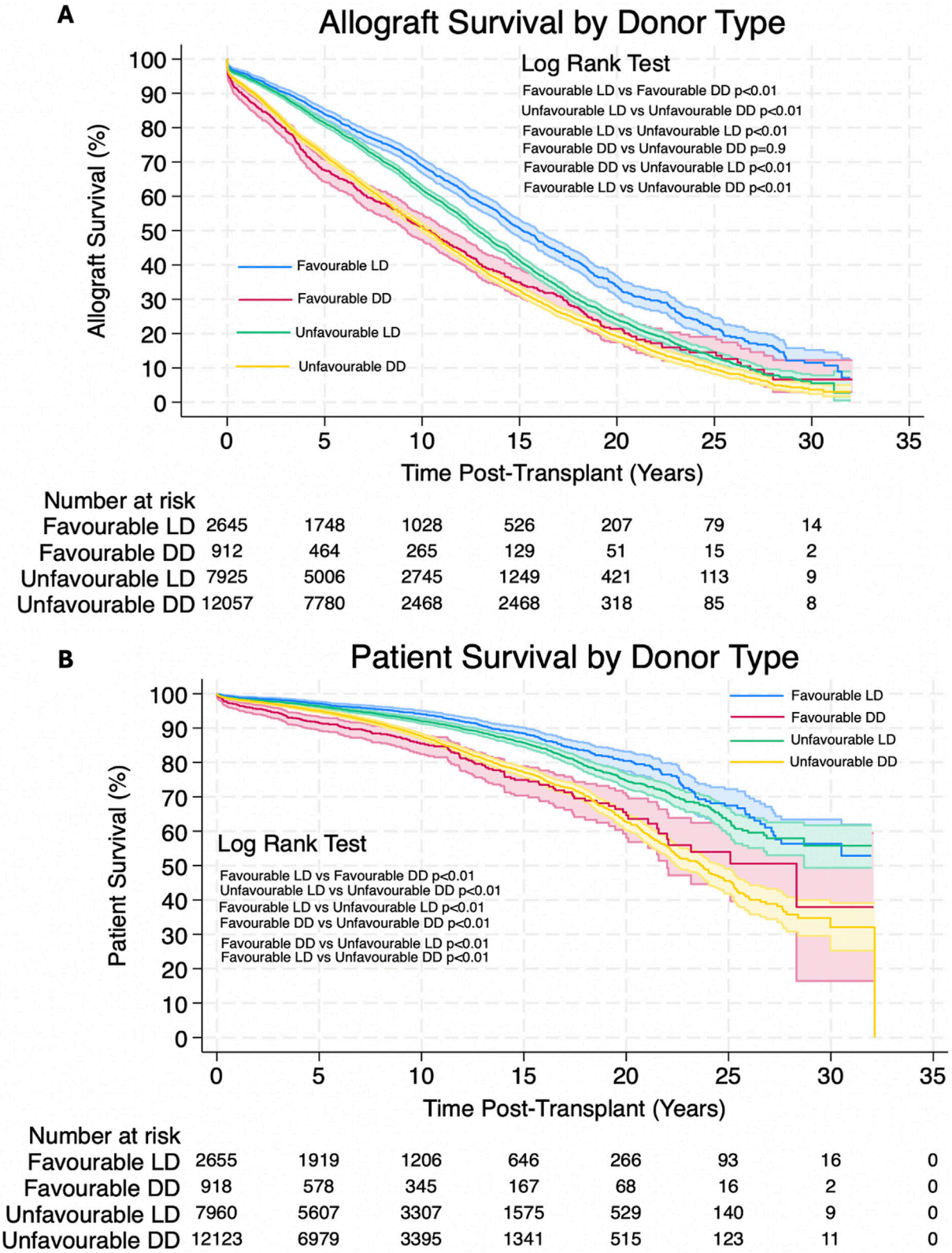


FIGURE 3 | (A,B) Estimated Kaplan-Meier allograft and patient survival (respectively) post-transplant for favourable and unfavourable HLA matches by donor type. Shaded areas represent 95% confidence intervals.

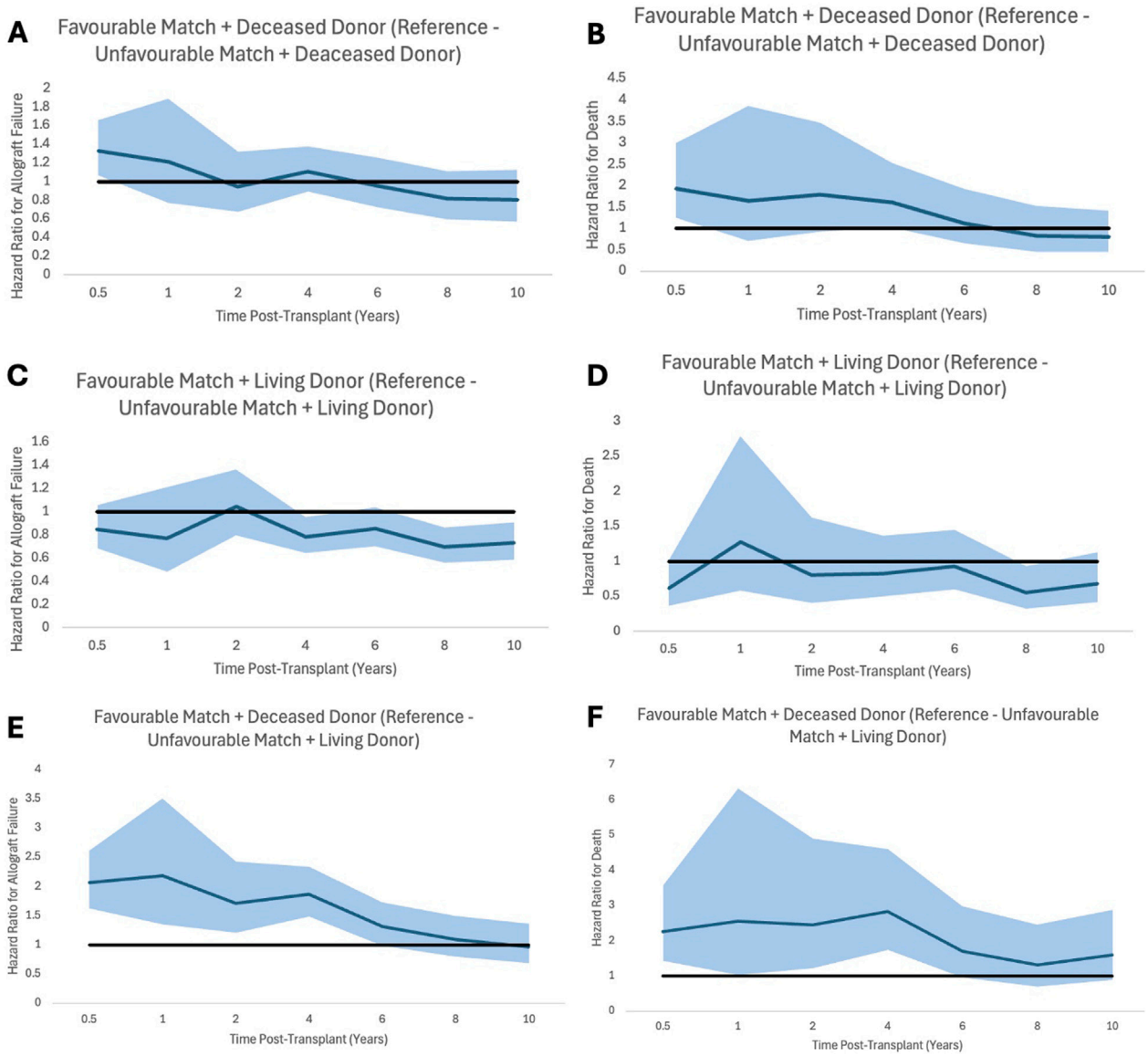


FIGURE 4 | Proportional hazard ratios for allograft failure **(A,C,E)** and for death **(B,D,F)** by time post-transplant for favourable HLA matches with reference to unfavourable HLA, stratifying for donor type. Shaded areas represent 95% confidence intervals.

Re-Transplantation Outcomes

Patients who had a favourable HLA match at their first transplant, were equally as likely to receive a favourable HLA match at their second transplant as those with unfavourable HLA match at their first transplant (n = 48, 16.9% vs. n = 262, 17.4%) (p = 0·84). Patients with a favourable HLA match at their first transplant were however more likely to receive a pre-emptive 2nd transplant compared to those with an unfavourable HLA match at their first transplant (n = 66, 23.2% vs. n = 267, 17.7%) (p = 0.03).

Kaplan-Meier survival estimates for allograft survival of the 2nd allograft and patient survival after the 2nd transplant was not significantly different between patients receiving favourable and unfavourable HLA matches during their first transplant. 1, 3, 5, 10 and 20 years allograft and patient survival for these patients is summarized in **Table 8** and survival curves can be seen in **Figures 7A,B**.

DISCUSSION

To date, this study describes the clinical outcomes of the largest cohort of pediatric kidney transplant recipients in the literature. Overall, the results from this study have shown that HLA matching does play an important role in both short-term and long-term outcomes, however, we identified other factors which may make a more significant impact on clinical outcomes in pediatric kidney

TABLE 7 | Estimated Kaplan-Meier allograft and patient survival for patients transplants with favourable HLA matches after a period on dialysis and pre-emptive transplants with unfavourable HLA matches at 1, 3, 5, 10, 20 and 30 years post-transplant, 95% confidence intervals given in (), p-value is the result of the Log-Rank Test.

Survival	Group	1 year	3 years	5 years	10 years	20 years	30 years	p-value
Allograft survival	Favourable HLA Match on Dialysis	92.9 (91.8–93.9) %	85.2 (83.7–86.6) %	76.9 (75.0–78.6) %	61.0 (58.7–63.3) %	28.9 (26.0–31.9) %	5.8 (2.9–9.9) %	**0.02**
	Number at risk	*2,069*	*1,736*	*1,414*	*812*	154	5	
	Pre-emptive Unfavourable HLA Match	96.4 (95.8%–96.9%	91.7 (90.8–92.5) %	84.6 (83.4–85.8) %	65.4 (63.6–67.1) %	25.2 (22.5–281) %	-	
	Number at risk	*4,087*	*3,341*	*2,609*	*1,275*	130	0	
Patient survival	Favourable HLA Match on Dialysis	98.3 (97.7–98.8) %	97.0 (96.2–97.7) %	95.0 (93.9–95.8) %	90.5 (89.0–91.9) %	74.9 (71.4–78.0) %	47.5 (37.1–57.1) %	**<0.01**
	Number at risk	*2,182*	*1,928*	*1,634*	*999*	206	7	
	Pre-emptive Unfavourable HLA Match	99.1 (98.8–99.4) %	98.6 (98.2–98.9) %	97.8 (97.3–98.2) %	93.4 (92.3–94.3) %	76.9 (73.0–80.3) %	-	
	Number at risk	*4,188*	*3,508*	*2,861*	*1,477*	146	0	

Bold values indicate statistical significance.

transplantation than HLA matching. This is the first study to show that pre-emptive transplants and living donation led to improved allograft and patient survival even in those with unfavourable HLA matches, suggesting that those factors should be prioritized over HLA matching.

Patients receiving unfavourable HLA matched allografts were more likely to experience DGF, and shorter allograft and patient survival compared to patients with favourable HLA matched allografts, although these risks are more significant in later years post-transplant. This finding is in keeping with already reported data in the literature [7, 8, 21]. It may therefore be somewhat concerning that there continues to be a rise in unfavourably HLA matched transplants for children in the USA and also worldwide due to changes in the allocation policies in an attempt to improve access and reduce waiting times [6, 22]. However, it is also important to not look at the changes after new allocation policies in isolation. The introduction of both the Share35 and the 2014 kidney allocation policy has also led to an increase in young donors for pediatric recipients, an increase in pre-emptive transplantation and an improvement in the racial disparities in access to transplantation [2, 5, 6]. Although there's been an improvement in the racial disparities, our data shows ethnic minorities continue to be more likely to receive unfavourably HLA matched allografts compared to their Caucasian peers. This could potentially be due to the fact that there is a higher prevalence of euro-caucasian HLA types in the USA and this would be reflected in the donor pool [23]. This is something that still needs to be improved upon further to provide equal access to transplant. It is however reassuring that our data showed that these disparities are not seen in long-term allograft and patient survival.

Another disparity shown in this study was the otucomes between males and females. Males were found to have a lower risk of allograft failure and death, although a reason for this was not found in this study. We suspect that as males make up a higher proportion of patients with congenital renal anomalies than females [24], and that subset of patients does not have the added risk of recurrent renal disease, that this is what may be causing that disparity, although further research is needed to explore this further.

We also found that when stratifying the risk of allograft failure and death by recipient age, the impact of an unfavourably HLA matched allograft is not as significant in younger recipients, specifically in recipients under the age of 5 years than in older recipients. We suspect that this is due to younger recipients being less immunogenic than older recipients, and less likely to amount an immune response against mismatched antigens [25, 26], although this needs to be researched further to confirm this.

Our data, in contrary to the literature, shows that receiving an unfavourable HLA matched allograft as first transplant does not decrease the likelihood of having a favourably matched graft at re-transplantation. However, it does reduce the likelihood of being transplanted pre-emptively at transplantation, which is important to consider due to the negative implications of being exposed to dialysis. One reason, that may be the case, although not demonstrated in this study, is that patients with unfavourable HLA matches at first transplant may be more highly sensitised and so may wait longer to be matched for subsequent transplants, thereby having to start dialysis [8, 18, 27]. These factors are particularly important to consider in the pediatric population who have a longer potential lifespan and so are likely to require multiple transplants in their lifetime.

While it is important to strive for favourable HLA matches in pediatric kidney transplantation, we show that it may be more important to strive for living donation and pre-emptive transplantation for pediatric recipients. Recent meta-analysis on a cohort of over 20,000 pediatric kidney transplants has shown that pre-emptive kidney transplantation leads to a lower risk of allograft loss and acute rejection [28]. Another large study found that living donation leads to significantly improved allograft survival when compared to deceased donation [9]. Studies have also shown that even HLA incompatible transplants in which recipients have a positive HLA crossmatch, are possible and can have good clinical outcomes [29]. While the literature has been able to identify multiple factors that independently improve outcomes, we have been able to show that in direct comparison to HLA matching, living donation and pre-emptive transplantation have a more significant impact and play a bigger role in long-term clinical outcomes [30, 31]. On the other hand, our data on time-varying hazards for allograft failure and death show that the protective

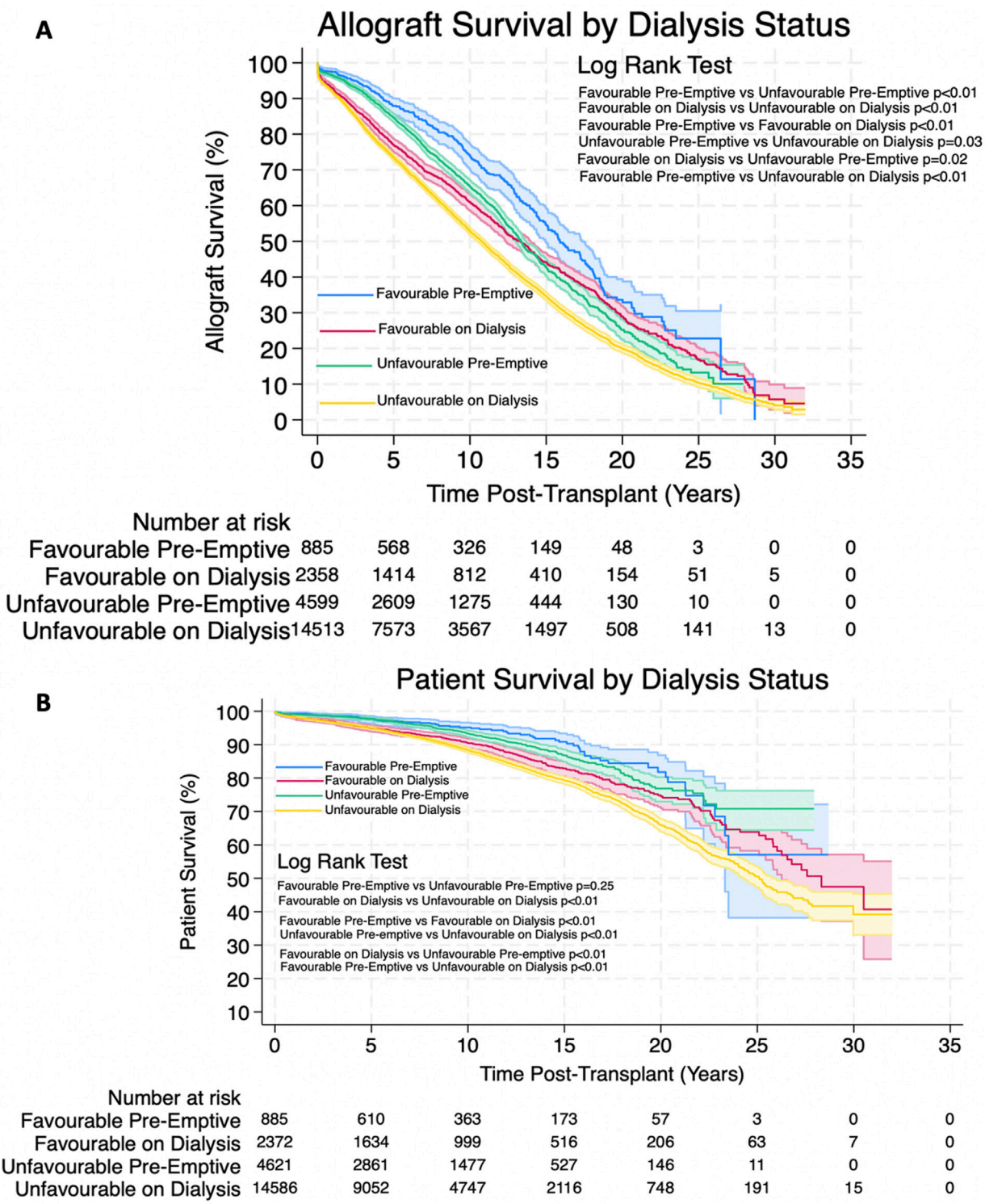


FIGURE 5 | (A,B) Estimated Kaplan-Meier allograft and patient survival (respectively) post-transplant for favourable and unfavourable HLA matches by dialysis status prior to transplant. Shaded areas represent 95% confidence intervals.

effects of living donation and pre-emptive transplantation are more significant early on post-transplant and their protective effects diminish when approaching 10-years post-transplant.

Our multivariate cox proportional hazards regression model suggests that for unfavourable HLA mismatches the hazard ratio for allograft failure and death increased by 0.21–0.31 and

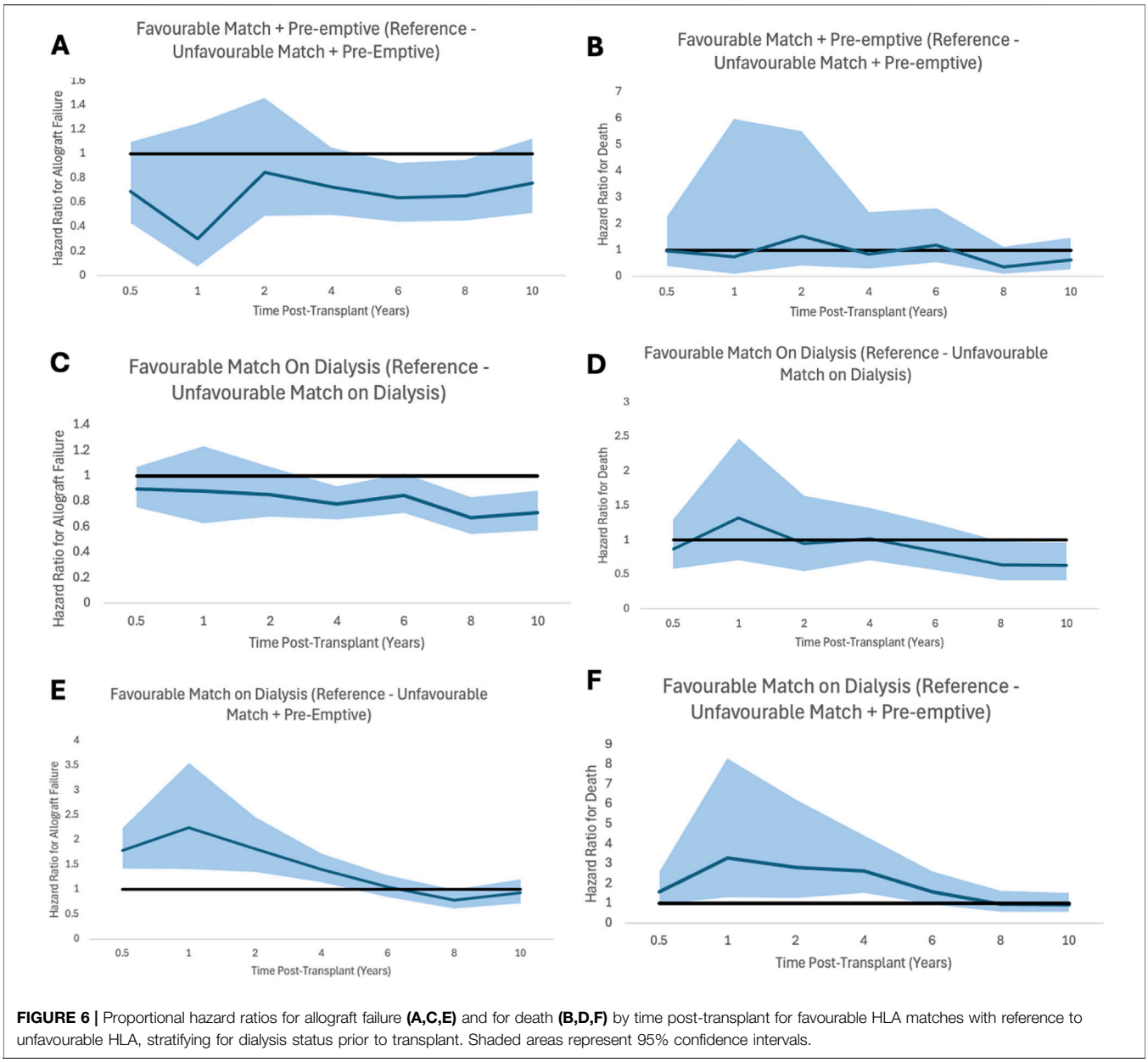


FIGURE 6 | Proportional hazard ratios for allograft failure **(A,C,E)** and for death **(B,D,F)** by time post-transplant for favourable HLA matches with reference to unfavourable HLA, stratifying for dialysis status prior to transplant. Shaded areas represent 95% confidence intervals.

0·16–0·60 and respectively depending on which model used. However, both deceased donation and dialysis exposure led to a larger increase in hazard ratio for allograft failure and death than HLA mismatching (0.36–0.37 and 0·56–0.58 respectively for deceased donation, and 0.23–0.25 and 0.44–0.45 respectively for dialysis exposure). This trend was then confirmed when directly comparing favourable HLA matched allografts from deceased donors to unfavourable HLA matched allografts from living donors, as well as favourable HLA matched allografts after a period on dialysis and pre-emptive poorly HLA matched allografts. Furthermore, our data also shows that 94.3% of all deceased donor transplants had an unfavourable HLA match. So, if a patient has a potential living donor, even if they are an unfavourable HLA match, it is unlikely they will find a better match by waiting for an organ coming from a deceased donor, and in that process, one may miss the opportunity for a pre-emptive transplant.

Efforts should therefore concentrate on increasing living donation rates and transplanting pre-emptively where possible. Unfortunately living donation rates for pediatric recipients appeared to be declining in the USA. [32]. There are multiple proposed reasons for this including the kidney allocation policy changes meaning pediatric patients get priority for younger donors and shorter waiting times thereby removing some of the motivating factors for living donation [2, 5, 6, 33]. Another potential reason is the

TABLE 8 | Estimated Kaplan-Meier allograft and patient survival after re-transplantation for patients who received favourable and unfavourable HLA matches for their first transplant at 1, 3, 5,10 and 20 years post-re-transplant, 95% confidence intervals given in (), p-value is the result of the Log-Rank Test.

Survival	Group	1 year	3 years	5 years	10 years	20 years	p-value
Allograft survival of 2nd transplant	Favourable HLA Match at 1st Transplant	89.7 (85.4–92.7) %	75.5 (69.8–90.3) %	64.5 (58.3–70.1) %	47.5 (40.7–54.0) %	18.8 (12.4–26.3) %	0·29
	Number at risk	*239*	*188*	*146*	*75*	12	
	Unfavourable HLA Match at 1st Transplant	89.9 (88.2–91.3) %	79.3 (77.0–81.3) %	68.9 (66.2–71.3) %	47.7 (44.5–50.8) %	18.3 (14.7–22.1) %	
	Number at risk	*1,264*	*987*	*727*	*332*	48	
Patient survival after 2nd transplant	Favourable HLA Match at 1st Transplant	98.6 (96.2–99.5) %	97.8 (95.2–99.0) %	93.2 (89.2–95.8) %	85.5 (79.4–89.9) %	59.1 (45.1–70.6) %	0·72
	Number at risk	*262*	*237*	*195*	*104*	15	
	Unfavourable HLA Match at 1st Transplant	97.6 (96.7–98.3) %	95.6 (94.4–96.6) %	92.9 (91.4–94.2) %	84.8 (82.2–87.0) %	59.6 (53.2–65.5) %	
	Number at risk	*1,368*	*1,149*	*897*	*456*	65	

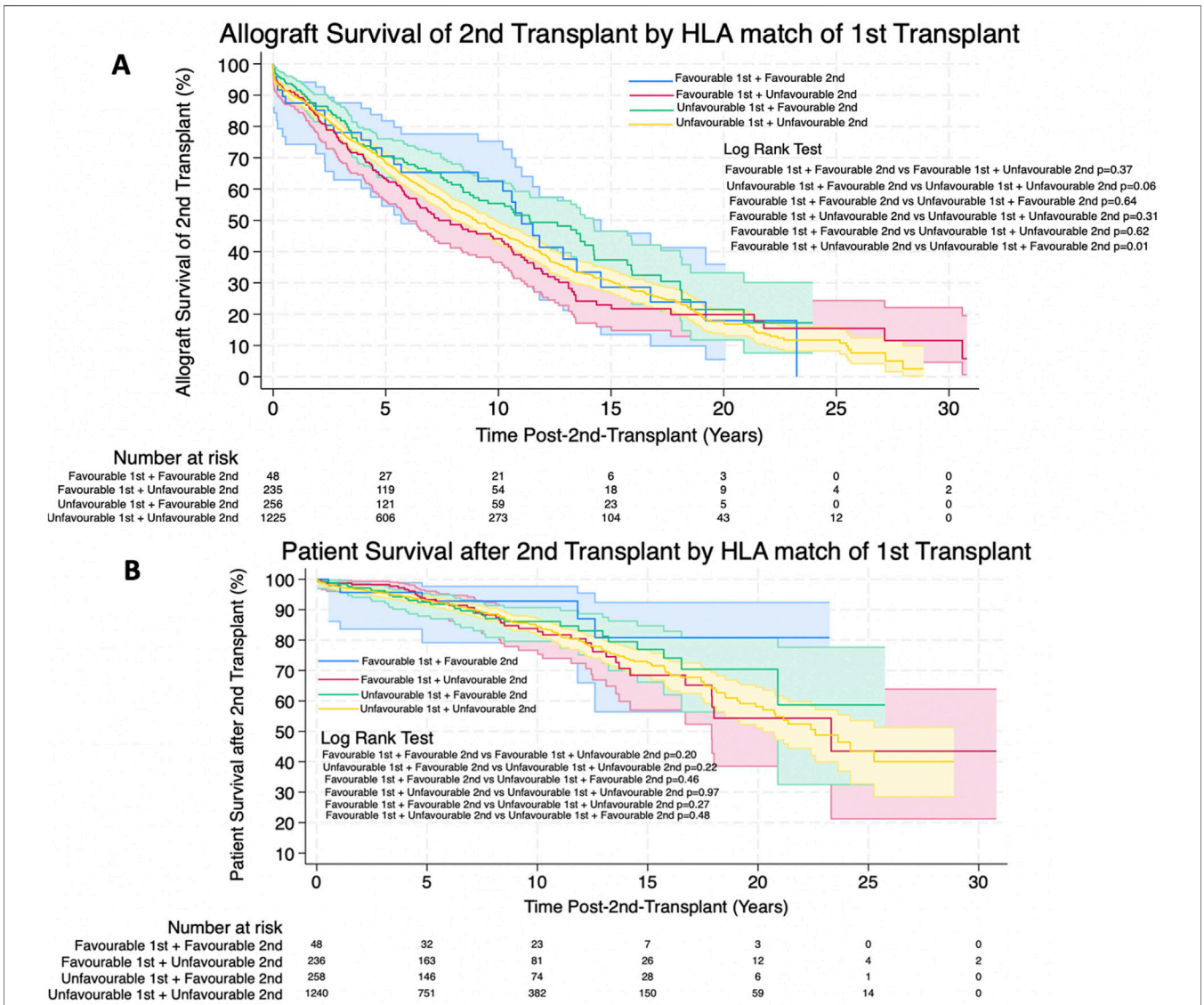


FIGURE 7 | (A,B) Estimated Kaplan-Meier allograft and patient survival (respectively) post-re-transplant for favourable and unfavourable HLA matches by HLA match of first transplant. Shaded areas represent 95% confidence intervals.

widespread adoption of more refined testing of potential living donors which could be excluding many living donors who may otherwise have been accepted in previous years [33]. There is a general decline in the health of the overall population thereby excluding a significant proportion of the population to living donation [33, 34]. The literature also suggests that the decline in living donation is more pronounced in those with lower household incomes suggesting that financial status is another key contributor [33, 35]. It is crucial to address all these factors in order to try and increase living donation rates to provide better outcomes for our patients and ensure equity in access to transplantation. Strategies that have been shown to be successful include education programs both in the home [36] and at dialysis centers [37]. An effort should also be made at reducing the barriers to living donation such as reducing the financial disincentives which should be done on a national level. Other methods such as reducing the risk of living donation with laparoscopic or robotic donor nephrectomies have also been successful at increasing living donation rates for both adult and pediatric recipients [38].

Another promising approach is the use of paired donation schemes. Evidence shows that there is no difference in the outcomes of paired and non-paired living donor kidney transplants and these may be underutilized in the USA [39] compared to other countries. Paired donation schemes are a way of increasing the donor pool and allows more patients to benefit from living donation. For example, in the UK in the previous year an additional 97 kidney transplants were carried out through the living donor kidney sharing scheme [40]. Furthermore, Spain–which has the 2nd largest paired donation scheme, has shown excellent outcomes following paired donation [41]. At present, only a limited number of centers in the USA participate in a paired kidney donation programme which limits the number of paired donations that can take place [42]. Strategies to increase the number of participating centers and regions could not only improve the number of pediatric transplants that occur from living donors but can also potentially improve HLA matching between paired donors and recipients.

Encouragingly, our data shows that overall pre-emptive transplantation has increased over time, which could potentially be due to changes in allocation systems [22] but also a greater emphasis being placed on pre-emptive transplantation following the emergence of strong evidence supporting its superiority in providing longer allograft and patient survival [28]. In order to achieve the best outcomes for our patients, it is important that pre-emptive transplantation rates continue to improve.

The main strength of this study is the large sample size – this is a national study on the largest dataset within pediatric kidney transplantation that involves over 20,000 patients. This has allowed us to report on trends and identify key differences in outcomes between different groups which is crucial to advance our understanding of this cohort of patients.

However, one of the limitations of this study is that it has not considered some of the heterogeneity within HLA matching. The study spands across 3 decades across different eras of immunosuppressants and different allocation systems which could acts as a confounding factor in this study. There is also emerging evidence of some mismatch types being more significant than others and that molecular mismatches such as eplet mismatch load may play a more significant role on clinical outcomes [11–14]. While this isn't utilized yet in clinical practice and allocation systems, it requires further research in large multi-center studies to further our understanding of HLA matching.

Furthermore, there are other variables which we were not able to control for or evaluate in this study, such as different immunosuppression regimes, different allocation policies used over time, donor age, episodes of rejection and the use of different induction agents between each centre and between different eras which will undoubtedly have also had an impact on graft outcomes.

CONCLUSION

In conclusion, this to date largest study on pediatric renal transplant recipients, has shown that living donation and pre-emptive transplantation play a significant role in long-term clinical outcomes and are more significant than HLA matching when directly compared to organs coming from deceased donors, and transplants occurring after a period of dialysis. The protective effects of living donation and pre-emptive transplantation are particularly significant in the first 10 years post-transplant.

In our study, children receiving unfavourably HLA matched allografts from living donors had better allograft and patient survival compared to children receiving favourably HLA matched allografts from deceased donors. Children receiving pre-emptive transplants with an unfavourable HLA match also had lower rates of delayed allograft function as well as better allograft and patient survival when compared to children receiving non-pre-emptive transplants with a favourable HLA match. However, patients receiving unfavourably HLA matched allografts were less likely to be transplanted pre-emptively when it came to re-transplantation.

Transplanting pediatric recipients with unfavourably HLA matched living donors may be considered before consideration of being listed on the deceased donor waiting list for a better HLA match. Strategies to increase rates of living donation and pre-emptive transplantation are crucial to improving the outcomes in pediatric kidney transplant recipients. Further research is needed to fully understand the implications of HLA and HLA epitope matching on paediatric kidney transplant recipients.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://optn.transplant.hrsa.gov/data/view-data-reports/request-data/.

ETHICS STATEMENT

This was a registry study from a publicly available registry with no patient identifiable information so did not require ethical approval.

AUTHOR CONTRIBUTIONS

AP, IK, IL, NK, and JS participated in research design. AP and JS participated in the writing of the paper. AP completed data analysis. All authors had access to the data. NK and JS supervised the research study. JS co-ordinated the submission of the paper. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research 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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ORIGINAL RESEARCH
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The Variation in Practice of the Living Donor Kidney Transplant Pathway in the UK: Results of a National Survey

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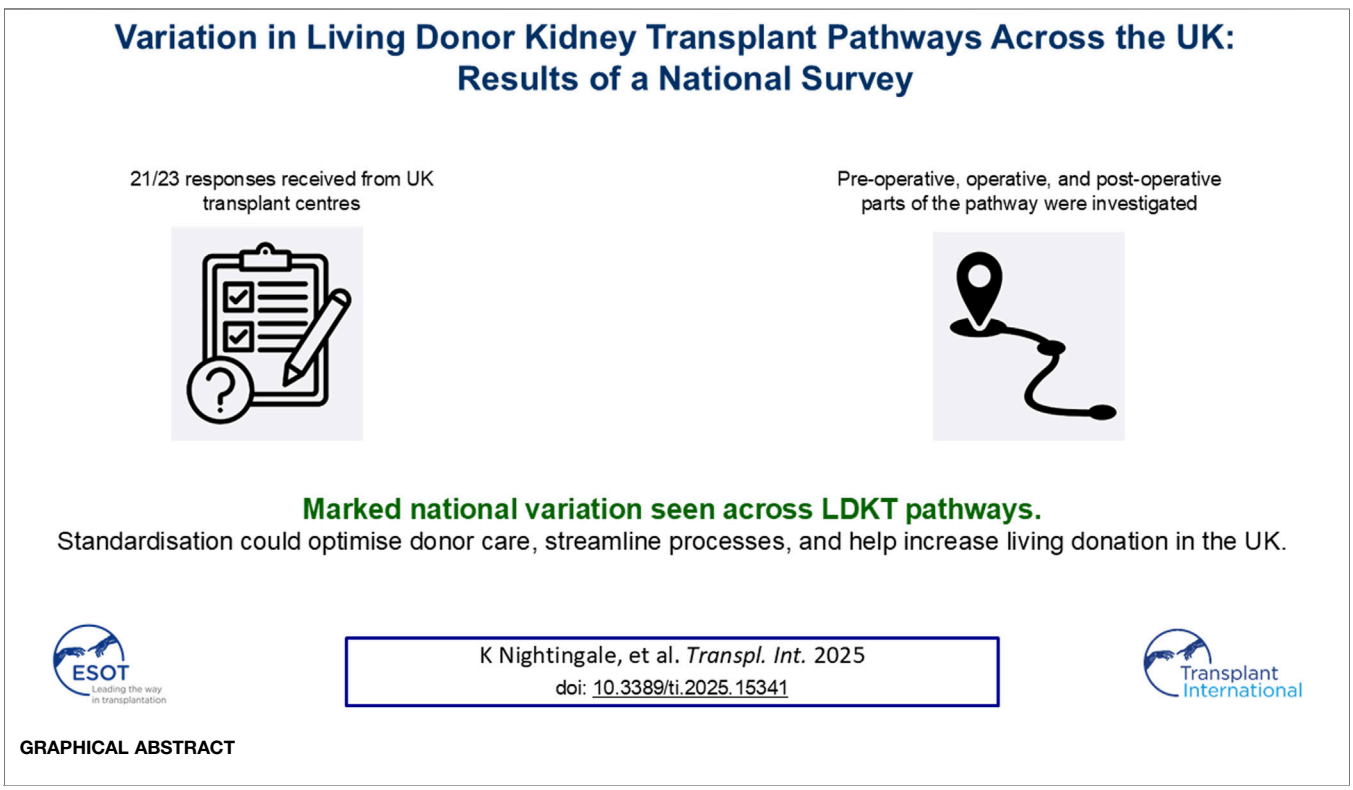
Living donor kidney transplantation (LDKT) accounts for 35% of kidney transplants in the UK. The Organ Donation and Transplantation 2030 initiative underscores the necessity to enhance LDKT rates to meet growing demand. There is limited data on national

variations in live donor workup pathways from initial referral to long-term follow-up. We conducted an online survey across all 23 UK transplant centres performing LDKT, covering the entire living donor pathway. We aimed to explore and highlight practice variation and identify opportunities for improvement. Responses were received from 21 centres (91.3%). Marked variation was identified in donor acceptance criteria, including age limits, body mass index thresholds, and donor evaluation timelines (6–36 weeks). Differences were also noted in multidisciplinary team processes, kidney laterality decisions, and perioperative enhanced recovery protocols. All centres used laparoscopic techniques, with hand-assisted transperitoneal nephrectomy being most common (57.1%). Donor nephrectomy and implantation were conducted sequentially in 15 (71.4%) of centres, and in parallel in six (28.6%). Variation was also seen in follow-up duration with 47.6% of centres offering lifelong follow-up. Despite excellent national outcomes, this survey highlights significant variation. Standardising key processes could streamline donor pathways, improve experiences, and support increased LDKT activity in the UK.

Keywords: living donor kidney transplantation, laparoscopy, donor nephrectomy, variation, perioperative care



GRAPHICAL ABSTRACT

HIGHLIGHTS

What We Know

- Living donor kidney transplantation (LDKT) is vital but may be under-utilised.
- Living donors provide only 35% of UK kidney grafts in the United Kingdom (UK).
- National strategy (Organ Donation and Transplantation 2030) calls for higher uptake.

What the Study Adds

- This national survey of 21 transplant centres in the UK highlights significant variability in the donor selection and evaluation criteria.

- Donor work-up at these centres differs beyond medical screening. Multidisciplinary-team approval steps, laterality choice, and enhanced recovery protocols are handled differently across many sites.
- Follow-up duration is inconsistent. 48% of centres guarantee lifelong monitoring; others report offering a follow-up between 3 and 24 months.

Potential Impact

- Greater standardisation of ERAS protocols and enhanced collaboration could facilitate process optimisation and unify the donor experience to align with standards aimed at increasing LDKT activity in the UK.

INTRODUCTION

Living donor kidney transplantation (LDKT) has, over the last 70 years, consistently proven to be the optimal form of renal replacement therapy for eligible individuals, particularly when performed pre-emptively [1, 2]. Outcomes after LDKT surpass those of deceased donor kidney transplantation, offering superior graft survival and patient longevity [3]. In the United Kingdom (UK), LDKT accounts for ~35% of annual kidney transplants [3].

The donor pathway—from identification and evaluation, through nephrectomy and follow-up—is complex and prioritises donor safety and suitability without compromising the long-term health of the donor. The NHS Blood and Transplant (NHSBT) annual report demonstrates excellent outcomes across all 23 UK adult transplant centres [4]. Nevertheless, variation in donor evaluation and surgical pathways likely exist. The UK Transplantation 2030 strategy articulated the pressing need to increase both organ donation and transplantation rates to address a substantial unmet demand [5]. The strategy calls on all transplant centres to innovate and optimise pathways to maximise the potential for LDKT.

While perioperative variation has been studied [6], no prior study has examined variation in donor evaluation across UK centres. We conducted a national survey to explore differences in evaluation, perioperative care, and follow-up practices among MDTs performing LDKT in all UK transplant centres.

MATERIALS AND METHODS

A comprehensive online survey consisting of 65 questions was collaboratively created with contributions from clinicians, transplant coordinators, and the UK Living Donor Network, who are regularly involved in and conducting LDKT (see **Supplementary Appendix S1**). This survey encompassed all aspects of the donor pathway, such as evaluation timelines, discussions regarding surgical risks, criteria for donation (including age, body mass index (BMI), and co-morbidities), the use of imaging, and kidney selection for nephrectomy.

Questions pertaining to the perioperative phase included details about admission, whether surgeries were performed sequentially or concurrently, enhanced recovery after surgery (ERAS) protocols, surgical techniques, management of vascular issues, perfusion fluids, anaesthesia, fluid management, as well as post-operative care and follow-up schedules.

The survey was disseminated to transplant leads at all 23 UK centres from 1 December 2023 to 31 December 2024, with two reminders issued to those who did not respond. Each centre completed the survey after engaging in multidisciplinary discussions to reduce individual bias. Data collection was conducted in two phases: an initial questionnaire followed by a subsequent follow-up sent to all respondents to clarify and elaborate on emerging themes. The extended collection period reflects this two-phase approach; centres were requested to report their current routine practices at the time of their response, thereby reducing temporal variation.

According to the guidelines set forth by the Health Research Authority UK [7], ethical approval was not deemed necessary, and the study was registered with our local governance department [8]. The responses were analysed utilizing descriptive statistics.

RESULTS

21 of 23 (91.3%) centres responded. Results are grouped into pre-operative, intra-operative, and post-operative variations.

Preoperative Evaluation

Evaluation in Clinic

An 18-week donor turnaround time is offered by 16 (76.2%) of centres with two centres (9.5%) providing expedited pathways of under 6 weeks. The number of preoperative clinic visits required varies widely across centres (**Figure 1**). 16 (76.2%) centres operate distinct surgical and nephrology clinics. Five centres (23.8%) provide combined clinics, while eight centres (38.1%) include living donor MDT clinics with supplementary anaesthetic evaluations. Seven centres (33.3%) also integrate independent assessment clinics with surgical or medical assessment clinics to minimise the number of appointments and expedite donation.

Surgical Risk Estimates

Within the clinics, the mortality rate communicated to patients varies between 1:1500 and 1:6000. One centre (4.8%) cites a rate of 1:1500–3000; thirteen centres (61.9%) report a rate of 1:3000, three centres (14.3%) mention 1:3500, two centres (9.5%) indicate a range of 1:3000-1:4000, one centre (4.8%) describes a range of 1:3000-1:6000, and one centre (4.8%) discusses the risk as being less than 1%.

For the risk of kidney failure, the rates communicated to patients range from 1:1000 to 1:7000. Four centres (19.1%) utilise the Johns Hopkins Risk Calculator to tailor the risk assessment [9]; while the remaining centres rely on published literature. Among these 17 centres, four (23.5%) report a risk of 1:1000, one centre (5.9%) states 1:3500, another centre (5.9%) mentions 1:7000, six centres (35.3%) indicate a risk of less than 1%, two centres (11.8%) quote a risk of 1:200, and three centres (17.6%) discuss a risk that is 5–10 times greater than the current risk.

Risk information was delivered predominantly by surgeons, with some centres involving nephrologists or donor advocates.

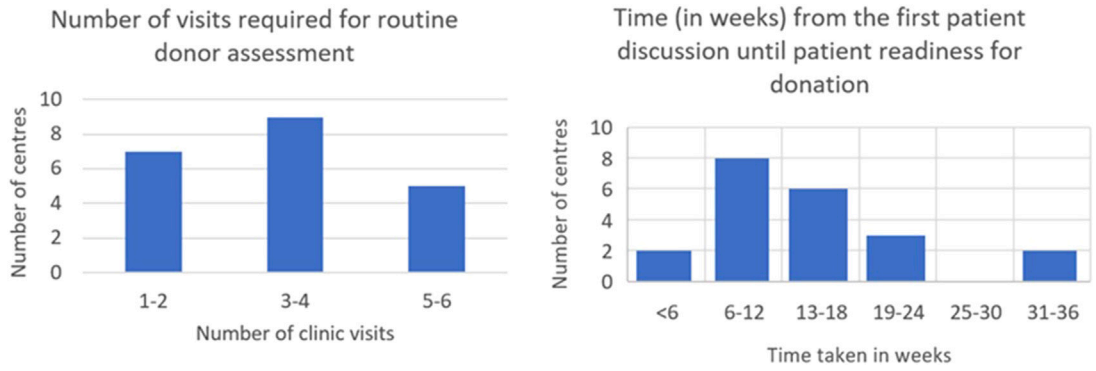


FIGURE 1 | Time and visits required for donor nephrectomy assessment.

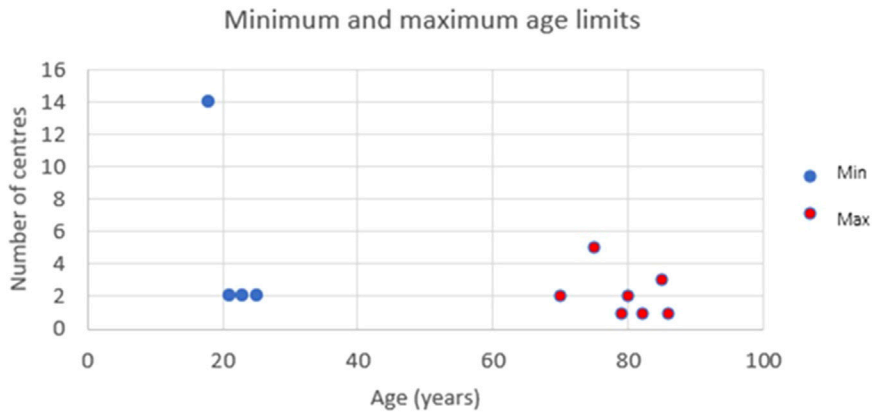


FIGURE 2 | The minimum and maximum accepted age ranges per centre for donor nephrectomy.

Donor Selection Criteria

Fifteen centres, representing 71.4%, accept donors aged 18 years or older; six centres, accounting for 28.6%, require donors to be at least 21 years old. The upper age limits vary, with two centres (9.6%) setting the limit at 70 years, while four centres (19%) have no age cutoff. One centre (4.8%) has reported accepting a 90-year-old for LDKT. (**Figure 2**).

Eleven centres (52.4%) accept donors with a BMI exceeding 30 $kg.m^{-2}$, of which five centres (45.5%) impose an upper limit of 35 $kg.m^{-2}$. Five centres (23.8%) report a minimum BMI threshold of 17–18 $kg.m^{-2}$, whereas 16 centres (76.2%) did not have a minimum threshold.

All centres (100%) accept donors with hypertension that is managed with one medication, while fifteen centres (71.4%) accept donors on two medications. Additionally, 19 centres (90.5%) are willing to accept Jehovah's Witnesses as donors, while two centres (9.5%) do not permit this.

Imaging

All centres utilise CT angiograms; additionally, two (9.5%) employ MR angiograms to outline vascular anatomy. All centres reported favouring the left kidney because of its longer vein, although anatomy, size, and function also play a role in decision-making.

Intraoperative Differences

Admission

Thirteen (61.9%) centres evaluate the venous thromboembolism (VTE) risk upon admission; seven (33.3%) provide preoperative intravenous (IV) fluids; four (19%) administer pre-emptive analgesia; five (23.8%) utilise carbohydrate-loading drinks.

Ten (47.6%) centres indicate that they admit donors the day prior to surgery; ten (47.6%) admit them on the same day; one (4.8%) allows for both options. Eight (38.1%) have cross-matched blood routinely available, while thirteen (61.9%) rely on group and save.

Surgical Technique

All responding centres conduct laparoscopic nephrectomy, utilising one of five main techniques: 12 (57.1%) provide hand-assisted, eight (38.1%) offer totally laparoscopic, and two (9.5%) each implement hand-assisted or fully retroperitoneal technique. Robotic-assisted nephrectomy is either available or planned at 16 (76.2%) centres. The extraction incisions differ:

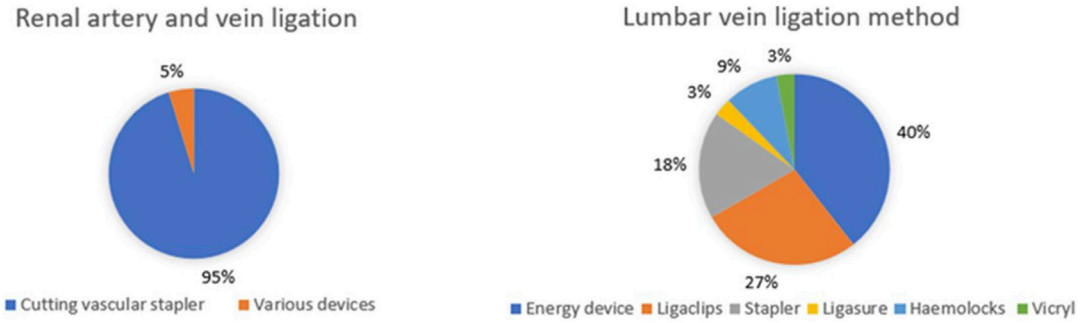


FIGURE 3 | Intra-operative management of renal and lumbar vessels during donor nephrectomy.

Pfannenstiel and iliac fossa (38.1% each), supra-umbilical (28.6%), and infra-umbilical and hypochondrial (4.8% each).

Conduct of Surgery

15 (71.4%) centres operate sequentially; and six (28.6%) operate in parallel. 18 (85.7%) use separate surgical teams for donor and recipient procedures; three (14.3%) centres use the same surgeon.

Vascular Management

Renal vessels are managed similarly (**Figure 3**): 20 (95.2%) centres use cutting vascular staplers (mostly Ethicon). None of the centres reported to use the Hemolok clips on the main renal artery. Seven centres (33.3%) use clips on smaller veins; whereas the remaining 14 (66.6%) do not use Haemolock clips at all for vessels. Six (28.6%) of the responding centres routinely administer mannitol prior to clamping of the renal vessels. Broader variation is seen in how the lumbar veins are ligated, with six different methods being used nationwide. There is also technical variation in the way the ureter is managed, with three main techniques: Hemolock clips (8 centres, 38%), Ligaclips (6 centres, 28.6%) and stapler (6 centres, 28.6%), with one centre (4.8%) using an energy device.

Organ Storage and Perfusion

Ten (47.6%) centres bag and box the kidney whereas nine (42.9%) centres store it on ice. The remaining two centres (9.5%) use a combination of the two methods. In three centres (14.3%), a member of the donor operating team perfuses the kidney. In 12 (57.1%) centres it is exclusively carried out by another team member and six centres (28.6%) use either method.

Kidney perfusion Following Nephrectomy

Perfusion fluid varies centre to centre. Seven centres (33.3%) currently use Custodial fluid, six centres (28.6%) use Histidine-Tryptophan-Ketoglutarate (HTK), three (14.3%) Servator B, two (9.5%) University of Wisconsin solution (UW), one (4.8%) UK, one (4.8%) Hyperosmolar citrate (Soltran) and one (4.8%) Celsior. This was affected by the period of the survey with centres reporting changes in the preferred fluid depending on national availability. Most centres run the fluid until it is clear, with five (23.8%) units perfusing a minimum of 1 L even if already clear. Five centres (23.8%) use unfractionated heparin in the fluid and 16 (76.2%) do not.

Anaesthetic Technique

Inhalational anaesthesia is used for maintenance in 12 (57.1%) centres; total intravenous anaesthesia (TIVA) in four (19%); and a combination of techniques used in five (23.8%). Arterial line and cardiac output monitoring are routinely utilised in two (9.5%) centres. Compound sodium lactate was the preferred IV maintenance fluid (61.9%), followed by saline (23.8%) and Plasmalyte (14.3%).

Spinal anaesthesia with intrathecal diamorphine as part of multimodal analgesia is used by 17 (81%) centres. **Figure 4** illustrates the diverse range of nerve blocks and opioid analgesics utilised with 10 (47.6%) of 21 units routinely performing local anaesthetic (LA) infiltration at the wound/port sites. Five (23.8%) administer cyclo-oxygenase (COX) 2 inhibitors intra-operatively.

Postoperative Management and Follow-Up

ERAS protocols are implemented in 13 (61.9%) centres; the same number also co-manage both donors and recipients within a single ward. There is variability in the timing of urinary catheter removal, choice of post-operative patient-controlled analgesia (PCA) opioid, and VTE prophylaxis following discharge. It is noteworthy that seven centres (33.3%) do not offer routine VTE prophylaxis at discharge, instead opting to provide mobility advice (**Figure 5**).

The duration of follow-up also varies, ranging from 3 months to lifelong: 12 (57.1%) centers offer lifelong care; 8 restrict it to a period of 3–12 months; and one (4.8%) provides care for 2 years.

DISCUSSION

This national survey reveals significant variation in the pre-operative, intra-operative, and post-operative elements of LDKT, with **Table 1** displaying some of these results.

It underscores essential opportunities to enhance and streamline the LDKT process, ultimately fostering increased donor participation and improved patient experiences. The findings of this national survey contribute to the aims of the Organ Donation and Transplantation 2030 strategy by establishing a benchmark for current practice across UK transplant centres [5]. The Kidney Care UK Transplant report 2024 identified unacceptable discrepancies in the care provided to individuals [10] and emphasises the variation

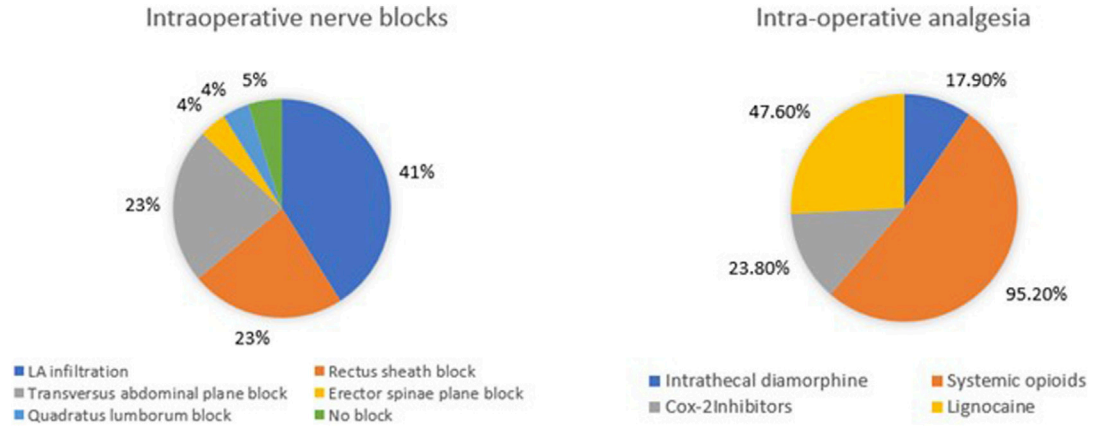


FIGURE 4 | Intra-operative analgesic techniques utilised for donor nephrectomy.

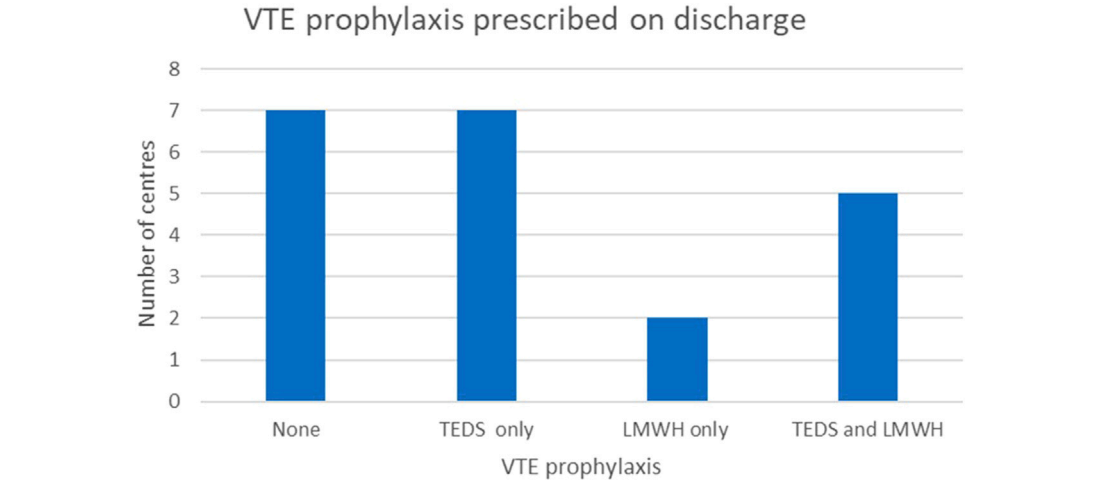


FIGURE 5 | Postoperative venous thrombo-embolism (VTE) prophylaxis strategies utilised across UK transplant centres.

among units, akin to our study, regarding the likelihood of a person receiving a living donation or being placed on a waitlist prior to starting dialysis. It also revealed differences in the workup and listing processes.

The survey demonstrates that LDKT practice across the UK is highly heterogeneous. The British Transplantation Society (BTS) guidelines [11] recommend that donor assessments be structured to minimise inconvenience and incorporate flexibility regarding timelines, consultations, investigations, and surgery scheduling. Despite this, only 50% of centres meet the recommended 18-week evaluation timeframe, whilst just two (9.5%) centres offer expedited workups under 6 weeks. These fast-track pathways represent models of good practice and could be considered for wider adoption, particularly in more pressing or pre-emptive transplant scenarios. Although pre-emptive transplantation is widely recognised as the optimal scenario for recipient outcomes [1, 2], this survey did not collect centre-specific or national proportions of pre-emptive LDKT. Consequently, we could not assess whether expedited donor pathways increase pre-emptive transplantation rates. Future national data collection should link evaluation efficiency with transplant timing to determine whether accelerated—but safe—donor preparation enables more recipients to avoid dialysis.

Variation in the number and structure of pre-operative clinic appointments points to potential inefficiencies. Centres offering combined clinics—including integrated MDT and Independent Assessment appear best placed to minimise patient burden and accelerate the pathway without compromising safety. These expedited pathways represent an opportunity for broader national adoption, potentially enhancing the donor experience, streamlining donor care and improving accessibility to transplantation. In the USA, it has been shown that donor evaluation may be too long and that long duration can lead to missed opportunities for LDKT [12]. Streamlined clinics should be tailored to patient needs with opportunities to slow down the process if required.

Risk communication exhibits variability across different centres. Although all centres address the risks associated with surgery and

TABLE 1 | Per centre summary table including expedited pathway availability, follow-up duration, eligibility cut-offs and ERAS implantation.

Centre	High vs. low volume centre (<40 or 40 and above)- adult LDKT performed in 23/24	Pre-op visits required	Pre-op pathway <18 weeks	Pre-op pathway <10 weeks	Follow up duration	Follow up details if provided
Regional Nephrology and Transplant Unit, Belfast City Hospital, Belfast Health and Social Care Trust, Belfast BT9 7AB, UK	High	1	Yes	Yes	Life long	
Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2TH, UK	High	4	No	No	Within first 3 months	
NHS Blood and Transplant, Stoke Gifford, Bristol, UK	High	3	No	No	Life long	6 weeks, 6 months then annually
Addenbrookes hospital Addenbrooke's, Hills Road, Cambridge, CB2 0QQ	Low	2	Yes	Yes	Life long	
Cardiff Transplant Unit, University Hospital of Wales, Cardiff and Vale University Health Board, Cardiff CF14 4XW, UK	High	4	Yes	Yes	Life long	
University Hospital Coventry, University Hospitals Coventry and Warwickshire NHS Trust, Coventry CV2 2DX, UK	Low	7	Yes	No	Within 3 months	
Edinburgh Transplant Unit, Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh EH16 4SA, UK	High	2	Yes	Yes	Life long	
West of Scotland Kidney Transplant Unit, Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde, Glasgow G51 4TF, UK	High	5	Yes	Yes	Within a year	
St James' University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds LS9 7TF, UK	Low	3 or 4	Yes	No	Life long	6–8 weeks post-op initial f/u with donor surgeon, then lifelong follow up
Leicester General Hospital, University Hospitals of Leicester NHS Trust, Gwendolen Road, Leicester LE5 4 PW, UK	Low	4	Yes	No	Life long	2 weeks, 3 months, then yearly
Renal and Transplant Centre, Royal Liverpool University Hospital, Liverpool University Hospitals NHS Foundation Trust, Prescot Street, Liverpool L7 8XP, UK	Low	2	Yes	No	within first 3 months	
Manchester Centre for Transplantation, Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Oxford Road, Manchester M13 9WL, UK	High	3	No	No	2 years	Telephone follow up at 2 days by coordinator, telephone by surgeon at 6 weeks. Bloods at 4 weeks. Annual review for 2 years by coordinators and subsequently by GP
Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne NE7 7DN, UK	High	5	No	No	Life long	
Renal and Transplant Unit, Queens Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham NG7 2UH, UK	Low	4	Yes	No	Life long	

(Continued on following page)

TABLE 1 | (*Continued*) Per centre summary table including expedited pathway availability, follow-up duration, eligibility cut-offs and ERAS implantation.

Centre	High vs. low volume centre (<40 or 40 and above)- adult LDKT performed in 23/24	Pre-op visits required	Pre-op pathway <18 weeks	Pre-op pathway <10 weeks	Follow up duration	Follow up details if provided
Oxford Transplant Centre, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford OX3 7LE, UK	High	2	Yes	Yes	Life long	6 weeks post op then annually
Southwest Transplant Centre, Derriford Hospital, University Hospitals Plymouth NHS Trust, Plymouth PL6 8DH, UK	Low	2	Yes	No	Within first 3 months	
Wessex Kidney Centre, Queen Alexandra Hospital, Portsmouth Hospitals University NHS Trust, Portsmouth PO6 3LY, UK	Low	7	Yes	No	Within first 6 months	
Department of Renal Transplantation, Northern General Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield S5 7AU, UK	Low	2	Yes	Yes	Life long	
Department of Transplantation and Dialysis Access Surgery, St Georges Hospital, St Georges University Hospitals NHS Foundation Trust, London SW17 0QT, UK	High	3	No	No	Life long	2, 6, 12 weeks then annually
Department of Nephrology, Urology and Renal Transplantation, Royal Free Hospital, Royal Free London NHS Foundation Trust, London NW3 2QG, UK	Low	7	Yes	No	Within first 3 months	
Royal London Hospital Transplant Department, The Royal London Hospital, Barts Health NHS Trust, Whitechapel Road, London E1 1FR, UK	Low	minimum of 4	Yes	No	Within first 3 months	

Follow up conducted by	Eligibility BMI (min/max)	Eligibility age (min/max)	Patients accepted on one antihypertensive?	Patients accepted on dual antihypertensives?	ERAS?	Standard operation
Surgeon, transplant coordinator	35	23–85	Y	Y	Yes	Fully transperitoneal laparoscopic
Surgeon	32	18–75	Y	Y	Yes	Hand assisted transperitoneal
Surgeon, then Nephrologist	18–35	18–80	Y	Y	Yes	Fully transperitoneal laparoscopic
Surgeon and transplant coordinator	18–35	No limit	Y	Y	Yes	Fully transperitoneal laparoscopic
Nephrologist	30	23–79	Y	Y	Yes	Hand assisted transperitoneal
Surgeon, nephrologist, transplant coordinator	32	18- no limits	Y	Y	No	Fully transperitoneal laparoscopic
Surgeon	30	18-no limit	Y	Y	Yes	Hand assisted transperitoneal
Donor coordinator	No limit	21–80	Y	N	Yes	Hand assisted transperitoneal
Surgeon and transplant coordinator	30	No limit	Y	Y	Yes	Fully transperitoneal laparoscopic
Surgeons and transplant coordinator	33	18–85	Y	Y	No	Hand assissted retroperitoneal
surgeon	28	18–70	Y	N	No	Fully retroperitoneal
Surgeons	35	25–86	Y	Y	Yes	Hand asissted transperitoneal laparoscopic
surgeon then transplant coordinator	30	21-no limit	Y	Y	Yes	Fully transperitoneal lapacroscopic
surgeons and transplant coordiantor	30	25–75	Y	N	No	Fully transperitoneal and hand-assissted transperitoneal

(Continued on following page)

TABLE 1 | (*Continued*) Per centre summary table including expedited pathway availability, follow-up duration, eligibility cut-offs and ERAS implantation.

Follow up conducted by	Eligibility BMI (min/max)	Eligibility age (min/max)	Patients accepted on one antihypertensive?	Patients accepted on dual antihypertensives?	ERAS?	Standard operation
Living donor and MDT coordiantor	35	18–82	Y	Y	No	Full transperitoneal laparoscopic
Surgeon	18–32	18–75	Y	Y	No	Hand assissted transperitoneal
Surgeon	30	18–85	Y	N	Yes	Hand asissted transperitoneal laparoscopic
Surgeon first year then transplant coordinator	30	18–70	Y	N	No	Hand assisted transperitoneal
Surgeon, transplant coordinator, nephrologist	17–32	18–75	Y	Y	No	Hand-assissted transperitoneal
Surgeon and trnasplant coordinator	17–33	18–35	Y	N	Yes	Fully retroperitoneal and hand assissted laparoscopic
Surgeon, neprhologist and trnasplant coordinator	No limit	No limit	Y	Y	Yes	Hand assisted transperitoneal and hand assisted retroperitoneal

anaesthesia, the statistics related to donor mortality and renal failure are presented through a diverse array of figures. A recent study by Massie et al. estimates donor mortality at 3 in 10,000 (or 1 in 3333), which is regarded as the most precise statistic when evaluating LDKT from 1994 to 2009 [13]. Furthermore, the systematic review by Kortram et al. [14] highlights the necessity for guidelines that facilitate the provision of information and the acquisition of informed consent to adequately prepare prospective donors. While this survey captured quantitative risk figures, it did not capture *how* risks are conveyed—who provides counselling, whether decision aids or written materials are used, or if a reflection or "cooling-off" period is offered. We have acknowledged this omission as a limitation and recommend national adoption of evidence-based communication tools, including validated decision aids, short educational videos, standardised written leaflets, and teach-back techniques. Involving donor advocates and documenting comprehension checks would further align consent processes with the *Montgomery* principles [15].

Variation in donor eligibility criteria, particularly around age, BMI, and hypertension, suggests an opportunity for greater national collaboration. For instance, centres with more permissive criteria could accept donors referred from stricter centres, increasing the overall donor pool and reducing transplant waiting times. With obesity rates rising, flexible inter-centre referrals for donors outside local BMI thresholds could substantially benefit national transplant activity but is important to recognise that obesity is a factor that could also affect long term risk for kidney failure. Additionally, nearly all centres accept Jehovah's Witness donors, demonstrating an encouraging trend toward inclusivity.

Preoperative imaging, protocols, and admission practices exhibit notable differences. While most centres prefer CT angiography and the retrieval of the left kidney, the decisions made by individual centres are often nuanced. Admission practices also show significant variation, with approximately half of the centres admitting donors the day prior to surgery. Although admitting patients on the day of surgery could enhance convenience for the patient and decrease hospital bed occupancy, practical constraints, especially for donors involved in paired or pooled exchanges, must be considered. The impact of preoperative intravenous fluid administration on the day of admission remains unclear.

Technically, all centres offer laparoscopic nephrectomy, however laparoscopic surgical techniques are diverse and encompass five different laparoscopic approaches. Hand assisted transperitoneal, hand assisted retroperitoneal, fully retroperitoneal, fully transperitoneal and robotic transperitoneal. Given the anatomical variation in donors, wider adoption of multiple techniques in a centre may benefit patient outcomes and broaden surgeon experience. However, this is entirely dependent on centre volume and linked to training and mentoring opportunities. This area forms a fertile area for national collaboration for patient benefit. Further exploration of technique-specific benefits could optimise patient outcomes and inform surgeon training. Only three (14.3%) centres reported to have a dedicated living donor surgical fellow/trainee in the department. This is a rich training resource, and more dedicated national living donor nephrectomy surgical fellowships should exist. No centres use the Hemolok clips on the main renal artery which is consistent to advice provided by the FDA [16]. Perfusion fluid usage prior to implantation varies widely, with seven different fluids in use. While centres report changes based on national availability, this inconsistency may affect graft outcomes and warrants further exploration or national procurement guidance.

Anaesthetic protocols also show wide variability. While most centres prefer inhalational anaesthesia for maintenance, some centres employ a TIVA technique. This may be due to a better recovery profile of TIVA [17]. Intrathecal diamorphine and local infiltration techniques remain the most common regional analgesic technique utilised intra-operatively. Though spinal anaesthesia was utilised for intraoperative pain by multiple centres, the study by Bhatia et al, failed to show any significant differences in donor outcomes, when it was compared with the surgically performed rectus sheath block for hand-assisted donor nephrectomy [18]. The evidence of good analgesia after intrathecal diamorphine in doses >200 μg was reported to be very low in one meta-analysis [19]. Quadratus lumborum block was being utilised in nearly 40% of centres as per this survey but it was not found to be superior to standard multimodal analgesia technique in a recent study [20].

Standardising anaesthetic care, where evidence supports improved recovery or outcomes, may further support ERAS protocols and enhance the donor experience and fast track recovery.

Intra-operatively, compound sodium lactate s was the preferred crystalloid for fluid maintenance in majority of centres followed by 0.9% normal saline and Plasmalyte. Recent randomised trial by Collins et al. [21] suggested that a balanced crystalloid solution should be utilised as the standard IV fluid for deceased kidney transplantation. The implications of using 0.9% saline on donors following LDKT, warrants further research given its association with hyperchloraemic metabolic acidosis.

Cross-matched blood is routinely available in theatre for LDKT in 38.1% of centres. Blood transfusion rates of <1% have been reported in LDKT [22, 23] and the use of minimal invasive techniques have further contributed to lower blood loss during donor nephrectomy. The maximum surgical blood order for LDKT should be a group and save (type and screen) sample because of the high crossmatch to transfusion ratio. This presents a potential opportunity for cost-saving in this cohort.

Post-operatively, 62% of the centres manage donors and recipients on the same ward. Variation exists in the length of catheterisation, analgesia, and mobilisation strategies. Of note, seven centres offered no routine VTE prophylaxis at discharge, relying on mobility advice alone. While rare, donor mortality due to pulmonary embolism has been reported and underscores the need for further research and consensus on postoperative VTE prophylaxis. Follow-up practices are equally diverse, with only half of centres offering lifelong follow-up as recommended by BTS guidelines [8]. Standardising long-term care is essential to ensuring ongoing donor safety and identifying late complications.

Future research is needed to link variation in practice to clinical outcomes such as donor complications, graft function, and donor satisfaction to identify which practices offer the best results. This study highlights the benefit of further research in the investigation of Shared Eligibility Models. Specifically to explore inter-centre referral models for donors who fall outside individual centre thresholds (e.g., age or BMI) and evaluate their feasibility, safety, and acceptability.

In summary, this national survey demonstrates the diversity of LDKT practice across the UK, with marked variability in all phases of care. There is no evidence from the national data that this has led to a variation in outcomes. However, while clinical outcomes remain excellent, targeted standardisation of key aspects—risk communication, eligibility criteria, surgical techniques, perioperative protocols, and follow-up could streamline the donor journey, improve experience and safety, and ultimately support the national objective to increase LDKT, particularly pre-emptive transplants.

STRENGTHS AND LIMITATIONS

The strengths of the survey include a high response rate ensuring a broadly representative sample of UK transplant centres. The 65-question survey with contributions from a range of professionals involved in LDKT, covered all aspects of the donor pathway, providing the UKs first holistic overview of practice variation. The findings align with and contribute to the goals outlined in the UKs 'Organ Donation and Transplantation 2030' strategy, providing areas for improvement. The study not only identified variation but also highlighted examples of good practice, offering models that other centres could adopt.

However, several limitations should be acknowledged. First, the survey relied on centre-reported data, which may be subject to recall or social-desirability bias. Second, it captured routine practice but not evaluated patient outcomes, precluding inference on clinical effectiveness. Third, specific data on the proportion of pre-emptive LDKTs, the content of donor follow-up, and the methods of risk communication were not collected. These omissions have been explicitly stated, and corresponding recommendations are included in the Discussion. Fourth, the 12-month data collection period during which the survey was performed overlapped with changes in national supply and practice; thus, temporal bias cannot be excluded. Finally, descriptive analyses were used, and no inferential testing was performed.

CONCLUSIONS

Living donor nephrectomy (LDN) is a unique and ethically complex surgical procedure in which a healthy individual donates a kidney to benefit a recipient with kidney failure. It remains the treatment of choice for many patients with end-stage kidney disease and has been actively promoted over the past 50 years, both globally and within the UK. While historically dominated by related and directed donations, the living donation landscape has evolved significantly in the last decade.

This national survey, capturing data from 21 of 23 UK transplant centres, reveals considerable variation in practice of management of LDN. The findings highlight a clear opportunity for greater national alignment in key areas of the LDKT pathway. While many suggested improvements may seem incremental, applying the principle of "aggregation of marginal gains" could have a meaningful cumulative impact on donor experience and pathway efficiency. This, in turn, may help increase the number of LDN performed in the UK and provides a strong foundation for further collaborative discussion. By addressing variation and promoting best practices, the quality and consistency of donor care can be improved. Addressing research gaps identified in this study are recommended to drive continued improvement in living donor transplantation across the UK.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**. Further enquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

KN 1st author- project design, data collection and interpretation, manuscript writing and submission. JS 2nd author- data interpretation, manuscript writing, editing and formatting. TA and KB are joint senior authors on the project- involved in project design, execution, and heavily editing of the manuscript All of the remaining

authors completed the detailed questionnaire for their corresponding centres and provided essential data for the study. All were involved in the editing and writing process of the manuscript prior to submission.

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CONFLICT OF INTEREST

The authors declare that the research 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) declare that no Generative AI was used in the creation of this manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.15341/full#supplementary-material

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Late Onset Thrombotic Microangiopathy in Kidney Transplants; Poor Outcome Despite Eculizumab Treatment

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Atypical hemolytic uremic syndrome (aHUS) is a rare cause of end stage kidney disease (ESKD) associated with a high rate of recurrence in kidney transplants causing a post-transplant thrombotic microangiopathy (TMA). Prophylactic eculizumab can prevent disease recurrence in select patients. Treating at the time of post-transplant TMA occurrence is the only option if the diagnosis of aHUS is not established pre-transplant. We report our experience of using eculizumab at the point of post-transplant TMA in those with a diagnosis or suspicion of aHUS. We conducted a case note review of 26 patients treated with eculizumab for post-transplant TMA. Screening for complement pathway defects included testing for variants in genes of the complement pathway and anti-factor H autoantibodies. 34.6% of recipients had an identified complement pathway defect. Median time to presentation with post-transplant TMA was 8.4 months. Death-censored graft survival 12 months after starting eculizumab was 68% for the cohort and was worse in those presenting >12 months post-transplant where this figure was 42.9%. The outcome is poor despite eculizumab treatment for those presenting >12 months after transplantation with TMA.

Keywords: kidney, transplantation, rare disease, recurrence, thrombotic microangiopathy, aHUS, eculizumab

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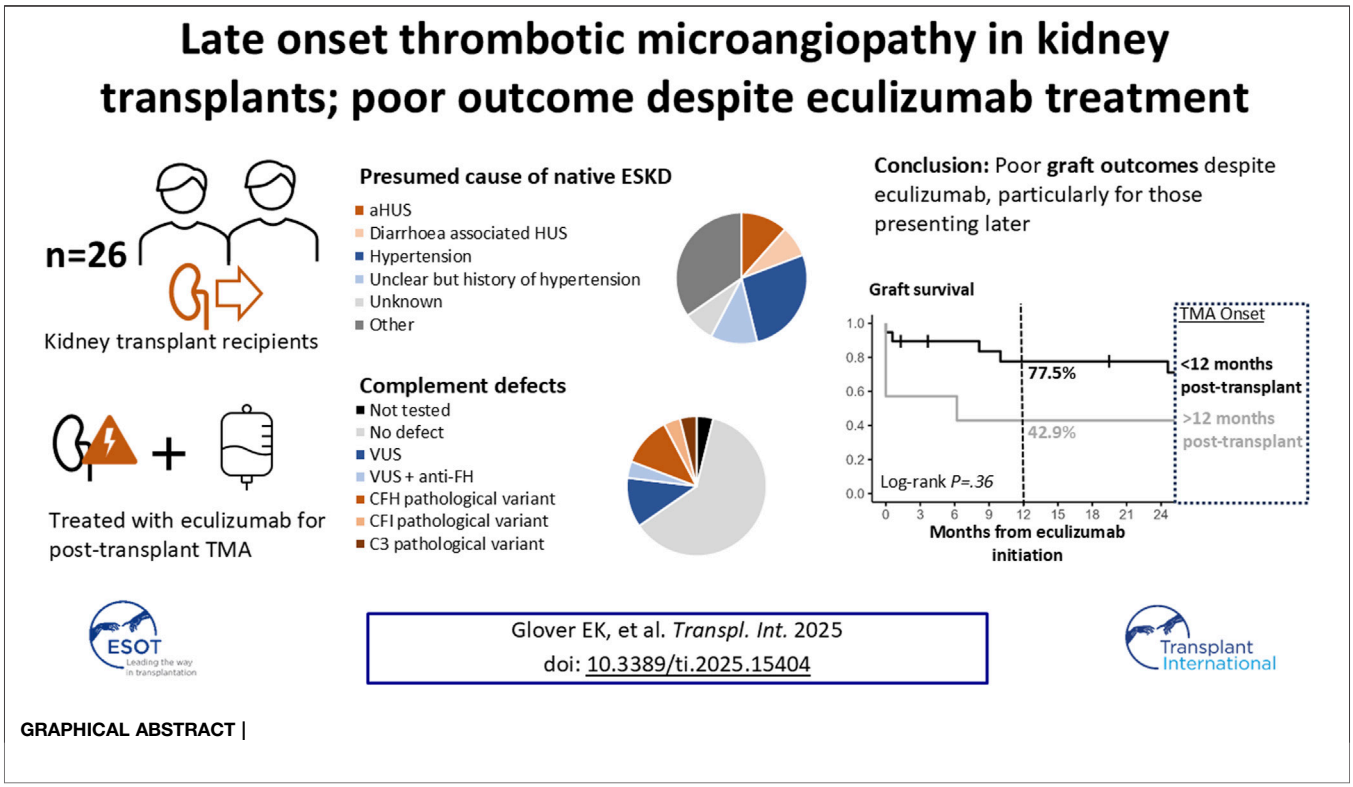

GRAPHICAL ABSTRACT |

INTRODUCTION

Atypical hemolytic uremic syndrome (aHUS) is a rare cause of thrombotic microangiopathy (TMA) with a high rate of recurrence in kidney transplantation, particularly in the early post-transplant period [1–3]. It is a complement mediated disease that can be treated with eculizumab, a monoclonal antibody targeting C5 to block complement terminal pathway activity [4–7]. Prophylactic eculizumab treatment, starting from transplantation, is effective at reducing aHUS recurrence and graft loss in certain individuals with medium and high risk complement pathway defects (**Supplementary Table S1**) [1, 8, 9]. However, this approach is not available to those without an existing diagnosis of aHUS, presenting for the first time with TMA after transplantation.

Diagnosing complement mediated aHUS as the cause of post-transplant TMA is challenging, as it cannot be readily distinguished on biopsy from other causes of TMA including calcineurin inhibitor (CNI) toxicity, antibody mediated rejection (AMR), anti-phospholipid syndrome, ischemia reperfusion injury, bleeding, viral infections, recurrence of primary disease (systemic lupus erythematosus, scleroderma) and Shiga toxin-producing *Escherichia coli* HUS [10, 11]. Genetic testing and factor H (FH) autoantibody testing for causes of alternative complement pathway dysregulation are key in supporting a diagnosis of aHUS. However, for those presenting *de novo* post-transplant a provisional diagnosis will be required whilst awaiting these results.

In those with an existing diagnosis of aHUS, data from Zuber et al. [8, 12] has shown a benefit in treating aHUS recurrence at the point of post-transplant TMA occurrence with eculizumab. In the larger of their cohorts, all recipients also had a high or medium risk complement pathway defect [8]. Duineveld et al. have found reactive eculizumab treatment at the point of aHUS recurrence to be a reasonable approach, particularly when coupled with a strategy to minimise endothelial injury [13, 14].

In England, patients with suspected aHUS are referred to a single specialist centre [15] for further investigation and access to eculizumab. We report the features and outcomes of post-transplant TMA in kidney transplant recipients eligible for eculizumab treatment for a suspected diagnosis of aHUS.

PATIENTS AND METHODS

Study Group

We conducted a retrospective case note review of patients referred to the National Renal Complement Therapeutic Centre, Newcastle upon Tyne, UK (NRCTC; http://www.atypicalhus.co.uk) for post-transplant TMA and who were treated with eculizumab for this episode. Patients who received prophylactic eculizumab treatment from implantation of their kidney transplant were excluded.

Referrals made before 14th March 2021 were included to allow sufficient follow-up after eculizumab initiation.

The decision to treat with eculizumab post-transplant for TMA occurrence was made through the NRCTC multidisciplinary team meeting and considered timing of presentation in the post-transplant period, hematological evidence of microangiopathic hemolytic anaemia (MAHA), thrombocytopenia, transplant biopsy results and cause of native end stage kidney disease (ESKD). Complement pathway abnormality screening was requested on all referrals but results were frequently not available at the time of decision making. Only those with a known diagnosis of aHUS, HUS or an unconfirmed cause of native ESKD would be considered for eculizumab to treat post-transplant TMA. In recipients where the native kidney disease had been attributed to hypertension, there was a higher suspicion of complement mediated disease as a high prevalence of complement pathway defects has been identified in this group [11, 16]. Other causes of post-transplant TMA had to be considered unlikely to approve eculizumab, with particular considerations for exclusion being concerns of CNI toxicity, histological evidence of AMR and a clear non-complement mediated native kidney disease diagnosis. In all cases, other causes of TMA were considered depending on the clinical scenario.

The dosing schedule for adults starting eculizumab was 4 weekly doses of 900 mg, one dose of 1,200 mg after a further week, then 1,200 mg every 2 weeks [17]. Dose adjustments for children and in the case of significant blood loss or breakthrough complement activity have been previously described [1, 17].

To protect against the increased risk of *Neisseria meningitides* infection whilst on eculizumab [17], vaccination against serotypes ACWY and B was required before starting eculizumab or within 2 weeks of starting [18]. Prophylactic antibiotics were also recommended whilst treatment continued [18].

Data Collection

Available medical notes were reviewed for transplant recipient sex, age at transplantation with current transplant, year of transplantation, time post-transplant of eculizumab initiation, reason for eculizumab cessation with a functioning graft, graft failure defined as chronic dialysis or re-transplant, cause of death in those who died with a functioning graft, cause of native ESKD and cause of previous transplant loss. Where available, data on native and transplant kidney biopsy results, transplant mismatch, ABO incompatibility, presence of DSAs, immunosuppressive regime and patient survival after graft loss were collected. Any previous use of eculizumab was recorded.

For the purposes of this work, *de novo* disease was defined as being when the first recognition of TMA thought secondary to aHUS occurred post-transplant and so a diagnosis of aHUS was not present at the time of implantation.

Screening for Complement Pathway Defects

Variant screening in complement pathway genes *CFI,* [19] *CFH,* [20] *CFB,* [21] *C3* [22] and *CD46* [23] and chromosomal rearrangements [24, 25] *(CFH, CFRH1, CFHR2, CFHR3, CFHR4, CFHR5, CD46* and *CFI)* and in non-complement genes associate with aHUS (*DGKE*, [26] *MMACHC*, [1]*VTN*, [1] *PLG*, [27] *THBD*, [1] *IFN2* [28]) was conducted as previously described.

Rare genetic variants were evaluated using Alamut Visual 2.10 (2017 Interactive Biosoftware). Variants were classified in 2019 according to American College of Medical Genetics and Genomics guidelines with refinement developed by Sequence Variant Interpretation Working Group.

Anti-FH autoantibody testing was performed in selected cases using the consensus ELISA assay, as previously described [1, 29].

Statistics

Kidney graft survival was analysed with Kaplan-Meier curves and censored for patient death with a functioning graft and for functioning graft at last follow. Log-rank test assessed the difference between survival of groups.

Subgroup characteristics were compared with Fisher exact test for categorical variables, t-test to compare means of numerical variables and Kruskal-Wallis to compare medians of time to presentation.

Analysis was performed using Rstudio Team (2021). RStudio: Integrated Development Environment for R. R Studio, PBC, Boston, MA URL http://www.rstudio.com/. $P < 0.05$ was considered statistically significant.

RESULTS

Demographics

Our cohort consists of 26 transplant recipients treated with eculizumab for post-transplant TMA (Supplementary dataset). The majority (73.1%) of transplant recipients were female. There was one child (#4) included in the cohort, age nine at both transplantation and eculizumab initiation.

Transplants were implanted between 2005 and 2020 (median 2016) with referrals for post-transplant TMA being made between 2012 and 2021.

Previous Renal History

Cause of ESKD and Native Kidney Biopsies

Causes of native ESKD and biopsy results are given in **Table 1** and included three with recognised aHUS before transplantation. All recipients with evidence of TMA (n = 8) or microangiopathy without thrombosis (n = 1) on native kidney biopsy had an ESKD diagnosis of aHUS, HUS or a history of hypertension. Rationale for eculizumab treatment in those with alternative initial native kidney diagnoses is detailed in **Table 1**, with many in this group having no native kidney biopsy result.

Previous Causes of Graft Loss

Nine recipients included in our cohort had previously lost a kidney transplant including two from post-transplant TMA and a further showing IgA recurrence on biopsy with concurrent TMA. One recipient had lost two previous transplants with one attributed to rejection and the other suspected hydronephrosis or CMV. The remaining five previous transplants failed from

TABLE 1 | Native kidney disease history of recipients (n = 26) treated with eculizumab for post-transplant thrombotic microangiopathy (TMA) detailed as pre-transplant diagnosis for end stage kidney disease (ESKD) and associated native renal biopsy findings.

Cause of ESKD	Native renal biopsy	Rationale for eculizumab treatment
Existing diagnosis of aHUS		
aHUS (n = 3)	TMA (n = 3)	
De novo		
Hypertension (n = 7)	TMA (n = 2) Consistent with hypertension (n = 2) Extensive chronic damage (n = 1) Microangiopathy (no thrombosis) (n = 1) Biopsy not available (n = 1)	Involvement of hypertension in native kidney disease
Unclear cause but history included hypertension (n = 3)	Extensively damaged parenchyma with possibility of TMA (n = 1) TMA (n = 1) Biopsy not available (n = 1)	
Diarrhoea associated HUS (n = 2)	TMA (n = 1) Biopsy not available (n = 1)	Previous diarrhoea associated HUS.
Unknown (n = 2)	Fibrosis (n = 1) Biopsy not available (n = 1)	Unclear native kidney diagnosis
Reflux nephropathy (n = 2)	Biopsy not available (n = 1) Data not available (n = 1)	Previous graft loss from TMA at 5 years in one and family history of possible aHUS in the other
Chronic pyelonephritis (n = 1)	Biopsy not available (n = 1)	Uncertainty surrounding native kidney disease as presented with two small kidneys
HIV nephropathy (n = 1)	Biopsy not available (n = 1)	Pathological *CFI* variant and previous early graft loss from arterial thrombus and lack of native kidney biopsy
FSGS (n = 2)	FSGS (n = 2)	FSGS considered secondary with unclear cause in one case and following diarrhoea associated HUS in childhood for the other
IgA nephropathy (n = 1)	Crescentic IgA (n = 1)	Previous graft with TMA on biopsy at 8 months and graft loss at 19 months
Mesangial proliferation (n = 1)	MPGN, later reclassified as mesangial proliferation (n = 1)	Native kidney disease was initially described as MPGN on biopsy which can be complement mediated
Bilateral nephrectomy (n = 1)	Wilm's tumour (n = 1)	Highly sensitized patient unlikely to be retransplanted and with *CFI* variant of uncertain significance

Reasons for considering complement mediated disease, and therefore rationale for eculizumab treatment, in those without an existing diagnosis of atypical hemolytic uremic syndrome (aHUS) before this transplant was implanted are detailed. FSGS, focal segmental glomerulosclerosis; HUS, hemolytic uremic syndrome; MPGN, membranoproliferative glomerulonephritis.

TABLE 2 | Complement pathway abnormalities detected in transplant recipients tested for genetic variants (n = 25) and autoantibodies against factor H (anti-FH; n = 20).

Genetic testing	N (% tested)
No defect identified (%)	16 (64)
Variant of Uncertain Significance (%)	4 (16)
Pathological variant (%)	5 (20)
CFH	3
CFI	1
C3	1
Anti-FH autoantibody testing	
anti-FH autoantibody	1 (5)

The one recipient with anti-FH autoantibodies detected also had a variant of uncertain significance.

TABLE 3 | Details of kidney transplant treated for post-transplant TMA with eculizumab. SD, standard deviation.

Transplant details	Study cohort n = 26
Age at transplantation (mean ± SD)	40.8 ± 14.5 years
Live donor transplant (%)	13 (50)
First kidney transplant (%)	17 (65)
Mismatch (mean ± SD)	1.8 ± 1.4, n = 18
ABO incompatible transplant	2
Induction immunosuppression	
Basilixumab	8
Alemtuzumab	6
Data not available	12
Maintenance immunosuppression	
Tacrolimus + Mycophenolate mofetil + Prednisolone	17
Tacrolimus + Mycophenolate mofetil	1
Ciclosporin + Mycophenolate mofetil	1
Data not available	7

arterial thrombus, primary non function, AMR (n = 2) and chronic allograft nephropathy.

No transplant recipients included in our cohort had received eculizumab before.

Complement Defect Status

Identified complement defects are detailed in **Table 2**. The majority of those tested (n = 25) had no identified complement pathway abnormality (64%). One recipient died shortly after presentation and so was not tested. One of those tested (n = 20) had anti-FH autoantibodies detected and this was alongside a variant of uncertain significance (VUS).

Of the nine recipients with variants in complement pathway genes, three had an existing diagnosis of aHUS (Supplementary

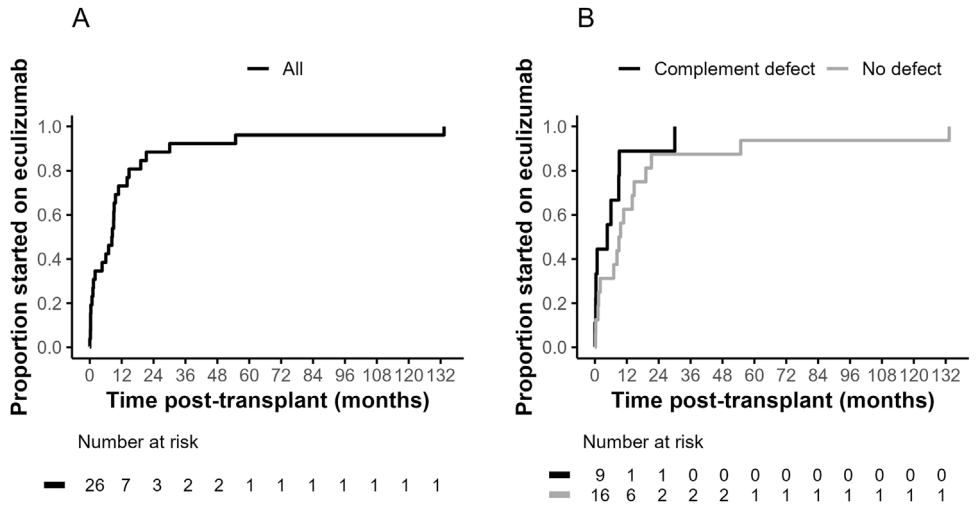

FIGURE 1 | Kaplan-Meier curves for time post-transplant to initiation of eculizumab for treatment of post-transplant thrombotic microangiopathy. Data is shown for cohort as a whole **(A)** and grouped by presence of complement pathway defects **(B)** for those tested (log-rank $P = 0.12$).

dataset). No variants in non-complement genes associated with aHUS were identified in the genes that were tested.

Current Transplant History

Details of the kidney transplants and recipients treated with reactive eculizumab are given in **Table 3** including immunosuppression, where available.

No transplant recipients received plasma exchange before transplantation with the aim of preventing aHUS recurrence. However, two (#592, #53, Supplementary dataset) had plasma exchange pre-transplant for desensitization in combination with rituximab.

Presentation With Post-transplant TMA

Timing

Time from transplant to initiation of eculizumab for post-transplant TMA is shown in **Figure 1A** for all recipients in the cohort and grouped by presence of complement pathway defects (**Figure 1B**). Median (range) time at treatment was 8.4 months (6 h–11 years) post-transplant. Median time to presentation was under 12 months both for those with (4.5 months, range 6 h to 2.5 years) or without (9.0 months, range 7 days–11 years) complement pathway defects.

Renal Presentation of Post-transplant TMA

Five recipients (19.2%) required dialysis at the point of referral for post-transplant TMA for either acute kidney injury (AKI, n = 4) or delayed graft function (n = 1). Other renal presentations included AKI not requiring dialysis (n = 9), an acute rise in creatinine not meeting AKI criteria for magnitude (n = 5) [30], failure to achieve expected function of kidney transplant (n = 3) and non-acute progressive renal impairment (n = 4).

Patients who were biopsied (n = 24) had histological evidence of post-transplant TMA. Chronic damage was graded [31], where possible, from the available details in biopsy reports and is detailed in the Supplementary dataset with the majority graded as minimal or mild (n = 15). Timing of onset did not vary with degree of chronic damage (**Supplementary Figure S1**). The one adult recipient (#562) who did not have a transplant biopsy had hypertension as the presumed cause of native ESKD and a VUS in *C3*. She presented 9 days after transplantation of a well-matched live donor kidney, hypertensive with evidence of MAHA and a rising creatinine. The child (#4) who was not biopsied at the time of recurrence was treated as she had deteriorated within hours of transplant with concerns of MAHA including an elevated serum lactate dehydrogenase (LDH; 3334 IU/L), known aHUS and previous primary non function of first transplant.

Hematological Features at Presentation

Fifteen recipients (57.7%) had evidence of MAHA on presentation with post-transplant TMA with 13 having concurrent thrombocytopenia. A further three (11.5%) had isolated thrombocytopenia with the remainder having neither thrombocytopenia nor evidence of MAHA (n = 8, 30.8%). There was no difference in presence of hematological features by complement pathway defect status (Fisher exact test $P = 1.0$).

Five of the 18 (27.8%) with hematological features of TMA required dialysis at presentation compared to none of the 8 without hematological features of TMA ($P = 0.281$, **Supplementary Table S2**). There was no difference in time to onset of post-transplant TMA by hematological features ($P = 0.405$, **Supplementary Table S2**).

Of those presenting with MAHA (n = 15), LDH levels were available for 12 (Supplementary dataset). Median (range) serum LDH concentration in this group was 1,050 (222–3,338) IU/L. Data on LDH levels was not available for presentations without MAHA.

Evidence of Rejection

Two had evidence of peritubular capillary C4d staining on transplant biopsy at the time of post-transplant TMA

occurrence. In one recipient (#593) with a pathological variant in *CFI* and previous transplant loss from arterial thrombus, peritubular capillary C4d staining was minimal and not diagnostic of AMR. Although no DSAs were detected, she was treated with methylprednisolone and received a trial of eculizumab for 2 weeks. Eculizumab was stopped due to a lack of improvement in renal function and the transplant failed shortly after at 5 months post-transplant. Graft loss was attributed to TMA rather than rejection. Cause of ESKD was listed as HIV nephropathy but was not biopsy confirmed.

In the other recipient (#591) peritubular capillary C4d staining was equivocal but associated with mild-moderate capillaritis. She was highly sensitized (98% panel reactivity at transplantation) and had existing low level DSAs to MHC class II antigens at transplantation. Eculizumab was authorised as a VUS in *CFI* was identified. Post-transplant TMA occurred 5 months post-transplant and a course of eculizumab was stopped after 2 months when AMR was thought more likely. Graft loss occurred 8 months later (15 months post-transplant) and was attributed to chronic AMR.

Four other recipients had glomerulitis and peritubular capillaritis (n = 3) or borderline changes suspicious for acute T cell mediated rejection on biopsy (n = 1). None had DSAs or peritubular capillary C4d staining.

Four had a history of DSAs but no biopsy features of rejection. Only two (#53, #589) had DSAs reported (against DQ6 and Cw6 respectively) at the point of post-transplant TMA occurrence and both were low levels.

Other Treatments for Post-Transplant TMA

Plasma Exchange

Of those with available data (n = 24), 58.3% received plasma exchange at the time of post-transplant TMA occurrence (Supplementary dataset).

Change in CNI

Of the 25 recipients with available data, all were taking tacrolimus at the time of post-transplant TMA. Eight had their tacrolimus reduced or suspended initially with 2 subsequently reintroducing it. Belatacept was started in place of tacrolimus in four with a further one starting after an initial switch to sirolimus. Three did not have adjustments to their tacrolimus and one switched to ciclosporin. There was no data on adjustments to CNI immunosuppression for eight recipients.

Outcomes

At last follow-up, 3 (11.5%) recipients had died with a functioning graft, 11 (42.3%) had grafts that continued to function and 12 (46.2%) had failed. In those surviving transplant recipients with a functioning graft, median (range) follow-up was 4.1 years (1.6–11.8 years) from initiation of eculizumab for post-transplant TMA.

Deaths

Two transplant recipients died with a functioning graft within the first year of transplantation. One (#566) died of a respiratory infection 1 month after starting eculizumab and 10 months after transplantation. This was his first transplant and native ESKD occurred in the context of severe hypertension and sepsis. The second (#577) died from a subarachnoid hemorrhage 5 months post-transplant. She had started eculizumab in the second month post-transplant and continued for 7 weeks until CNI toxicity was thought the more likely cause of post-transplant TMA. Tacrolimus had been stopped.

The third death with a functioning transplant was from an intracranial hemorrhage that occurred 10.3 years post-transplant and after almost 8 years of eculizumab treatment. This was the recipient's (#273) third kidney transplant.

No deaths were recorded after graft failure (follow-up 3–59 months, median 19 months).

Graft Survival From Eculizumab Initiation

Death-censored kidney graft survival from the point of starting eculizumab for post-transplant TMA is shown in **Figure 2A**. One year after starting eculizumab, death-censored transplant survival was 68.0%.

Death-censored graft survival was 70.7% for those with and 65.5% for those without complement pathway defects, 1 year after starting eculizumab treatment (**Figure 2B**). Amongst those who presented within 12 months of transplant, there was no clear difference in outcome between those with or without complement pathway defects (**Supplementary Figure S2**). Graft outcomes were similar in those with or without hematological features of TMA at presentation (**Supplementary Figure S3**) and between grades of chronic damage on biopsy (**Supplementary Figure S4**).

There is a suggestion that later presentation with post-transplant TMA is associated with worse kidney graft survival subsequently but this difference did not reach statistical significance (P = 0.36). Death-censored graft survival 12 months after eculizumab initiation was 42.9% for those starting after the first year of transplantation, compared to 77.5% for those starting earlier (**Figure 2C**). There was no difference in proportion with complement pathway defects, hematological features of TMA or existing diagnoses of aHUS between those presenting early or late (**Supplementary Table S3**). Those presenting later more commonly required dialysis at presentation (P = 0.01, **Supplementary Table S3**).

In the 6 recipients with pathogenic variants in complement pathway genes or anti-FH autoantibodies, 5 presented within 12 months of transplant including 3 grafts that failed during follow-up. One graft failed shortly after starting eculizumab whereas the other two continued to function over 4 years into eculizumab treatment. For those with pathogenic variants or anti-FH autoantibodies, graft survival appears similar to prophylactic eculizumab treatment (**Supplementary Figure S5**) [1, 14].

Outcomes in Those on Dialysis at Presentation

Of the 5 recipients on dialysis at the point of referral for post-transplant TMA, all those (n = 4) presenting more than 12 months post-transplant either remained dialysis dependent (n = 3) or experienced graft loss 6 months after starting eculizumab (n = 1). In the other case, post-transplant TMA occurred early in the post-transplant period and the graft continued to function 3 years later.

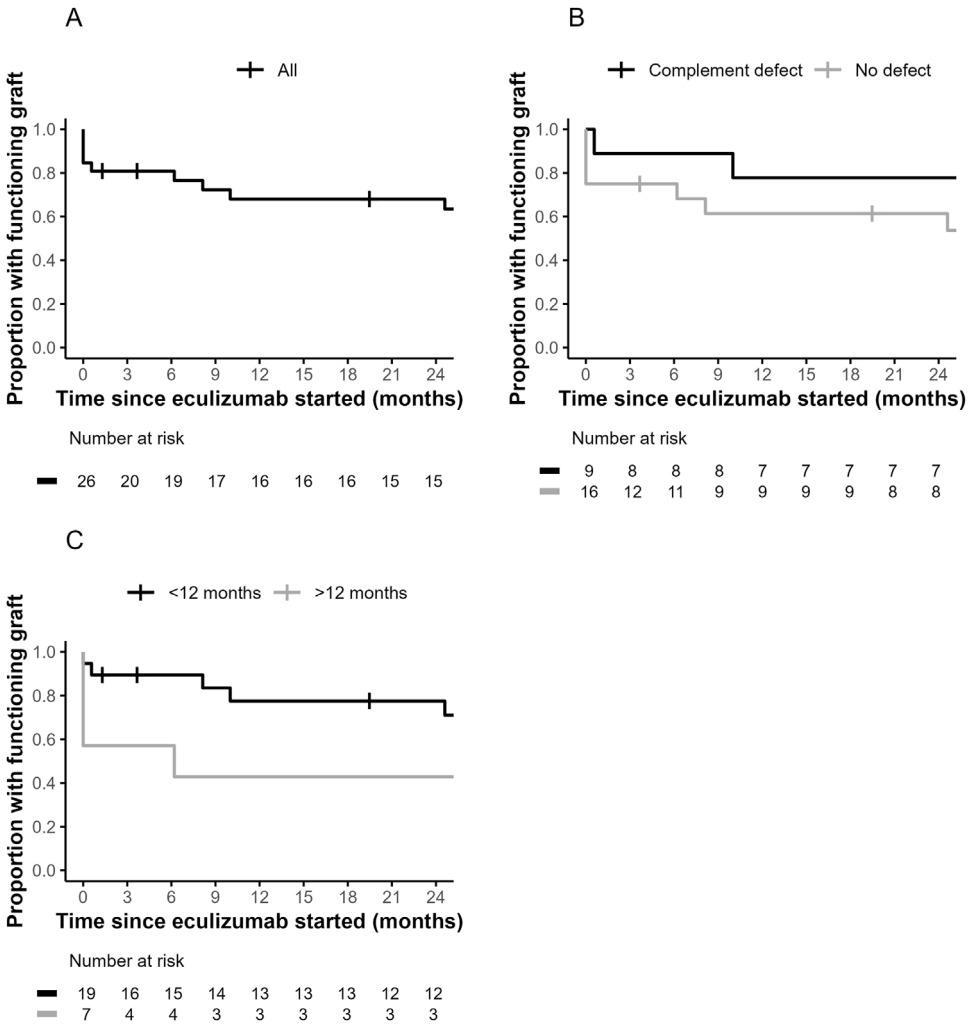

FIGURE 2 | Death-censored Kaplan-Meier analysis of kidney graft survival from time of eculizumab initiation to treat post-transplant thrombotic microangiopathy. Data is shown for cohort as a whole **(A)**, grouped by presence of complement pathway defects (pathological variants or variants of uncertain significance in complement pathway genes or presence of autoantibodies against factor H) in those tested (log-rank $P = 0.23$) **(B)** or grouped by timing of eculizumab initiation in the post-transplant period (log-rank $P = 0.36$) **(C)**. Numbers at risk in each group at 3 monthly time points are detailed below the graph.

Cause of Graft Loss

Graft loss was attributed to either TMA (n = 10) or rejection (n = 2). One case (#591) attributed to rejection is discussed above and eculizumab was stopped before graft loss. In the second case (#99) graft loss occurred 5.2 years into eculizumab treatment which was started 12 days after transplantation.

Graft loss from TMA mostly occurred within 12 months of starting eculizumab treatment. In five cases transplant loss was less than 1 month after presentation, in two cases it occurred six to 8 months later and in a further three cases the graft functioned for at least 2 years from starting eculizumab.

TMA Recurrence on Eculizumab Treatment

There were no reported episodes of clinical TMA recurrence in transplants included in this cohort, after the episode treated with eculizumab.

One recipient (#590) was biopsied for worsening proteinuria 5 months after stopping eculizumab and this showed evidence of acute TMA and damage from previous TMA. No further eculizumab was given as the native kidney disease had been reassessed as not being complement mediated. The graft continued to function at 3 years.

Cessation of Eculizumab

Eleven (42.3%) stopped complement blockade at a point when their graft was still functioning. In two the rationale was failure for graft function to improve and both grafts were lost to TMA shortly after. In three cases it was a local team decision or patient preference to stop eculizumab treatment after at least six completed months. Two had no identified complement pathway defects and the third had a VUS in *CFI*. Follow-up in these three recipients is at least 2 years from treatment cessation, with no reported TMA recurrence.

In the remaining six transplant recipients, eculizumab treatment was stopped when TMA was thought more likely secondary to an alternative diagnosis. This was most commonly CNI toxicity but also included possible IgA recurrence and AMR. In all these cases, eculizumab was stopped within 6 months of initiation. One recipient died a few months later from unrelated causes (#577) and another (#591) lost their graft to rejection 8 months after cessation. The remaining 4 had at least 18 months follow-up from stopping eculizumab and no reported clinical TMA recurrence, although one (#590) discussed above had TMA on repeat biopsy.

DISCUSSION

We present our experience of treating 26 selected cases of post-transplant TMA with eculizumab, coordinated through a national specialist centre. Our cohort adds to the existing data on eculizumab treatment for post-transplant TMA by including both *de novo* presentations and those with an existing diagnosis of aHUS, providing details on time to presentation, presence of inherited and acquired alternative complement pathway defects and rationale for treatment in those presenting without an existing diagnosis of aHUS. Follow-up extended to at least 18 months from eculizumab initiation for those whose grafts continued to function.

Perhaps the most comparable cohort to our dataset is the CUREiHUS cohort of 15 transplant recipients treated for post-transplant TMA with eculizumab, of which a third had no previous history of aHUS [13]. Despite the inclusion of *de novo* post-transplant TMA 60% were found to have a variant in a complement pathway gene. Only three (20%) grafts failed during the study period but three (25%) of the remaining grafts had follow-up of less than 4 months from eculizumab initiation which is short relative to what we present.

Genetic testing forms an integral part of diagnosing aHUS and it is generally reported that 50%–70% of people with aHUS have a genetic variant or autoantibody causing complement pathway dysregulation [1, 2, 8–10, 32, 33]. However, in our cohort the decision to treat with eculizumab was often made in advance of these results, given the time sensitivity of treatment initiation [8]. Ultimately, only 34.6% of the recipients had an identified complement pathway defect. The heterogeneity of our cohort likely explains the relatively low detection of complement pathways defects as only three (11.5%) had an existing diagnosis of aHUS. In support of this, others have found a low rate of 20% with complement pathway defects in recipients with *de novo* post-transplant disease [2].

Post-transplant TMA is not always associated with hematological features of thrombocytopenia and MAHA but can instead be limited to kidney involvement identified on biopsy [4, 34]. Some trials using eculizumab post-transplant excluded those without hematological features of TMA [35], this was not the case for our cohort where 30.7% did not have hematological evidence of TMA. This is similar to previously reported rates in a cohort of 21 cases of *de novo* post-transplant TMA where 38% had only kidney involvement [34]. Schwimmer et al. [34] found that those with hematological evidence of TMA presented earlier and were more likely to require dialysis. Amongst our cohort there was no difference in timing of TMA onset by hematological status and the higher requirement for dialysis was not statistically significant. The presence of complement pathway defects between those with and without hematological features did not differ either.

A key finding in our cohort is apparent poor graft survival following post-transplant TMA, despite eculizumab treatment, particularly for those presenting with post-transplant TMA >12 months after transplantation. Delayed recognition may worsen outcomes for those presenting later when monitoring is less frequent. Disease in transplanted kidneys can also take longer to respond to eculizumab compared to native kidneys [4], highlighting the need for prompt treatment. Supporting this hypothesis of more severe kidney injury with later presentations, more of those presenting >12 months post-transplant required dialysis (**Supplementary Table S3**). Alternatively, worse outcomes for later presentations may represent more non-complement mediated TMA, not expected to respond to eculizumab. aHUS recurrence after transplantation typically occurs early [1], although late presentations are documented [12, 14, 36]. Our cohort is a heterogenous one but there was no clear split in terms of existing and *de novo* disease or complement pathway defects between those presenting before or after 1 year of transplantation.

Complement mediated HUS is a rare cause of post-transplant TMA that requires prompt recognition to be appropriately treated. Genetic testing is an important element in the diagnostics but these results can take some time. Genetic testing can also support clinicians in revisiting the listed diagnosis of ESKD if variants are identified, particularly if historic native kidney biopsies were ambiguous. Indeed, in four (15.4%) of the cases presented here, complement pathway defects were identified after referral for post-transplant TMA raising the suspicion of aHUS contributing to native ESKD. It is essential to differentiate between hypertensive and complement mediated disease before transplant to better guide post-transplant care and genetic testing can contribute to this [11, 16].

We suggest screening for complement defects prior to transplantation to allow access to prophylactic eculizumab if a medium or high-risk variant is identified in selected patients: with ESKD due to Shiga toxin-producing *E. coli* HUS, when the cause of ESKD is unknown but associated with hematological features of TMA or accelerated hypertension or if there has been a TMA in a previous transplant. In those presenting post-transplant with a TMA, continuation of reactive eculizumab treatment should be reassessed early in those presenting after the first year of transplantation given poor graft outcomes.

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

EM, EW, SJ, MM, KM, DK, and NS critically reviewed and approved the final manuscript. EG and KM collected and analysed the data. EG wrote the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

NSS has provided consultancy for Alexion Pharmaceuticals, Novartis and Roche DK received consultancy income from Gyroscope Therapeutics, Alexion Pharmaceuticals, Novartis, Apellis, and Sarepta SJ served on the Scientific Advisory Board for the Alexion Global aHUS Registry. Has provided consultancy for and received honoraria for talks from Alexion Pharmaceuticals and Novartis (all paid to employing institution). EKWS has speaker agreements with Alexion and Novartis and has provided consultancy for Biocryst MM Honoraria for educational talks and honorarium for national lead of aHUS registry (Alexion/Astra Zeneca). Travel expenses reimbursement (Alexion/Astra Zeneca). Honoraria for attending an expert panel (Novartis). KJM has provided consultancy to and received materials in kind from Alexion Pharmaceuticals.

The remaining authors declare that the research 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.2025.15404/full#supplementary-material

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ORIGINAL RESEARCH
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Hidden in Plain Sight: High Tacrolimus Metabolism Doubles Kidney Transplant Failure and Drives Infection Related Mortality

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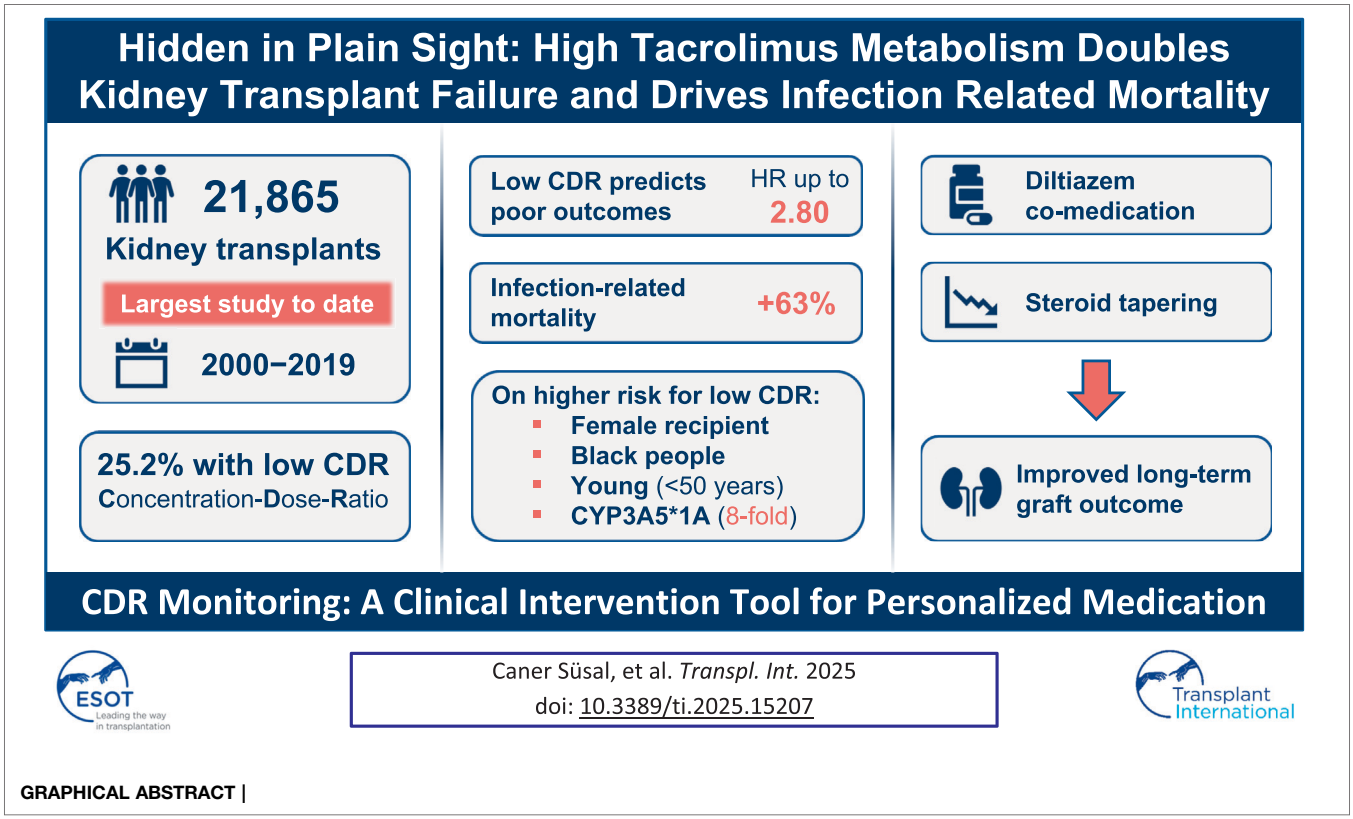
Low tacrolimus trough concentration-to-dose ratio (CDR) is recognized as an indicator of high tacrolimus metabolism. However, its impact on long-term transplant outcomes and potential for clinical intervention remains unclear. In the largest study to date, we analyzed the impact of a low CDR at post-transplant year 1 on graft loss and patient mortality in 21,865 kidney transplants. We also performed a longitudinal analysis of CDR dynamics and conducted a genetic correlation in a subset of 1,257 patients. Low CDR at year 1 was significantly associated with increased hazards of graft failure (HR up to 2.80) and infection-related mortality (HR = 1.63), even in patients with therapeutic trough levels and good graft function. In the longitudinal analysis, normalizing initially low CDR by year 2 significantly improves graft survival. Low CDR was identified in a substantial proportion of the cohort (25.2%). Black, female, and younger recipients (<50 years) had higher odds of having a low CDR. The *CYP3A5*1A* genotype was also strongly associated with low CDR (approximately 8-fold higher odds). Patients with a low tacrolimus CDR represent a large high-risk population. The normalization of tacrolimus CDR through co-medication with diltiazem and reductions in steroid dosing may improve graft survival. Our findings support personalized tacrolimus management based on metabolic profiling and genetic testing.

Keywords: kidney transplant, tacrolimus concentration-to-dose ratio, allograft loss, mortality, infection

Abbreviations: CDR, concentration-to-dose ratio; C_0, whole-blood trough; CTS, Collaborative Transplant Study; CYP, cytochrome P450; mTOR, mammalian target of rapamycin-inhibitor.



GRAPHICAL ABSTRACT |

INTRODUCTION

Tacrolimus as the most frequently used calcineurin inhibitor in kidney transplantation has a relatively narrow therapeutic range, yet despite decades of clinical use, a fundamental paradox persists in its therapeutic monitoring. While current clinical practice relies predominantly on blood trough concentration (C_0) measurements to guide dosing decisions, mounting evidence suggests that this approach is not adequate to address the complex metabolic heterogeneity that profoundly influences transplant outcomes [1, 2]. A Collaborative Transplant Study (CTS) demonstrated that a trough level below 5 ng/mL at year 1 post-transplant is associated with significantly impaired graft survival [3]. However, rejection episodes and drug side effects occur also at trough levels 5 ng/mL or above [4].

The narrow therapeutic window of tacrolimus, combined with its significant intra- and inter-individual pharmacokinetic variability, calls for more sophisticated monitoring strategies that can identify high-risk patients before irreversible graft damage occurs. Therefore, besides C_0 trough level, the ratio between the C_0 concentration and dose (CDR) of tacrolimus as well as genetic variations in cytochrome enzymes involved in tacrolimus metabolism, have been investigated for their impact on kidney transplant outcomes [5, 6]. A low tacrolimus CDR was suggested as a modifiable risk factor to recognize high metabolizers who develop calcineurin inhibitor nephrotoxicity and BK nephropathy due to tacrolimus overdosing [7]. Others found that high metabolizers with a low CDR have an impaired kidney function due to acute rejection and delayed graft function caused by a too low tacrolimus trough level [8].

Variability in the genes of cytochrome P450 (CYP) 3A family of enzymes CYP3A4 and CYP3A5 has been shown to influence tacrolimus metabolism [9–11]. Expressors of the CYP3A5 enzyme homozygous or heterozygous for *CYP3A5*1* allele have been reported to have increased tacrolimus clearance [12] and require higher doses to achieve the target tacrolimus concentration than non-expressors [13, 14]. A 1.5–2-fold higher starting dose of tacrolimus is recommended for CYP3A5 expressors [15]. Prevalence of patients expressing CYP3A5 is much higher among Black (40%–50%) and Asian (50%–70%) patients than among European ancestry patients (10%) [16, 17]. Carriers of certain *CYP3A4* alleles also exhibit varying levels of enzyme activity, including loss-of-function or low-function enzyme alleles [18, 19].

Overall, studies investigating the impact of tacrolimus metabolism on transplant outcomes and its association with genetic variations are confined to data generated from small-sized cohorts with short follow-up periods and were limited in representing different ancestries. We studied the impact of tacrolimus CDR on the robust endpoints “graft survival” and “patient mortality” in 21,865 kidney transplants, comprising 1,783 transplants in Black patients [20]. Additionally, we analyzed the dynamic impact of CDR changes over time and the factors associated with a high or low tacrolimus CDR.

METHODS

Study Population and Data Collection

21,865 kidney transplantations performed during 2000–2019 in adult patients and reported to the CTS were investigated. Only patients with a functioning graft for more than 1 year, for whom 1-year tacrolimus dosage and C_0 trough level data were available, were included; tacrolimus CDR was calculated from trough levels and doses at year 1, with additional year 2 data analyzed. Multi-organ transplantations (except simultaneous kidney-pancreas transplantation) and transplantations in patients receiving mammalian target of rapamycin-inhibitor (mTOR) or cyclosporine A in addition to tacrolimus were excluded.

Exposures

CDR was calculated by dividing the measured trough concentration by the daily dosage. The impact of CDR on the three most common causes of death, namely infection (ICD-10 A00–B99), diseases of the circulatory system (I00–I99), and malignancies (C00–C97) was analyzed.

Outcomes

Primary outcomes were the impact of the first-year CDR on all-cause graft failure, death-censored graft failure, and mortality during the second and third post-transplant years as well as the identification of factors associated with a low 1-year CDR of <1.05. The influence of CYP3A4 and CYP3A5 polymorphisms on death-censored graft failure was evaluated in a subgroup of 1,257 patients of European ancestry from Europe and North America with an available DNA sample.

Statistical Analysis

CDR's influence on outcomes was evaluated by Kaplan Meier estimates and Cox regression. Factors associated with low 1-year CDR were studied by logistic regression. For the analysis of the effect of tacrolimus CDR on the clinical outcomes, demographic, clinical, basic follow-up data, and transplant outcomes, including hospitalization for infection, graft failure, death-censored graft failure, and mortality were obtained from standardized follow-up questionnaires completed by the participating centers at 3-, 6-, and 12-month post-transplant and annually thereafter. An extended voluntary follow-up questionnaire with additional data, such as dose and trough level of immunosuppressive medication, was provided at years 1, 2, 3, and 5 post-transplant and every 5 years thereafter. The impact of the 1-year tacrolimus CDR (day*10^{-3}/L) on outcomes during years 2 and 3 post-transplant as well as the combined influence of 1- and 2-year CDR on death-censored graft survival during years 3 and 4 post-transplant, were illustrated using Kaplan-Meier curves. All shown differences were confirmed through multivariable Cox regression analysis for a 2-year follow-up period to account for the potential influence of known factors on graft failure and patient mortality. The following confounders were included in all Cox regressions: geographical region, transplant year, first or retransplant, recipient and donor age, recipient sex and ancestry, original disease leading to end-stage renal failure, donor relationship (deceased, living), simultaneous kidney-pancreas transplantation, HLA-A+B+DR mismatches, time on dialysis prior to transplantation, general evaluation of the patient for transplant candidacy at the time of transplant, pretransplant antibodies, cause of donor death, marginal donor status, cold ischemia time (in the case of deceased donor), antibody induction, steroids, smoking, treatment for diabetes, and CDR at year 1. The use of antihypertensive drugs was recorded as a yes/no variable at the time of transplant admission. Other variables available at year 1, such as serum creatinine, tacrolimus trough level, and steroid dose could not be considered as confounders because of their significant correlation with CDR and were used only for stratification. A back-step elimination algorithm was used to exclude confounding factors with a threshold P value of >0.1. Interactions between the main exposure (CDR) and covariates pre-specified based on clinical relevance and prior literature (e.g., transplant number, recipient age, sex, ancestry, donor relationship, HLA mismatches, and original disease) were assessed. No interactions were statistically significant, and none were retained in the final models.

In the multivariable logistic regression analysis of factors associated with a low CDR <1.05 the following recipient-related pre-transplant variables were evaluated: transplant year, first or retransplant, recipient age, gender, and ancestry, treated for diabetes mellitus, original disease, smoking, pretransplant antibodies, preemptive transplant, medication (steroids, antibody induction, antihypertensive drugs), and in the genotyped subpopulation, in addition, the *CYP3A5*1A* and *CYP3A4*22* genotypes. Quantitative data were presented as median and interquartile range, qualitative data as percentage and frequency. Chi-squared and Mann-Whitney U-tests were used for the comparison of the demographic characteristics. The software package IBM® SPSS® Statistics, version 29.0 (IBM Corporation, Armonk, NY, USA) was used. P values below 0.05 were considered statistically significant. Detail of genotypic analysis is described in **Supplementary Material**.

RESULTS

Demographic and Clinical Characteristics

The demographics of the whole study cohort and the subgroup that was genotyped for *CYP3A4* and *CYP3A5* are shown in **Table 1**. 89.1% of all patients and 84.9% of the genotyped group were first graft recipients. As depicted in **Supplementary Figure S1**, genotyped patients demonstrated an almost identical all-cause graft survival as the subgroup of 9,349 patients of European ancestry who were not genotyped. Moreover, the 1-year tacrolimus trough and CDR levels were also not significantly different in genotyped versus not-genotyped recipients (P = 0.20 and P = 0.39, respectively). The vast majority of patients received immediate-release tacrolimus formulations, while a small proportion (6.6%) were on modified-release formulations (Advagraf® or Envarsus®).

TABLE 1 | Demographics of study patients (n, % or median with interquartile range).

Characteristic	All patients n = 21,865	Typing with CYP3A4, CYP3A5 n = 1,257
Events during post-tx years 2 and 3		
Graft failure	677	36
Death	729	33
Transplant year		
2000–2006	4,118 (18.8)	381 (30.3)
2007–2012	8,557 (39.1)	637 (50.7)
2013–2019	9,190 (42.0)	239 (19.0)
Geographical region		
Europe	10,059 (46.0)	806 (64.1)
Latin America	9,755 (44.6)	0 (0.0)
Other	2,051 (9.4)	451 (35.9)
Transplant number		
First transplant	19,480 (89.1)	1,067 (84.9)
Retransplant	2,385 (10.9)	190 (15.1)
Recipient sex		
Female	8,440 (38.6)	468 (37.2)
Male	13,425 (61.4)	789 (62.8)
Recipient age (years)	48 (37–58)	53 (42–62)
Recipient ethnic descent[a]		
European	15,562 (74.3)	1,257 (100.0)
Black African	1,783 (8.5)	0 (0.0)
Other	3,592 (17.2)	0 (0.0)
Donor relationship		
Deceased	15,446 (70.6)	1,090 (86.7)
Living	6,419 (29.4)	167 (13.3)
Donor age (years)	48 (37–57)	51 (40–59)
1-year serum creatinine (μmol/L)		
<130	12,829 (58.7)	752 (59.8)
≥130	9,036 (41.3)	505 (40.2)
1-year tacrolimus trough level (ng/mL)	7.3 (5.8–9.1)	7.3 (6.0–9.0)
1-year tacrolimus dose (mg/day)	4.0 (3.0–7.0)	4.0 (3.0–6.0)
1-year tacrolimus CDR (day*10^{-3}/L)	1.60 (1.04–2.40)	1.69 (1.15–2.50)

Tx, transplant; CDR, trough level/dose ratio.
[a]*4% unknown.*

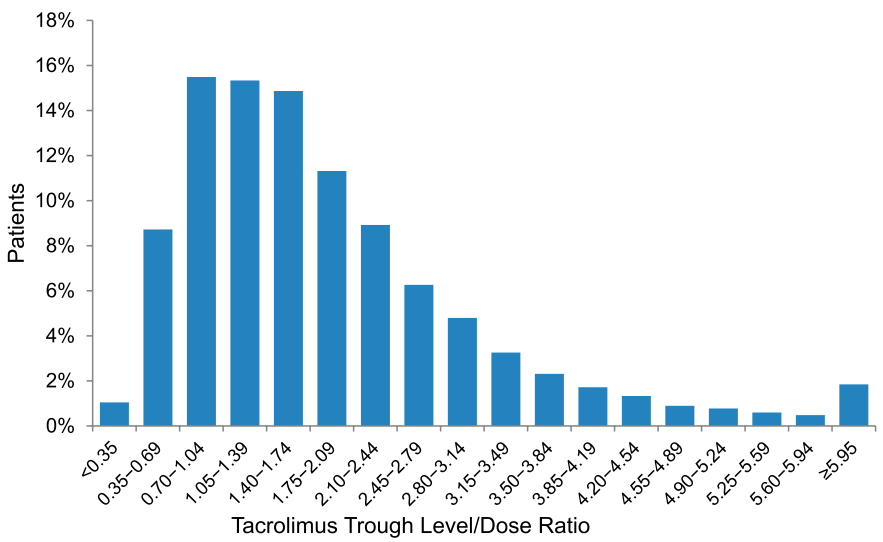


FIGURE 1 | Distribution of tacrolimus trough level/dose ratio (day*10^{-3}/L) at post-transplant year 1.

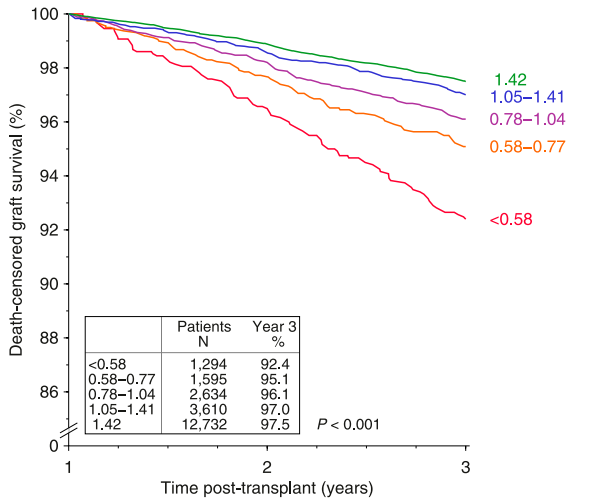


FIGURE 2 | Influence of tacrolimus trough level/dose ratio (CDR, day*10^{-3}/L) at year 1 on death-censored graft survival during post-transplant years 2 and 3 (log rank *P* value with trend of Kaplan-Meier analysis is shown).

Impact of CDR on the Outcomes

1-year CDR values of the cohort showed a right-skewed distribution making a subgrouping based on logarithmic values meaningful (**Figure 1**). Based on previously published studies [7, 21], we focused on lower CDR values, including 1.05, as they provided clinically meaningful insights and stratified the cohort into five groups using the CDR cut-offs 0.58, 0.78, 1.05, and 1.42, corresponding approximately to the equidistant ln(CDR) values −0.55, −0.25, 0.05, and 0.35.

In the Kaplan-Meier analysis, decreasing CDR values were associated with a stepwise decrease of death-censored graft survival ($P < 0.001$; **Figure 2**). An especially impaired graft survival was observed in patients with a very low 1-year CDR of <0.58, who made up 5.9% of the whole collective (n = 1,294).

In the multivariable Cox analysis, using CDR ≥1.42 as reference, CDR levels below 1.05 were associated with a significantly and progressively increased hazard of all-cause and death-censored graft failure, with the highest hazard observed in patients with very low CDR of <0.58 (all-cause failure, hazard ratio HR = 1.32 for CDR 0.78–<1.05, HR = 1.55 for CDR 0.58–<0.78, and HR = 2.05 for CDR <0.58; death-censored failure, HR = 1.47 for CDR 0.78–<1.05, HR = 1.69 for CDR 0.58–<0.78, and HR = 2.80 for CDR <0.58; $P < 0.001$ for all; **Table 2**). The impact of CDR on mortality was less pronounced and reached statistical significance starting at values below 0.78 (HR = 1.48 for CDR 0.58–<0.78 and HR = 1.44 for CDR <0.58; $P = 0.003$ and 0.019, respectively; **Table 2**).

Patients with a low CDR of <0.78 and a functioning graft at year 2 were more frequently hospitalized for infection during year 2 than patients with a CDR of ≥0.78 (11.8% vs. 9.5%; $P = 0.004$; data not shown). In line with this finding and as illustrated in **Figure 3**, also the cumulative incidence of death due to infection during years 2 and 3 was significantly higher in patients with a CDR of <0.78 compared to patients with a CDR of ≥0.78 (1.93% vs. 1.17%, $P < 0.001$; HR = 1.63, 95% CI 1.20–2.22; $P = 0.002$). In contrast, the incidence of death due to circulatory system disease or malignancy was similar in patients with a CDR of <0.78 and ≥0.78.

Table 3 demonstrates the impact on death-censored graft failure of very low (<0.58) and intermediately low (0.58–<1.05) CDR values in different patient subgroups, as compared to the reference group with a normal CDR of ≥1.05. A CDR below 0.58 significantly increased the hazard of graft failure in all analyzed subgroups, irrespective of recipient sex and age, donor relationship, 1-year creatinine value, 1-year tacrolimus trough level, and 1-year steroid dose. The only exception was the subgroup of ≥60-year-old recipients in whom the 58% higher hazard did not reach statistical significance ($P = 0.28$). The highest hazard was observed in female recipients (HR = 3.59; $P < 0.001$), and in 18–49-year-old younger recipients, the hazard of graft failure increased approximately three-fold (HR = 2.99; $P < 0.001$). An intermediately low CDR of 0.58–<1.05 was also associated with a significantly increased hazard of graft failure in almost all subgroups, except for ≥60-year-old recipients, living donor

TABLE 2 | Influence of categorized trough level/dose ratio (CDR, day*10^{-3}/L) at year 1 on all-cause graft failure, death-censored graft failure and patient mortality during second and third post-transplant years. Multivariable Cox regressions are used to calculate the hazard ratios (HR) with 95% confidence interval (CI).

CDR (day*10^{-3}/L)	All-cause graft failure		Death-censored graft failure		Patient mortality	
	HR	95% CI *P* value	HR	95% CI *P* value	HR	95% CI *P* value
<0.58	**2.05**	1.70–2.47 <0.001	**2.80**	2.20–3.55 <0.001	**1.44**	1.06–1.96 0.019
0.58–<0.78	**1.55**	1.29–1.87 <0.001	**1.69**	1.31–2.19 <0.001	**1.48**	1.14–1.93 0.003
0.78–<1.05	**1.32**	1.12–1.55 0.001	**1.47**	1.17–1.86 <0.001	1.18	0.94–1.49 0.15
1.05–<1.42	1.05	0.90–1.23 0.54	1.17	0.93–1.46 0.18	0.98	0.79–1.22 0.87
≥1.42	1.00	Ref.	1.00	Ref.	1.00	Ref.

Overview of the covariates included and excluded from the final models is provided in ***Supplementary Table S2****; univariable results are presented in* ***Supplementary Table S3****. Bold numbers indicate statistically significant HR values.*

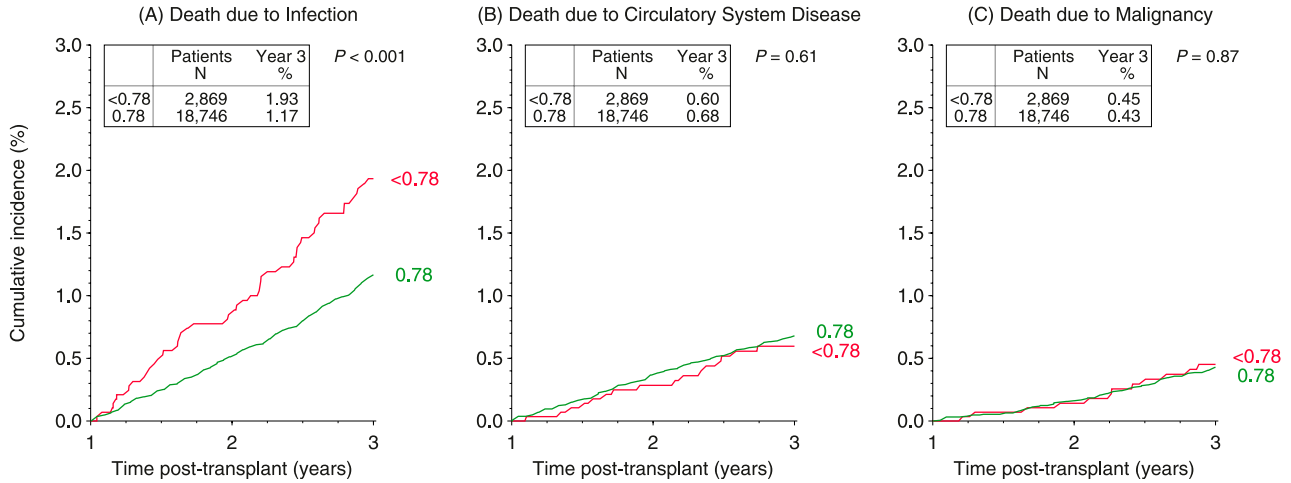


FIGURE 3 | Influence of tacrolimus trough level/dose ratio (CDR, day*10^{-3}/L) at year 1 on cumulative incidence of death due to **(A)** infection, **(B)** circulatory system disease, and **(C)** malignancy during post-transplant years 2 and 3 (log rank *P* values of Kaplan-Meier analyses are shown).

TABLE 3 | Influence of 1-year trough level/dose ratio (CDR, day*10^{-3}/L) on death-censored graft failure during second and third post-transplant years in different subpopulations. Multivariable Cox regressions were used to calculate the hazard ratios (HR) with 95% confidence interval (CI) and CDR ≥1.05 as reference.

Subpopulation	N	CDR<0.58			CDR 0.58 – <1.05		
		HR	95% CI	P	HR	95% CI	P
All patients	21,865	**2.76**	2.20–3.47	<0.001	**1.52**	1.27–1.82	<0.001
Recipient sex							
Female	8,440	**3.59**	2.61–4.94	<0.001	**1.46**	1.10–1.92	0.008
Male	13,425	**2.15**	1.53–3.02	<0.001	**1.57**	1.24–1.99	<0.001
Recipient age							
18–49 years	11,849	**2.99**	2.30–3.91	<0.001	**1.58**	1.26–1.97	<0.001
50–59 years	5,421	**2.22**	1.23–3.99	0.008	**1.68**	1.13–2.48	0.010
≥60 years	4,595	1.58	0.69–3.62	0.28	1.11	0.66–1.86	0.70
Donor relationship							
Deceased	15,446	**2.87**	2.24–3.68	<0.001	**1.60**	1.31–1.94	<0.001
Living	6,419	**2.31**	1.31–4.08	0.004	1.19	0.74–1.92	0.47
1-year serum creatinine							
<130 µmol/L	12,829	**2.35**	1.39–3.99	0.001	**1.69**	1.16–2.47	0.006
≥130 µmol/L	9,036	**2.41**	1.87–3.11	<0.001	**1.33**	1.08–1.63	0.006
1-year trough level							
<4.5 ng/mL	1,888	**1.93**	1.23–3.04	0.005	1.10	0.70–1.75	0.68
≥4.5 ng/mL	19,977	**2.55**	1.92–3.39	<0.001	**1.51**	1.24–1.84	<0.001
1-year steroid dose							
≤5.0 mg/day	17,385	**2.73**	2.07–3.61	<0.001	**1.65**	1.34–2.03	<0.001
>5.0 mg/day	3,427	**2.20**	1.41–3.42	<0.001	1.16	0.79–1.71	0.45

Covariates: geographical region, donor relationship, transplant number, recipient and donor age, HLA mismatches, pretransplant antibodies, original disease, cause of donor death, marginal donor, smoking; univariable results are presented in ***Supplementary Table S4****. Bold numbers indicate statistically significant HR values.*

recipients, and recipients with a 1-year tacrolimus trough level below 4.5 ng/mL or 1-year steroid dose of >5.0 mg/day. Even in patients with a 1-year tacrolimus trough level of ≥4.5 ng/mL, a very low CDR was associated with a 2.55-fold and an intermediately low CDR with a 1.51-fold increased hazard of failure ($P < 0.001$ for both).

In a further subgroup analysis of 16,983 transplants with a follow-up of more than 2 years and an available CDR value also at year 2, we additionally analyzed the combinatory influence on death-censored graft survival of a low (<1.05) and normal (≥1.05) CDR at post-transplant years 1 and 2 by the Kaplan-Meier method (**Figure 4**). Irrespective of the level of CDR at year 1, an inferior graft survival was observed in patients with a low CDR at year 2, which was almost identical with that observed in patients with a low CDR at both post-transplant years. Approximately one-third of patients with a low 1-year CDR (35.3%) had a normal CDR at year 2. Importantly, compared to patients with a low CDR at both post-transplant years, a significantly better graft survival was observed in these patients ($P = 0.013$).

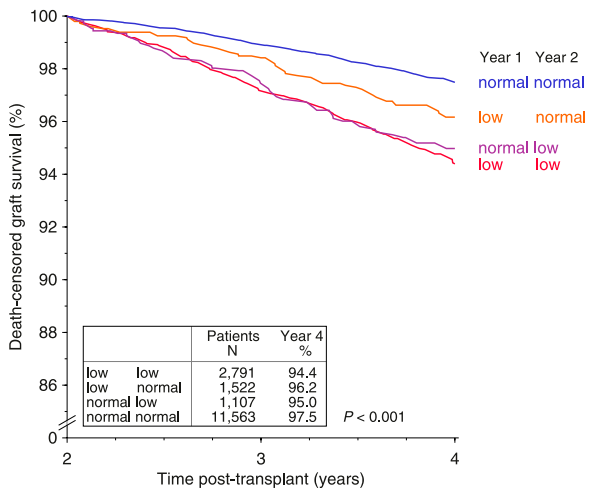


FIGURE 4 | Combinatory analysis of the impact of low (<1.05) and normal (≥1.05) tacrolimus trough level/dose ratios (CDRs, day*10^{-3}/L) at post-transplant years 1 and 2 on death-censored graft survival during years three and four post-transplant.

Factors With an Influence on CDR Levels

As depicted in **Figure 5**, Black and female recipients showed a higher odds of having a low CDR below 1.05 at post-transplant year 1, whereas higher recipient age and treatment for diabetes were associated with a lower odds of a low 1-year CDR. Patients who were on diltiazem at year 1 showed a significantly lower incidence of a low 1-year CDR of <1.05 compared to patients not receiving diltiazem (15.5% vs. 25.7%; $P < 0.001$; **Supplementary Figure S2**). Moreover, a significant association was observed with steroid dosage: patients on a higher 1-year steroid dose (>5 mg/day) had worse CDR values (**Supplementary Figure S3**, $P < 0.001$). This observation corresponds with the results presented in **Figure 4** when steroid dosages at 1 and 2 years post-transplant are taken into account. While the *low/low* and *normal/normal* groups showed average reductions in steroid dose during the second post-transplant year (−6.8% and −5.6%, respectively), the *normal/low* group, which experienced worsening CDR values, demonstrated a slight increase in steroid dose (+1.0%). In contrast, the *low/normal* group, which showed improved CDR values, exhibited the largest reduction in steroid dose during the second year (−9.7%). Consistent with these findings, renal outcomes also differed across groups. At year 3, median eGFR had declined in the *low/low* group (53 → 50 mL/min/1.73 m^2), the *normal/normal* group (57 → 56 mL/min/1.73 m^2), and the *normal/low* group (57 → 54 mL/min/1.73 m^2). In contrast, the *low/normal* group maintained stable renal function, with mean eGFR values of 58 mL/min/1.73 m^2 at both years 2 and 3.

To analyze whether a low CDR at year 1 has a genetic background, a subgroup of 1,257 patients were typed for the *CYP3A4* and *CYP3A5* genes. Expressor genotypes of the CYP3A4 enzyme *CYP3A4* without *22 and of the CYP3A5 enzyme *CYP3A5* with *1A were present in 90.4% and 14.6% of patients, respectively; in both cases without a statistically significant deviation from the Hardy-Weinberg equilibrium (CYP3A4, $P = 0.092$; CYP3A5, $P = 0.67$; **Supplementary Table S1**). *CYP3A5*1A* expressor genotypes were significantly associated with a low CDR of <1.05 at year 1 (phi coefficient $\phi = 0.42$, $P < 0.001$). In contrast, the association of the CYP3A4 expressor genotypes (*CYP3A4* without *22) with low CDR was statistically significant but much weaker ($\phi = 0.08$, $P = 0.005$). Importantly, while the 1-year CDR values were significantly lower in patients carrying the CYP3A4 and CYP3A5 expressor genotypes than in patients without these genotypes (**Figure 6**; $P < 0.001$ for both), tacrolimus trough levels at year 1 did not differ significantly between patients with and without the expressor genotypes of these enzymes (CYP3A4: 7.20 [6.00–9.00] vs. 7.45 [6.05–9.00] ng/mL, $P = 0.59$: CYP3A5: 7.20 [6.00–9.10] vs. 7.40 [5.90–9.00] ng/mL, $P = 0.84$). In the multivariable logistic regression, including the same covariates, that were significant in the overall cohort, the *CYP3A5*1A* genotype was associated with an 8.1-fold higher odds of having a low CDR of <1.05 (95% CI: 4.8–13.6, $P < 0.001$), whereas *CYP3A4*22* was not significantly associated with low

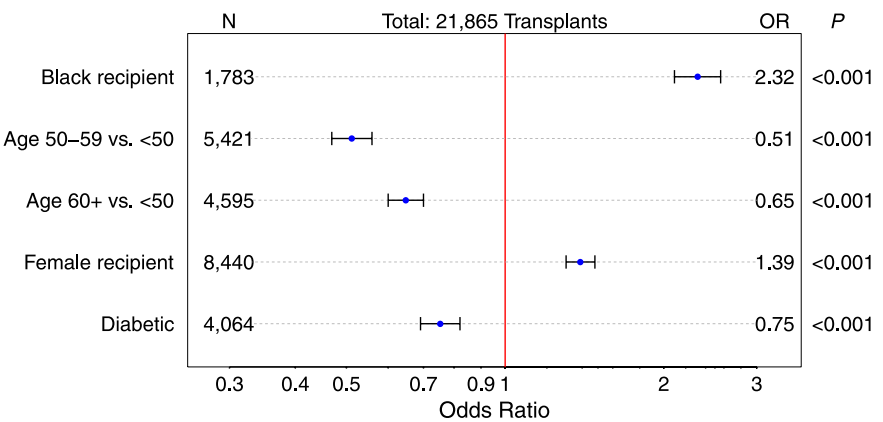


FIGURE 5 | Odds ratios (OR) with 95% confidence interval of variables with significant influence on a low 1-year CDR below 1.05 days*10^{-3}/L in multivariable logistic regression analysis (exact 95%-confidence intervals and results of univariable logistic regressions are presented in **Supplementary Table S5**).

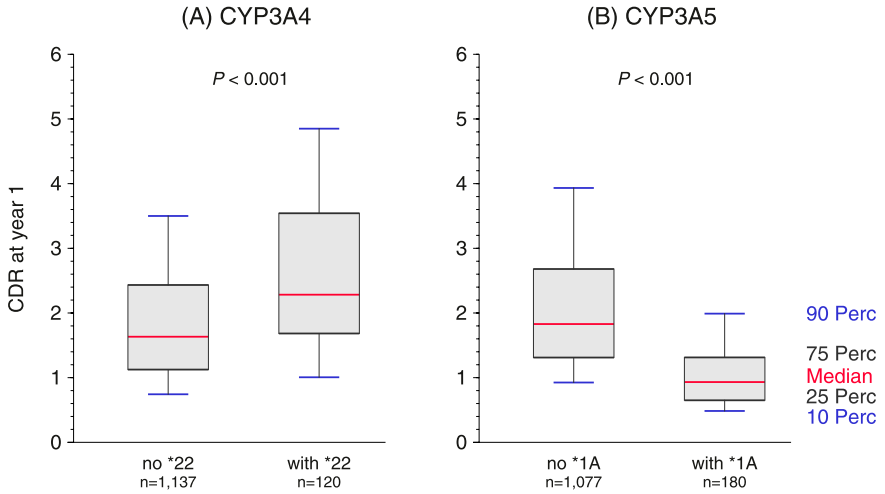


FIGURE 6 | Association of tacrolimus concentration/dose ratio (CDR) at post-transplant year 1 with genetic polymorphisms in **(A)** CYP3A4 and **(B)** CYP3A5. Each panel illustrates the CDR distribution according to genotype to show the individual effects of each variant.

CDR ($P = 0.44$, **Supplementary Table S5**). Presumably due to the low number of patients with the *CYP3A5*1A* genotypes (n = 180) and a low number of patients with death-censored graft failure in the typed subgroup (n = 36), the influence of the *CYP3A5*1A* genotype on death-censored graft failure did not reach statistical significance (HR = 1.60, 95% CI 0.72–3.53, $P = 0.25$).

DISCUSSION

In this largest study conducted so far to analyze the association between tacrolimus CDR and kidney transplant outcomes, we found a significant association between low CDR values at post-transplant year 1 and graft as well as patient survival during years 2 and 3. The hazard of all-cause and death-censored graft failure increased gradually at CDR values below 1.05, with a more than two-fold increased hazard at a very low CDR of <0.58. A CDR value below 1.05 was found in as many as 25.2% of patients with a functioning graft at year 1. Analysis of longitudinal CDR changes revealed that normalization of low CDR from year 1 to year 2 improved graft survival significantly, highlighting the potential for continuous CDR monitoring as a practical tool to optimize immunosuppression. Efforts to normalize CDR by addition of diltiazem and reduction of steroid dosing might be beneficial even in patients with normal serum creatinine (<130 μmol/L), corresponding to eGFR >60 mL/min/1.73 m^2. Low CDR was also associated with increased patient mortality; however, the effect was slightly less pronounced with increasingly significant association at values below 0.78. Importantly, the strong association between low CDR and higher death-censored graft failure was independent of recipient sex, recipient age, and donor relationship and was present also in patients with good graft function and a normal 1-year tacrolimus trough level.

As in our study, high tacrolimus metabolizers were defined as individuals with a low CDR of <1.05 in three other studies [7, 21, 22]. These findings, along with the incremental impact of post-transplant CDR on graft and patient survival and its strong effect in all important patient subpopulations, highlight the strength of this parameter in predicting kidney transplant outcomes.

Prior studies investigating the association between *CYP3A5* genotypes and clinical outcomes showed conflicting results. While some studies reported no association between genotypes and clinical outcomes [23, 24], others reported an association between expressors and poor clinical outcomes, including significantly higher incidence of delayed graft function and biopsy-proven rejections [25] and higher death-censored and all cause graft failure in Black kidney transplant recipients [26] and significantly higher frequency of *de novo* donor-specific HLA antibody development and antibody-mediated rejection [27]. Therefore, the Clinical Pharmacogenetics Implementation Consortium Guidelines made a strong recommendation to use a higher starting dose than the standard tacrolimus dose in CYP3A5 expressors [15]. On the other hand, this guideline concluded that more data are needed to understand whether genotype-based dosing will affect the clinical outcomes. Our study provides a critical element of the missing data by reporting a significant association between a low CDR and increased patient mortality, which was particularly attributable to deaths from infection. Also, the absolute risk difference for hospitalization due to infection during the second post-transplant year was 2.3% indicating the clinical relevance of the severity of infections in kidney transplant recipients. This finding suggests that patients with low CDR, potentially due to higher exposure to tacrolimus metabolites, face increased morbidity, supporting the need for CDR normalization to mitigate these outcomes. Despite having a normal tacrolimus trough level, patients with a low CDR are at an increased hazard of infection-related death due to increased tacrolimus exposure. However, not unexpectedly, an association of low CDR with mortality due to malignancy or cardiovascular events during years 2 and 3 post-transplant could

not be demonstrated as tacrolimus use is associated mainly with an increased incidence of tumors with lower mortality rates, such as skin cancer and Kaposi's sarcoma [28], and tacrolimus-related metabolic complications, such as hypertension, dyslipidemia, and diabetes mellitus, increase mortality in later phases after transplantation [29]. Schütte-Nütgen et al. observed a similar, but not significant trend between a low CDR below 1.05 and patient mortality [21]. In contrast, Bartlett et al. found a higher mortality rate in patients with a high CDR, most probably due to the 2.04 CDR cut-off used in this study being too high [30]. In our study, CDR values significantly associated with mortality were with <0.78 much lower.

In line with previous studies, also in our large cohort, Black and female recipients had higher odds of having a low 1-year CDR (**Figure 5**), most probably due to the previously reported higher frequency of certain cytochrome enzyme genes in Black patients and increased cytochrome enzyme activity in females [31–33]. These findings suggest potential disparities in CDR levels related to ancestry and sex, underscoring the need for tailored approaches to improve equity in transplant care. An interaction between diltiazem, a CYP450 inhibitor, and tacrolimus has also been reported [34, 35], Our finding on the reduced incidence of low CDR in patients on diltiazem is consistent with its CYP450 inhibitory properties that can lead to decreased tacrolimus clearance and suggests inclusion of diltiazem to the patient's drug protocol as a potential therapeutic strategy to mitigate high metabolism. No significant interaction was observed between CDR values and transplant number.

In a subgroup analysis of 1,257 patients, we obtained evidence that *CYP3A5*1A* genotypes are associated with higher odds of having a low CDR, whereas the expressor genotypes of the other cytochrome enzyme CYP3A4, namely *CYP3A4* without *22, were only weakly associated with low CDR. *CYP3A5* genotyping has proven effective in guiding tacrolimus dosing with CYP3A5 expressors requiring approximately 50% higher doses to reach the target therapeutic range compared to non-expressors [36]. These findings altogether indicate that recipients testing for the *CYP3A5*1A* polymorphism can identify patients at increased risk of having low CDR and it can be hypothesized that these patients would benefit from steroid dose tapering and the addition of diltiazem into their treatment regimen.

Conversely, the significantly lower odds of elderly patients having a low CDR at year 1 could be due to a decrease in the activity of enzymes involved in the drug's distribution, metabolism, excretion, and clearance at higher age [37]. The association of diabetes mellitus with low CDR at year 1 could be explained by the gastric delay associated with diabetic neuropathy [38, 39].

Although the 1-year CDR values were significantly lower in patients carrying the CYP3A4 and CYP3A5 expressor genotypes than patients without these genotypes, tacrolimus trough levels at year 1 did not differ significantly between patients with and without the expressor genotypes, indicating that the adjustment of tacrolimus dose to its trough level is an effectively practiced standard of care. Despite the strong impact of low CDR on the outcomes and despite the strong association of the *CYP3A5*1A* genotypes with low CDR in our study and a previous meta-analysis [40], the influence of this genotype on death-censored graft failure did not reach statistical significance, most probably due to the low percentage of patients with this genotype and low number of patients with graft loss in our genotyped subgroup.

The main strength of our study is the high number of recipients of deceased as well living donor kidney transplants from different ancestry backgrounds, across 129 different transplant centers in 31 countries, which minimizes bias from single-center practices, and provides a robust foundation for a statistically validated analysis of the CDR effect on the hard outcome measures "graft loss" and "patient mortality." While variability in co-medications could influence CDR, our multivariable regression analyses adjusted for co-medications and additional subgroup analyses in patients with a high and low steroid dose confirm the consistent association of low CDR with adverse outcomes. As a retrospective registry analysis, however, we could only identify associations but not causality because biopsy results, that would allow an analysis of the specific causes of allograft failure, were not captured in CTS due to high variation of results reported by different pathologists [41]. Therefore, future randomized controlled trials are warranted to confirm the association between tacrolimus CDR normalization and improved graft and patient survival, as well as to assess the contribution of tacrolimus metabolites to toxicity in patients with low CDR. However, low CDR was linked with BK virus infection and CNI toxicity in previous studies [7] so that a causal contribution of these factors to increased graft loss rates observed in our patients with low CDR is biologically plausible. CDR values prior to year 1 are not available in CTS which means that any clinically significant variation of CDR level during the first year was not captured. However, in all important patient subgroups, a progressively increasing hazard of graft failure was observed with gradually decreasing CDR values, underlining the robustness of this parameter in predicting the clinical outcomes. Moreover, the analyzed 1- and 2-year values can be considered as the best choice because they are obtained in a stable phase of medication after transplantation. Lastly, analyses were not adjusted for post-transplant donor-specific HLA antibodies (DSA), as routine DSA monitoring was not yet standard in the majority of transplant centers during the study period. Pretransplant panel reactive HLA antibodies and HLA mismatches were included, which allowed partial coverage of alloantibody effects.

The combined analysis of the impact of 1- and 2-year CDR values on death-censored graft survival revealed the important finding that improvement of a low 1-year CDR to a normal value at year 2 results in improved graft survival, highlighting the importance of continuous monitoring and actively normalizing CDR values throughout the entire post-transplant period. Our finding that approximately two-third of patients with a low 1-year CDR still had a low CDR at year 2 indicates the substantial potential for improving the clinical outcomes in kidney transplantation by considering CDR. This stratification by CDR trajectories further underscored the clinical relevance of CDR normalization. Patients with persistently low CDR values

(low/low), persistently normal values (normal/normal), or declining values (normal/low) all showed a decrease in median eGFR between year 2 and year 3 (e.g., 53 → 50, 57 → 56, and 57 → 54 mL/min/1.73 m^2, respectively). By contrast, patients who shifted from low to normal CDR values (low/normal) maintained stable renal function, with mean eGFR remaining unchanged at 52 mL/min/1.73 m^2. These findings suggest that normalization of initially low CDR values is not associated with nephrotoxicity but may instead contribute to preservation of renal function.

In our cohort, changes in measured CDR over time were observed and appeared to correspond with modifiable clinical factors. Specifically, co-medication with diltiazem and reductions in steroid dosing were associated with higher CDR values, whereas patients with increasing steroid doses showed declining CDR values (**Figure 4**; **Supplementary Figures S2–S3**). Thus, while the underlying CYP3A genotype is fixed, the measured CDR captures both genetic and modifiable influences, and its normalization can reflect clinically actionable changes that are associated with improved graft survival.

CONCLUSION

Findings of our large-scale study strongly indicate that monitoring of tacrolimus CDR, as a simple and cost-effective tool, can assist physicians in their daily clinical routine to identify tacrolimus-treated kidney transplant recipients at risk of inferior outcomes, even if they have good graft function and their tacrolimus trough levels are within the therapeutic range. Genetic analysis of cytochrome enzymes could be useful in patients with a low CDR to find out whether the reason for the increased tacrolimus metabolism has a genetic background.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The raw data are available upon request to the Collaborative Transplant Study in accordance with the consents of the patients and the participating transplant centers and registries. Requests to access these datasets should be directed to csusal@ku.edu.tr.

ETHICS STATEMENT

The Collaborative Transplant Study (CTS) involving human participants was reviewed and approved by the Ethics Committee of the Medical Faculty of Heidelberg University (No. 083/2005) and conducted in accordance with the principles of the Declaration of Helsinki in its currently valid version. The participating transplant centers certify that all patients provided written informed consent for the transfer of their data to the CTS.

AUTHOR CONTRIBUTIONS

CS contributed to research design, manuscript writing, and research execution. BD was involved in data analysis, research design, and manuscript writing. ED participated in manuscript writing and research execution. WI contributed to manuscript writing. MA was involved in research design, manuscript writing, and provided genetic testing.

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CONFLICT OF INTEREST

The authors declare that the research 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) declare that no Generative AI was used in the creation of this manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.15207/full#supplementary-material

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ORIGINAL RESEARCH
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Evolving Trends in Organ Donation and Transplantation Rates Across Muslim Majority Countries

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Muslim-majority countries differ in socio-cultural behavior and economic development but share a similar high burden of organ failure. Due to this heterogeneity, mapping organ donation and transplantation activity is of interest for future healthcare provision. Data was analyzed for 50 Muslim-majority countries (defined as Muslims comprising >50% of the population). Organ donation/transplantation rates were obtained from global registries between 2013–2023. Supplementary socio-economic and health data were obtained from open-source data repositories. Muslim-majority countries population increased from 1.53 billion to 1.88 billion between 2013–2023. Organ donation/transplant activity was only reported for 21/50 countries. Most organ donations came from living people rather than deceased donors (resulting in kidney and liver transplantation being the most common procedures). Other transplant activity rates were low. Poisson regression analyses identified multiple socioeconomic indicators to be associated with deceased- or living-donor activity, while negative binomial analyses comparing Muslim-majority to other countries within the region showed Muslim countries had lower deceased donation rates. Our study shows access to transplantation is lacking in many Muslim-majority countries. While socio-economic factors play a role, other challenges like religious and/or cultural barriers must be appreciated. With such global heterogeneity, bespoke country-specific interventions are warranted to improve transplantation opportunities in Muslim-majority countries.

Keywords: Islam, Muslims, organ donation, transplantation, resource

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Abbreviations: GODT, Global Observatory for Donation and Transplantation; IRoDaT, International Registry on Organ Donation and Transplantation; WHO, World Health Organization; IMF, International Monetary Fund; CKD, chronic kidney disease; GDP, Gross Domestic Product; RTA, road traffic accidents; DBD, donation after brain death; DCD, donation after circulatory death.

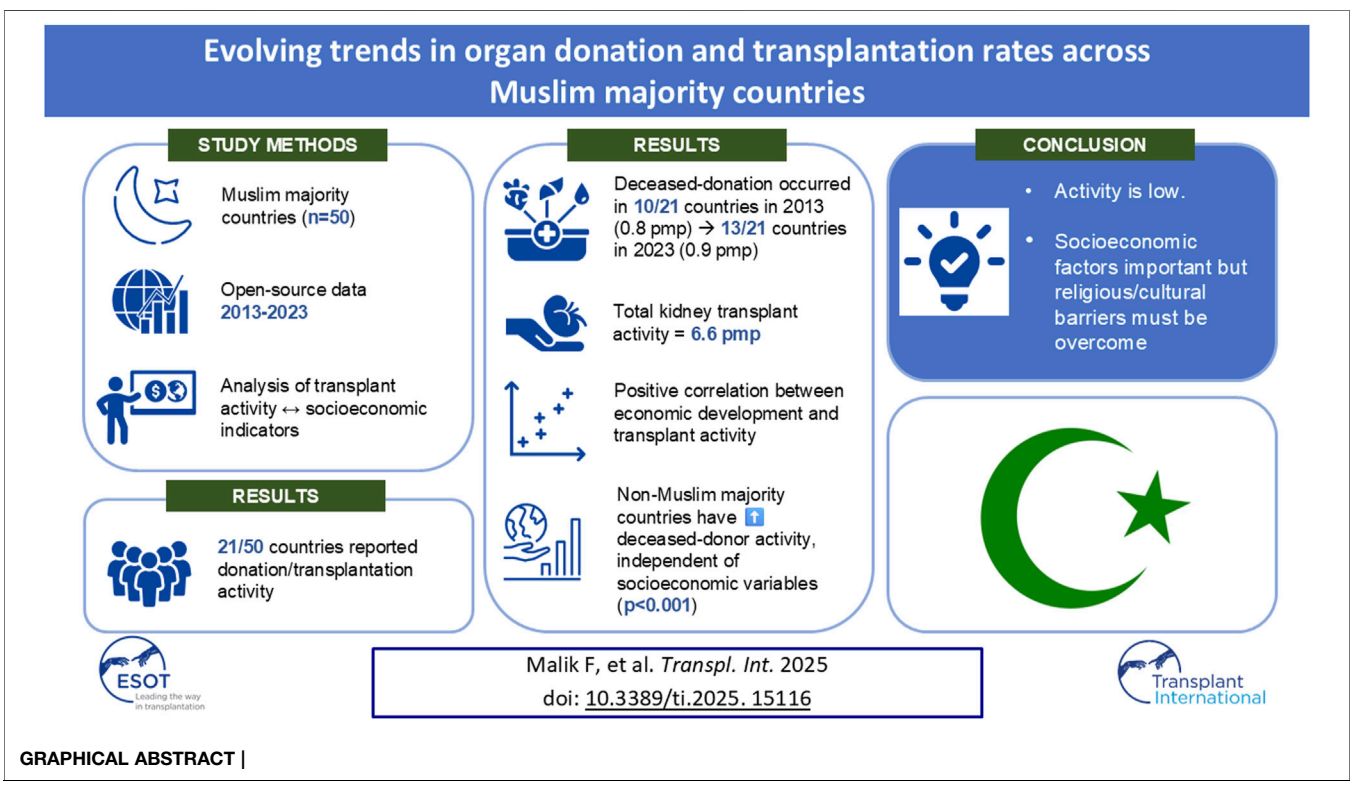
INTRODUCTION

Organ donation and transplantation are critical components of modern healthcare systems, offering life-enhancing or life-saving solutions to people suffering from end-stage organ failure. However, accessibility to transplantation for organ failure patients is not ubiquitous across the world [1]. There is significant heterogeneity in observed rates of organ donation and transplantation both within [2] and between countries [1], shaped by multi-factorial variables that include (but are not limited to) socio-cultural influences, resource constraints, necessary infrastructure and economic development. Such inequity leads to major health disparities and sub-optimal survival outcomes for people living with end-stage organ failure across the globe.

In Muslim-majority countries, defined as those where Islam is the predominant religion and plays a central role in shaping societal norms, the approach to organ donation is particularly complex. While there is increasing acceptance of the merits of organ donation to facilitate transplantation in many Muslim-majority countries, with theological and religious scholarly rulings in support, there remains a diverse range of practices and beliefs [3]. In parallel, despite religious unity, Muslim-majority countries represent a diverse and heterogenous group of countries scattered across the globe with varying degrees of socio-economic development and cultural legacies. Many Muslim-majority countries are recognized as low or middle-income countries (LMIC), and the burden of end-stage kidney disease [4], liver disease [5], heart failure [6] and lung failure [7] in such countries is well described. The requirement for transplantation is likely to be high in these countries and improving equity of access is acknowledged as an important policy innovation for countries [1]. However, developing targeted policy innovations requires an understanding of the current landscape and an exploration of any inter-country variation that probes heterogenous activity data.

Despite a high requirement for solid organ transplantation due to the underlying burden of end-stage organ disease, it is unclear what level of organ donation and transplantation activity exists in Muslim-majority countries. A previous narrative review reported some granular data regarding organ donation models across the 57 member states of The Organization of Islamic Cooperation, with limited analyses to explore the data further [8]. This is important to understand, as efforts to mitigate disparity of access must be undertaken in the context of current landscape realities. Distinguishing religious obstacles from socio-economic capacity as barriers to facilitate organ donation and transplantation infrastructure is critical. To date, no study has explored the evolving trends of organ donation and transplantation activity across Muslim-majority countries or studied variables that may impact upon such activity. As a sizable population cohort, understanding the scale of organ donation and transplantation activity among Muslim majority countries is important from a global healthcare perspective.

In this article, we aim to explore evolving trends in organ donation and transplantation across Muslim-majority countries over the last decade, providing a snapshot of activity across these heterogenous countries. By analyzing organ donation and



GRAPHICAL ABSTRACT |

transplant rates alongside key socio-economic indicators, this study aims to understand how Muslim-majority countries may successfully navigate organ donation and transplantation challenges.

MATERIALS AND METHODS

Country Selection

For this analysis, Muslim-majority countries were identified based on the proportion of the national population practicing Islam. For inclusion in this study, we selected those countries where more than 50% of the population is identified as Muslim, based on the most recent data available from the Pew Research Centre or the United Nations Demographic and Social Statistics report (see data sources and links below). This threshold ensured that any selected country possessed a predominantly Islamic cultural and social context, essential for examining organ donation and transplantation activity influenced by religious or societal norms. Countries were excluded if current data on religious composition was unavailable or deemed unreliable.

Data Sources

This study relied exclusively on freely available and publicly accessible data sources to assess organ donation and transplantation activity in Muslim-majority countries. Country profile information (including religious composition) was obtained from the Pew Research Centre [9] and the United Nations Demographic and Social Statistics report [10].

Organ donation and transplantation rates were obtained from the Global Observatory for Donation and Transplantation (GODT) for the latest available year (2023 in most cases) [11]. We referred to the International Registry on Organ Donation and Transplantation (IRoDaT) [12] if relevant data did not exist in the GODT.

Supplementary socio-economic and health data were obtained from data repositories including World Health Organization (WHO) [13], International Monetary Fund (IMF) [14] and the World Bank [15]. Chronic kidney disease (CKD) data was obtained from the Global Burden of Disease Study 2021 [16].

Variables of Interest

GODT and IRoDaT data were used to obtain deceased and living donor activity rates with corresponding solid organ transplantation activity data. Organ donation and transplantation activity was reported per million population (pmp). Other data sources were used for collating socio-economic variables which included population (in millions), Gross Domestic Product (GDP; *per capita* and per person), health expenditure (% of GDP), road traffic accidents (RTA) per 100,000 population, literacy rate among adults (%), life expectancy (in years), unemployment rate (%) and world economy rank.

Statistical Analysis

For categorical variables, chi-squared tests were employed to assess associations between different categories, such as country-specific donation rates or organ transplantation activity. For continuous variables, the Mann-Whitney U test was utilized to compare distributions, especially in cases where the data were not normally distributed or the sample sizes were unequal. To gain a comprehensive understanding of the data, several descriptive parameters were calculated, including the mean, median, standard deviation, and range, which provided a detailed overview of the central tendencies and variability of the variables in question.

Additionally, we performed multivariable Poisson regression or, for data with overdispersion, a negative binomial analysis to explore independent variables such as socio-economic factors and/or Muslim-majority status that may potentially confound the outcome variable (e.g., deceased or living donor rates). For the latter, we restricted the analyses to specific regions based upon World Bank classification that represented a variety of countries but encompassed most Muslim-majority countries. These regions were South Asia, Central Asia, Middle East, North Africa, Sub-Saharan Africa and East Asia, which included 47/50 Muslim-majority countries. Poisson or negative binomial results were reported as incidence rate ratios (IRR) with 95% confidence intervals (CI). All statistical analyses were carried out using R version 4.4.2.

RESULTS

Country Profiles

In total, 50 countries were identified as having a Muslim majority with 47 located in Asia or Africa (see **Figure 1**). Data completeness was excellent for socio-economic variables; population, GDP, life expectancy, world economic rank (100.0%), health expenditure (93.9%), literacy rate (93.9%), unemployment rate (98.0%) and RTA mortality rate (98.0%). However, there was significant degree of missingness in the organ donation and transplantation activity data, with a range from 38.8% (total kidney transplant activity) to 30.6% (simultaneous pancreas-kidney kidney transplant activity).

The global Muslim population increased from 1.53 billion to 1.88 billion between 2013 and 2023 (representing a 22.9% increase over the decade). With an estimated global population of 8 billion people in 2023 according to the United Nations [17], this represents 23.5% of the world population. A summary of individual country profiles is shown in **Table 1**. From the 50 Muslim-majority countries, 49 were categorized by their World Development Indicator defined by the World Bank (no Palestinian data recorded). Compared to non-Muslim majority countries, Muslim-majority countries were disproportionately more likely to be classed in a category other than high-income (see **Figure 2**).

Organ Donation and Transplantation Activity

Organ donation and transplant activity data was reported from 21 countries, but none from 29 countries. Data for the latest available year is summarized in **Figure 3**. Total organ donor

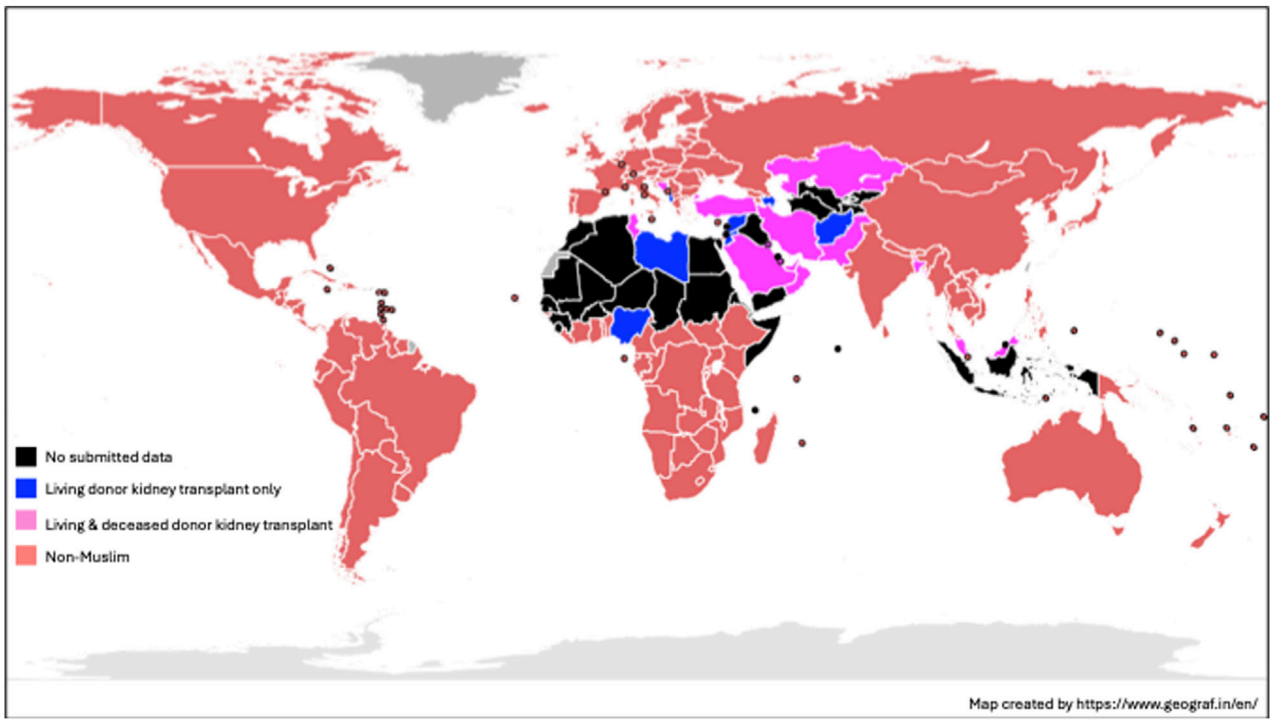


FIGURE 1 | World map of Muslim-majority countries and kidney transplant activity based upon 2023 data.

activity increased from 12,557 in 2013 (8.2 pmp) to 15,950 in 2023 (8.5 pmp). Deceased donation occurred in 10/21 and 13/21 countries in 2013 and 2023 respectively. Total actual deceased donors were 1,173 in 2013 (0.8 pmp) and 1,681 in 2023 (0.9 pmp), representing a 43.3% increase over the decade but only a marginal increase per million population in the context of population growth. This increase was almost exclusively in the context of donation after brain death (DBD), with only one country (Bosnia and Herzegovina) reporting donation after circulatory death (DCD) activity. A larger rise was seen in living donor activity. For example, living kidney transplant activity increased by 17.1% over the decade from 8,841 in 2013 (representing 82.0% of total kidney transplant activity at that time, n = 10,781) to 10,356 in 2023 (representing 83.2% of total kidney transplant activity at that time, n = 12,440). However, per million population this represents 5.8 pmp and 5.5 pmp living donor rates in 2013 and 2023 respectively, indicating stagnant rates despite population growth. Liver transplant activity increased by 53.9% from 2,543 in 2013 (65.6% of activity being derived from living donors) to 3,913 in 2023 (68.9% of activity being derived from living donors), equating to 1.7 pmp and 2.1 pmp respectively.

The observed rise in deceased donor rates only led to a marginal 7.4% increase in actual deceased donor kidney transplant rates from 1,940 in 2013 to 2,084 in 2023 (1.3 pmp and 1.1 pmp respectively). There was a higher 33.9% increase in actual deceased donor liver transplant rates from 901 in 2013 to 1,206 in 2023 (0.6 pmp and 0.6 pmp respectively). Transplant rates using other solid organs were low, reflective of such activity being derived from deceased donors only. Rates for heart/lung transplantation in 2013 and 2023 were 243 (0.2 pmp) and 329 (0.2 pmp) respectively (reported in 7 countries only), with a smaller number of pancreas transplants in 2013 (n = 37, <0.1 pmp)) and even lower numbers (n = 24, <0.1 pmp) in 2023 having been reported from 3 to 5 countries respectively). The lowest rates were reported for small bowel transplantation; just 3 countries performing a total of 14 in 2013 and 13 in 2023 (both <0.1 pmp). For the latest year available (relying upon registry data records only), countries that reported any non-kidney or liver-related transplant activity were as follows: heart/lung transplantation (Iran, Kazakhstan, Kuwait, Saudi Arabia, Tunisia, Turkey and the United Arab Emirates), pancreas transplantation (Iran, Kuwait, Saudi Arabia, Turkey and the United Arab Emirates) and small bowel transplantation (Iran, Saudi Arabia and Turkey).

Burden of Kidney Failure and Kidney Transplantation Activity

As kidney transplantation is the commonest solid organ transplant procedure, with the best cost effectiveness argument in the context of end-stage kidney failure, we explored the burden of chronic and end-stage kidney disease and its association with countries profile. Reviewing raw data from the Global Burden of Disease study 2021 [16], prevalence and death rates from chronic kidney disease were 134,048,251 and 207,102 respectively across Muslim-majority countries (see **Supplementary Table S1**). For the latest year

TABLE 1 | Muslim-majority country profiles.

Country	Population in 2023 (m)	GDP (*per capita*)	GDP (*per capita*) PPP	Health expenditure (% of GDP)	RTA (mortality per 100,000 population)	Literacy rate, adult total (%)	Life expectancy (years)	Unemployment total (%)	World economy rank
Afghanistan	42.2	352.6	2,173	21.83	24.1	37	63	14.4	111
Albania	2.7	8,367.80	20,018	7.27	10.8	99	77	11.6	124
Algeria	45.6	5,260.20	16,900	5.53	18.3	81	77	11.8	40
Azerbaijan	10.1	7,155.10	23,660	4.7	17.2	100	73	5.6	71
Bahrain	1.5	29,084.30	63,497	4.27	8.1	98	79	1.2	99
Bangladesh	173.0	2,529.10	9,211	2.36	18.6	76	74	5.1	24
Bosnia and Herzegovina	3.2	8,426.10	20,431	9.56	13.7	98	75	10.4	110
Brunei Darussalam	0.5	33,430.90	86,866	2.2	3.6	98	75	5.3	137
Burkina Faso	23.3	874.1	2,712	6.38	27.8	34	60	5.3	114
Chad	18.3	719.4	2,757	5.19	26.4	27	53	1.1	131
Comoros	0.9	1,587.20	3,725	6.34	29	62	64	5.8	179
Djibouti	1.1	3,606.40	7,988	2.88	23.3	No data	63	26.3	165
Egypt	112.7	3,512.60	20,180	4.61	9.4	75	70	7.3	17
Eritrea	3.7	643.8	712	4.15	17.7	77	67	5.9	171
Gambia	2.8	843.8	3,318	3.19	22	59	63	6.5	164
Guinea	14.2	1,663.90	4,156	3.76	37.4	45	59	5.3	117
Indonesia	277.5	4,940.50	15,553	3.71	11.3	96	68	3.4	8
Iran (Islamic Republic of)	89.2	4,502.50	18,658	5.77	20.6	89	75	9.1	23
Iraq	45.5	5,512.50	14,766	5.25	21.5	86	71	15.5	46
Jordan	11.3	4,482.10	No data	7.29	13.6	95	74	17.9	94
Kazakhstan	19.9	13,136.60	39,463	3.92	12.2	100	74	4.8	39
Kosovo	1.8	5,943.10	15,864	No data	No data	No data	80	No data	153
Kuwait	4.3	37,533.20	50,933	5.78	9.2	96	80	2.1	72
Kyrgyzstan	7.1	1,969.90	7,279	5.44	13.3	100	72	4	128
Lebanon	5.4	3,823.90	12,453	10.06	9.7	93	74	11.6	108
Libyan Arab Jamahiriya	6.9	7,330.00	14,781	4.02	34	No data	72	18.7	98
Malaysia	34.3	11,648.70	38,693	4.38	13.9	96	76	3.9	29
Maldives	0.5	12,667.40	32,541	10.03	1.3	98	81	4.1	158
Mali	23.3	897.4	2,762	4.47	20.2	31	59	3	115
Mauritania	4.9	2,149.40	7,874	4.12	9.5	67	65	10.5	144
Morocco	37.8	3,672.10	10,180	5.74	18.6	77	75	9.1	57
Niger	27.2	618.3	1,824	5.81	24.9	38	62	0.6	126
Nigeria	223.8	1,621.10	6,366	4.08	17.2	63	54	3.1	27
Oman	4.6	23,295.30	41,558	4.37	11	97	74	1.5	77
Pakistan	240.5	1,407.00	6,530	2.91	11.9	58	66	5.5	26
Palestine	5.2	3,367.6	3,372	No data	5	98	73	24.4	148
Qatar	2.7	87,480.40	111,789	2.89	7.3	98	82	0.1	61
Saudi Arabia	36.9	28,895.00	61,932	5.97	18.5	98	78	4.9	18
Senegal	17.8	1,746.00	4,786	4.35	20.8	58	68	2.9	102
Sierra Leone	8.8	433.4	3,359	8.55	13.8	49	60	3.2	151
Somalia	18.1	643.8	1,780		20.2	54	56	19	150
Sudan	48.1	2,272.50	3,158	2.84	19.6	61	66	11.4	95
Syrian Arab Republic	23.2	421.1	753	3.05	29.9	94	72	13.5	92
Tajikistan	10.1	1,189.00	5,147	8.01	13.9	100	71	7	125
Tunisia	12.5	3,895.40	13,892	6.97	16.3	85	74	15.1	83
Türkiye	85.3	12,985.80	38,390	4.57	6.5	97	78	9.4	12
Turkmenistan	6.5	9,190.70	No data	5.57	8	99	69	4.1	82
United Arab Emirates	9.5	52,976.80	74,713	5.31	5.9	98	79	2.7	38
Uzbekistan	36.4	2,496.10	10,992	7.74	9.3	100	72	4.5	56
Yemen	34.4	701.7	2,012	4.25	29.8	54	64	17.2	112

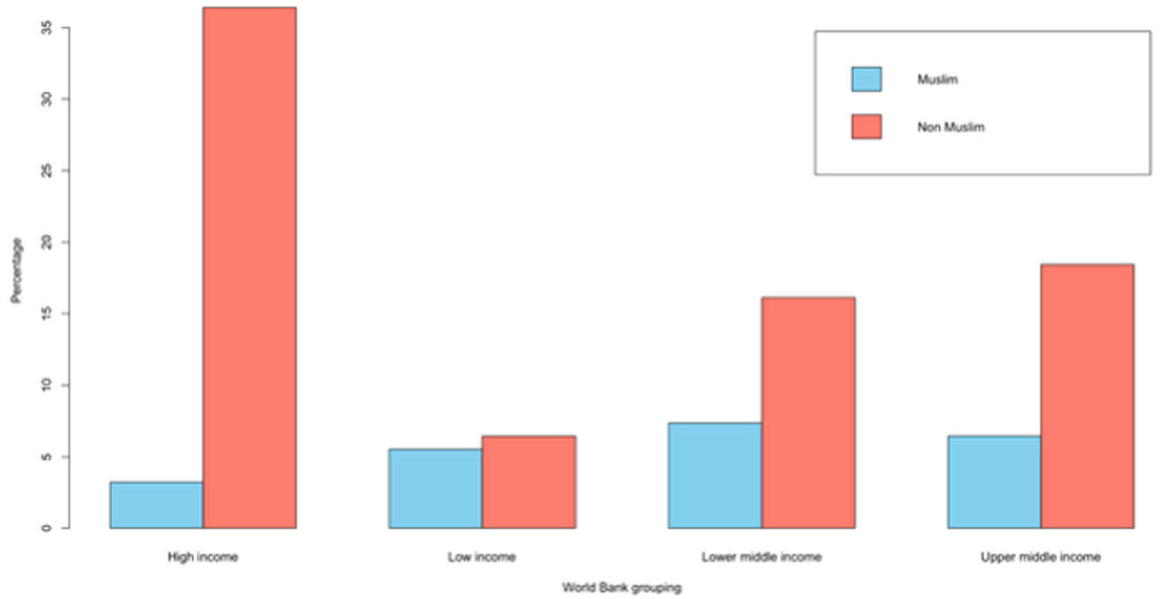


FIGURE 2 | Living and deceased donor activity across Muslim-majority countries in 2023.

Country	Total LD activity 2023	Total utilised DD 2023	Country	Total LD activity 2023	Total utilised DD 2023
Afghanistan	459	0	Libyan Arab Jamahiriya	45	0
Albania	26	0	Malaysia	199	43
Algeria			Maldives		
Azerbaijan	41	0	Mali		
Bahrain			Mauritania		
Bangladesh	317	1	Morocco		
Bosnia and Herzegovina	10	4	Niger		
Brunei Darussalam			Nigeria	253	0
Burkina Faso			Oman	25	2
Chad			Pakistan	1846	2
Comoros			Palestine		
Djibouti			Qatar	51	18
Egypt			Saudi Arabia	1662	138
Eritrea			Senegal		
Gambia			Sierra Leone		
Guinea			Somalia		
Indonesia			Sudan		
Iran (Islamic Republic of)	1267	1000	Syrian Arab Republic	348	0
Iraq	1063	0	Tajikistan		
Jordan	224	0	Tunisia	46	16
Kazakhstan	217	7	Türkiye	4739	190
Kosovo			Turkmenistan		
Kuwait	80	33	United Arab Emirates	133	85
Kyrgyzstan			Uzbekistan		
Lebanon			Yemen		

FIGURE 3 | World Bank defined income category status comparing Muslim-majority versus other countries.

TABLE 2 | Poisson regression exploring socio-economic indicators and deceased or living donor activity among Muslim-majority countries.

Variable	Deceased donor activity			Living donor activity		
	IRR	95% CI	p value	IRR	95% CI	p value
Population in 2023	1.000	1.000–1.000	<0.001	1.000	1.000–1.000	<0.001
Gross domestic product (*per capita*) PPP	0.999	0.999–0.999	<0.001	1.000	1.000–1.000	<0.001
Health expenditure (% of GDP)	1.560	1.435–1.694	<0.001	1.401	1.356–1.446	<0.001
Literacy rate (% adult total)	0.922	0.883–0.959	<0.001	1.073	1.061–1.086	<0.001
Unemployment rate (%)	0.999	0.961–1.039	0.954	1.231	1.209–1.254	<0.001
Road traffic accidents (mortality per 100,000)	1.109	1.093–1.126	<0.001	0.999	0.993–1.005	0.766
Life expectancy	2.656	2.366–3.000	<0.001	0.887	0.867–0.906	<0.001
World economy rank	0.910	0.900–0.920	<0.001	0.960	0.957–0.963	<0.001

TABLE 3 | Negative binomial analysis exploring socio-economic indicators and deceased or living donor activity among Muslim-majority countries.

Variable	Deceased donor activity			Living donor activity		
	IRR	95% CI	p value	IRR	95% CI	p value
Non-Muslim majority	4.058	2.989–5.521	<0.001	1.946	0.787–4.645	0.125
Population in 2023	1.000	1.000–1.000	<0.001	1.000	1.000–1.000	0.006
Gross domestic product (*per capita*) PPP	0.999	0.999–1.000	0.981	1.000	0.999–1.000	0.329
Health expenditure (% of GDP)	1.589	1.475–1.709	<0.001	1.695	1.353–2.097	<0.001
Literacy rate (% adult total)	1.024	0.997–1.051	0.071	1.087	0.962–1.219	0.110
Unemployment rate (%)	0.891	0.858–0.925	<0.001	1.060	0.912–1.233	0.409
Road traffic accidents (mortality per 100,000)	0.965	0.948–0.982	<0.001	0.912	0.860–0.968	0.001
Life expectancy	1.473	1.380–1.580	<0.001	0.968	0.880–1.068	0.499
World economy rank	0.949	0.942–0.955	<0.001	0.958	0.946–0.971	<0.001

available, kidney transplantation activity data were reported for 21 out of 50 Muslim-majority countries as highlighted above. Total kidney transplant activity was 12,440 at 6.6 pmp (deceased and living donor transplantation activity was 2,084 and 10,356 respectively). Only 13 countries reported both deceased and living donor kidney transplant activity, with 8 exclusively using living kidney donors only.

Adjusted Regression Analyses Comparing Muslim-Majority Countries

We performed a multivariable Poisson regression analysis to explore the impact of socio-economic variables on deceased or living donor activity (see **Table 2**). Socio-economic factors were significantly associated with IRRs, with some intuitive findings such as increased activity rates for both deceased- and living-donor activity with every unit increase in health expenditure or improved world economy ranking. However, some differences were also observed. For example, every unit increase in literacy rates was associated with lower deceased donor but higher living donor activity. In contrast, every unit increase in road traffic accidents was associated with higher deceased donor but lower living donor activity.

Adjusted Regression Analyses Comparing Muslim-Majority Countries

Due to overdispersion of the data, we performed a negative binomial analysis to explore the impact of socio-economic variables in addition to Muslim-majority status on deceased or living donor activity. As seen in **Table 3**, non-Muslim-majority countries were significantly more likely to have higher deceased donor activity but there was no difference in living donor activity. This observation was independent of socio-economic variables.

DISCUSSION

In this study, we highlight the evolving trends in organ donation and transplantation activity across Muslim-majority countries and identify significant heterogeneity in access to transplantation. Most countries report no data and can be assumed to lack any regulated organ donation or transplantation activity. The remaining countries mostly have living donor activity but there has been little improvement in deceased donor activity over the last decade (which is almost exclusively donation after brain death only). There was an association between markers of advanced economic development (e.g., increased economic status, literacy rates and life expectancy) and transplantation activity. Within regions, Muslim-majority countries had less deceased donor activity but similar living donor activity independent of socio-economic factors. This data confirms that a significant gap exists in organ donation provision and access to transplantation services across the Muslim-majority world. Even among economically advanced Muslim-majority countries, organ donation activity rates (especially deceased donation) are sub-optimal in comparison to regional countries. Our data suggests religious and/or cultural barriers

are likely to be as important as economic development to boost organ donation and meet transplantation needs in Muslim-majority countries.

Previous work in this area has either reported narrative summaries without further investigation [8] or explored the issue from a regional perspective only [18, 19]. It is well documented that organ donation rates among Muslim-majority countries are sub-optimal in comparison to countries with established organ donation and transplantation programs. When compared to countries like the United Kingdom (1,513 and 960 deceased and living donors respectively), Spain (2,346 and 437 deceased and living donors respectively) and the United States of America (16,336 and 6,942 deceased and living donors respectively) [11], it is sobering to observe low organ donation activity across Muslim-majority countries for the latest GODT data available. For example, the population of the United States according to the GODT registry for 2023 was 340 million persons; therefore, despite a fifth of the Muslim majority country population at 1.88 billion, the United States of America was achieving nearly 50% more organ donor activity. Barriers to develop organ donation and transplantation activity across Muslim-majority countries relate to appropriate staffing, resources and infrastructure. This is well known to the transplantation community [20]. However, there are important socio-cultural barriers that must be acknowledged specific to Muslim-majority countries. The commonly cited barrier of religious ambiguity may be resolved within the context of Islamic jurisprudence but swaying public opinion remains a challenge. While arguments for and against the use of organ donors (especially donation after brain death) within Islam are well versed [3], an overwhelming body of Muslim scholarly opinion agrees with all forms of organ donation being compatible with Islamic belief. However, public opinion does not automatically follow adopted scholarly opinion. Even among Western Muslims living in Muslim-minority countries with established organ donation and transplantation infrastructure, attitudes to organ donation can be ambivalent with significant reservations about religious barriers despite supportive religious scholarly opinion [21]. Promising results from a cluster, randomized-controlled trial using mosque-based, religiously tailored, ethically balanced education demonstrated significant kidney donation-related knowledge gains among Muslims in the United States [22]. Whether such interventions will help in Muslim-majority countries remains to be seen and there are likely to be varying religious and cultural factors that influence organ donation practice. However, while resolving religious and cultural issues to engage public opinion is critically important to address [23], this must be tackled in parallel to the immediate challenge of creating an appropriate infrastructure to support the establishment of a national organ donor procurement, allocation and transplantation service.

It is important to note the GODT and IRoDaT registries do not fully capture all organ donation and transplantation activity. For example, several North African countries report transplantation activity which are not reported to these registries (e.g., Egypt, Morocco, Algeria) [24]. Uzbekistan also has no captured registry data but published literature confirms transplantation activity driven predominantly with living organ donors [25]. By relying upon volunteered data registries only, organ donation and transplantation activity in Muslim-majority countries will be under-reported in our analysis but is unlikely to make any material difference to the observation of a significant shortfall in transplantation activity to meet organ failure requirements. However, this reinforces the importance of robust data capture within national or regional registries to ensure complete organ donation and transplantation activity. Not only will this allow adequate governance and oversight for healthcare provides but will provide data to determine numbers of illegal transplant tourism and/or trafficking activity. Bridging the gap between supply versus demand for organs is critical to mitigate the risk from organ trade and trafficking. People living in Muslim-majority countries will be particularly susceptible due to reported sub-optimal organ donation rates. Due to these inequities and inequalities, some may risk their health out of desperation for transplantation and contribute to the exploitation of vulnerable donors. Despite the published framework from the Declaration of Istanbul setting out country requirements for the ethical donation and transplantation of organs [26], organ trafficking or human trafficking for the purpose of organ removal remains a global challenge. A high degree of organization is needed to execute such illegal transplants, with the trade embedding transplant professionals with brokers and hospitality sectors. Healthcare professionals may directly or indirectly perpetuate illegal organ transplantation with their activity and/or complicity [27]. Underlying reasons include lack of awareness, a paucity of undergraduate and postgraduate education on organ trafficking, many simply turning a blind eye and/or the lure of significant monetary gain. There is no robust international registry to provide accurate metrics of organ trafficking or trafficking in persons for the purpose of organ removal. However, what information is available to review from data collected by the United Nations Office on Drugs and Crime suggests countries in sub-Sahara Africa, south Asia and the Gulf countries (which contain most of the Muslim-majority countries) are particularly susceptible [28, 29]. Despite prohibitive legislation, illegal transplants have been reported in Muslim-majority countries such as (but not limited to) Pakistan, Egypt and Bangladesh [30, 31]. The most effective intervention to mitigate risk of illegal and unethical transplantation is for government accountability and action to achieve national self-sufficiency in organ donation and transplantation [32].

It is important that Muslim-majority countries develop organ donation systems and transplantation infrastructure that are compatible with their strengths and abilities. For example, the countries with the highest living and deceased donor activity in our study, Turkey and Iran respectively, rank high in the world economic rankings but have evolved different organ donation and transplantation practices. Turkey performed its first live donor kidney transplant in 1975, followed by the first deceased donor kidney and liver procedures in 1978 and 1988 respectively [33]. However, their more contemporary GODT data suggests that even in Turkey the transplant program is predominantly driven by living donor activity. In contrast, the first living donor kidney transplant in Iran was performed in 1967 (living donor kidney procedure), but there was a long lag period until the

first deceased donor in 2000 after legislative changes sanctioned donation after brain death [34]. Since then, Iran has made significant progress over the last two decades to build an infrastructure to promote deceased donation from brain death donors [35]. This is parallel to implementation of a novel state-regulated paid living-unrelated donor kidney transplant program in 1988 [36]. The focus on deceased donor activity (deceased organ donation rates have increased 19-fold from 2003 to 2015) has resulted in liver, pancreas, heart, and lung transplantation programs also starting in Iran and more kidney transplants are currently from deceased donors rather than living [35]. These contrasting experiences have important implications for Muslim-majority countries which may have living organ donor activity but fledgling deceased organ donor models. As per our data, deceased donation activity lags living donor activity. The example from Iran demonstrates the importance of government support, religious scholarly approval and socio-cultural confidence for establishing a national organ procurement infrastructure to maximize use of deceased organ donors. While some countries like Saudi Arabia have established such foundations [37], with increasing deceased organ donation as a result, other countries like Pakistan are lagging behind due to the lack of a collaborative mandate to establish an effective national deceased organ procurement system [38]. Investment is mandatory to support staffing, resource and infrastructure for critical services facilitating organ procurement, allocation, distribution and monitoring. While this is likely to be a significant financial undertaking, the direct and indirect cost savings are likely to be significant [39]. Stakeholder engagement to establish country-specific protocols and guidelines is vital to encourage good clinical practice and the development of efficient transplant services. This is particularly true for the development of deceased donor models. While this has the best potential to expand the donor pool, further work is necessary to encourage wider societal acceptance. Innovative methods incorporating financial incentives have been used in some Muslim-majority countries. For example, Iran can justifiably claim some success with its experience of its state-regulated, paid, unrelated living kidney donors [36]. Saudi Arabia has also nurtured its fledgling deceased donor program with monetary compensation to the deceased donor's family (50,000 riyals) and 50% discount for travel on Saudi Airlines [19]. Columb et al. have argued for a re-conceptualization of organ commercialisation, with an important distinction to be made between "trade" and "trafficking" [40]. Finally, education for both healthcare professionals and the wider public through various platforms is key to normalize organ donation consideration as a routine aspect of end-of-life care.

The strength of our analysis is the inclusion of Muslim-majority countries from across the globe for an international perspective. Including socio-economic variables allows a more probing analysis of factors that have an association with deceased or living donor activity. Limitations of our study include that data may not be totally accurate. There was significant missing data in both GODT and IRoDaT registries regarding organ donation and transplantation activity. While for some countries it likely reflects the absence of any official transplant practice, for other countries no data was available despite published evidence of transplantation activity (e.g., Indonesia, Egypt). Correlation analyses do not imply causation and just because two variables move together it does not imply one causes the other. We did not explore the political, cultural, and/or social environment of each Muslim-majority country which are likely to be significant confounding factors. For example, factors like religious observance, the role of Islam in governance, and the diversity of Muslim practices (e.g., Sunni versus Shia belief) are influential variables in the socio-economic and cultural development of Muslim-majority countries but exploring this was beyond the scope of this work.

To conclude, organ donation and transplantation activity across Muslim-majority countries fall short of critical requirements in view of the burden of end-stage organ failure. While socio-economic factors are important, multi-factorial barriers that prevent establishment of comprehensive organ donation and transplantation services must be overcome. Development of organ donation and transplantation services, either country or region-specific, should be strongly encouraged to ensure equity of access to transplantation for people living with end-stage organ failure across global Muslim-majority countries.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://www.transplant-observatory.org; https://www.irodat.org/.

AUTHOR CONTRIBUTIONS

Participated in research idea all authors. Participated in research design FM and AS. Participated in the writing of the paper FM and AS. Participated in the performance of the research all authors. Participated in data analysis FM and AS. Participated in review all authors. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research 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.2025.15116/full#supplementary-material

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BRIEF RESEARCH REPORT
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Characteristics and Outcomes of 1500 Lung Transplantations in the Leuven Lung Transplant Program: Turning Past Lessons Into Tomorrow's Foundations

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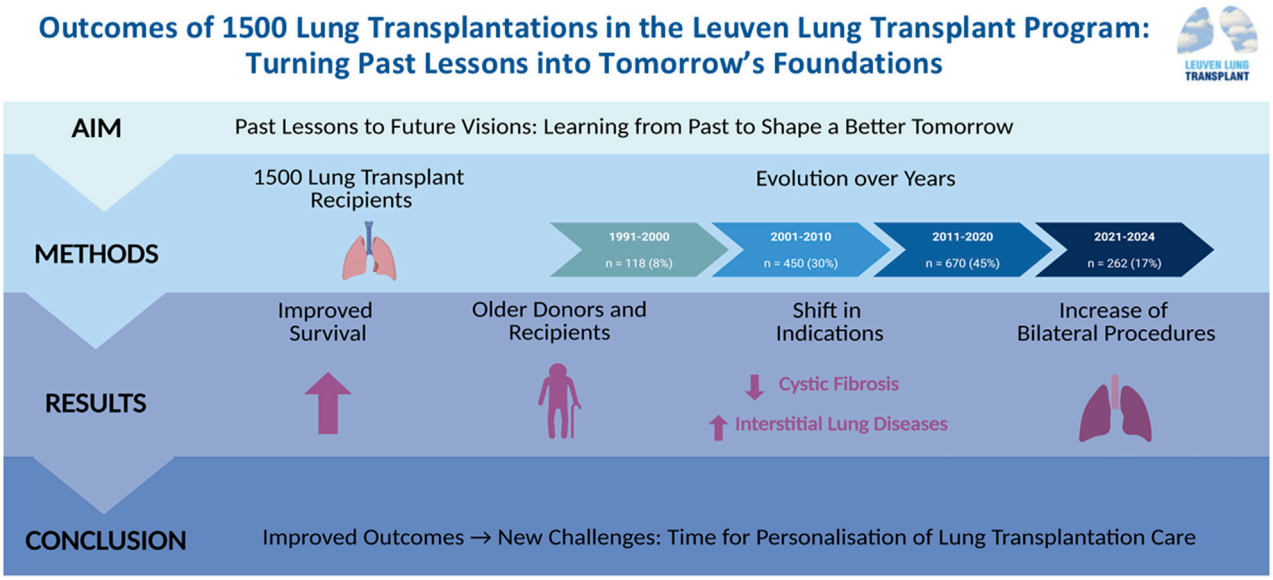
Lung transplantation has become an established life-saving treatment for selected patients with end-stage pulmonary disease. In December 2024, our center reached the milestone of 1,500 lung transplants, providing an opportunity to evaluate long-term trends, outcomes, and challenges. We analyzed donor and recipient demographics, procedural evolution, and graft survival. Contemporary guidelines and consensus recommendations were also reviewed to contextualize current practice and highlight unmet needs. Median graft survival improved markedly across eras: 3.5 years between 1991 and 2000, 9.9 years between 2001 and 2010, and 11.2 years between 2011 and 2020 ($p < 0.0001$). Shifts in procedure type, donor selection, and transplant indications mirrored broader developments in the field (all $p < 0.0001$). Donor and recipient age increased significantly over time, with older recipients experiencing poorer long-term outcomes. Despite these advances, chronic lung allograft dysfunction (CLAD) remains the most important barrier to durable success, with median CLAD-free survival of 6.7 years in the modern era (2010–2024) and a retransplantation rate of 4%. While survival now exceeds a decade in many recipients, extended longevity presents new challenges, including management of comorbidities and optimization of CLAD prevention, treatment, and retransplantation strategies. Continued translational research and evidence-based approaches remain critical to improving long-term results.

Keywords: lung transplantation, outcome, graft survival, evolution over time, future perspectives

Abbreviations: CF, Cystic fibrosis; CLAD, Chronic lung allograft dysfunction; CTS, Collaborative Transplant Study; COPD, Chronic obstructive pulmonary disease; BOS, Bronchiolitis obliterans syndrome; DBD, Donation after brain death; DCD, Donation after circulatory death; DLCO, Diffusing capacity of the lungs for carbon monoxide; FEV1, Forced expiratory volume in one second; ILD, Interstitial lung diseases; ISHLT, International Society for Heart and Lung Transplantation; LuTx, Lung transplantation; OPTN, Organ Procurement and Transplantation Network; RAS, Restrictive allograft syndrome; reLuTx, Lung retransplantation.



GRAPHICAL ABSTRACT |

INTRODUCTION

The first human lung transplantation (LuTx), performed by James Hardy in 1963, demonstrated technical feasibility of this procedure, but initial post-transplant outcome was poor [1]. Introduction of cyclosporine A into clinical practice in the early 1980s, combined with advances in surgical techniques, marked the beginning of the modern era of LuTx [2]. Since then, the annual number of LuTx procedures has steadily increased, now estimated to globally exceed over 5,500 transplantations per year, with in total more than 70,000 procedures performed to date [3, 4]. Notably, current registries (i.e., International Society for Heart and Lung Transplantation (ISHLT), Organ Procurement and Transplantation Network (OPTN), Collaborative Transplant Study (CTS), etc.) fail to capture all individual procedures performed world-wide, since reporting is not mandatory in every transplant center, and exact global transplant numbers are therefore unclear – and likely underestimated [3, 4]. Moreover, not all centers provide data on post-transplant outcomes, making actual graft survival—particularly long-term results—often uncertain. This underscores the need for better reporting of transplant centers' outcomes.

Today, LuTx has become an established treatment option for carefully selected patients with end-stage pulmonary diseases. Advances in medical therapies and management strategies for respiratory conditions such as chronic obstructive pulmonary disease (COPD), interstitial lung diseases (ILD), pulmonary arterial hypertension, and cystic fibrosis (CF)—the main indications for LuTx—have significantly influenced patient selection and referral patterns over the past decades, as well as post-transplant outcomes [3]. These developments also shaped ISHLT guidelines and referral recommendations over time [5, 6]. In parallel, improvements in donor management and optimized surgical techniques, along with introduction of novel, innovative technological approaches such as extracorporeal life support bridging, controlled temperature organ preservation, and *ex vivo* lung perfusion, are nowadays transforming LuTx from an urgent, unplanned intervention into a more predictable, even scheduled, surgical procedure [7–9]. While ISHLT-endorsed recommendations have provided valuable guidance for pre-, peri- and post-transplant patient care ([3, 10–26]; **Supplementary Table S1**), immune-mediated complications remain a major challenge for improving long-term outcomes. Chronic lung allograft dysfunction (CLAD) continues to limit long-term survival, with current median graft survival reported at just 6.3 years, according to the ISHLT Registry [27].

At our center, the 1,500th LuTx was performed in December 2024, an achievement that prompted a comprehensive analysis of our cohort's donor and recipient characteristics, surgical approaches, and long-term outcomes, to evaluate trends and progress over time, and to identify current challenges and conceptional unmet needs to further improve future long-term patient care.

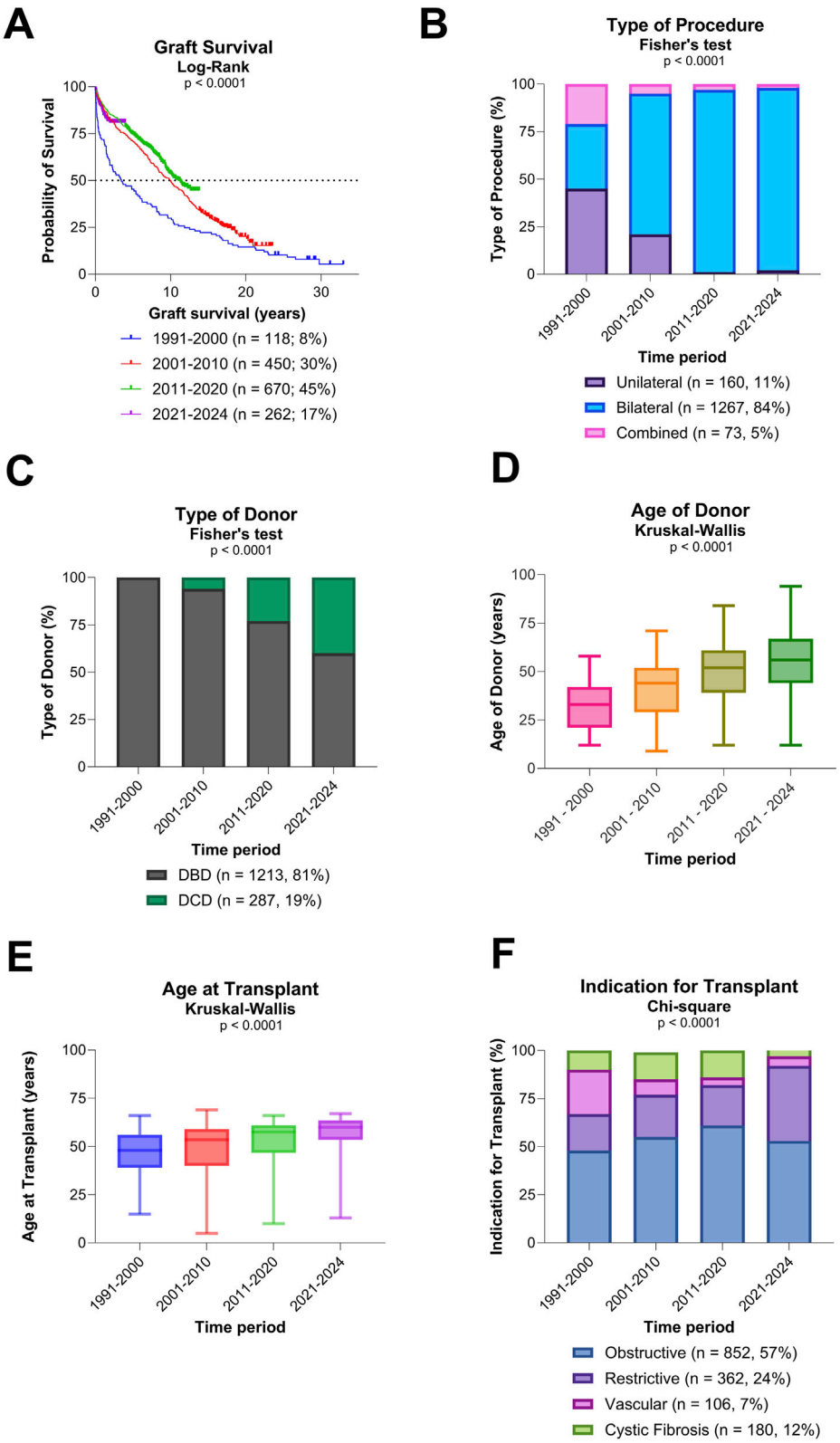


FIGURE 1 | Overall graft survival, type of procedure, and donor/recipient characteristics **(A)** Evolution of overall graft survival over time. **(B)** Evolution of type of procedure over time. **(C)** Evolution of type of donors over time. **(D)** Evolution of age of donors over time. **(E)** Evolution of recipient age at transplantation over time. **(F)** Evolution of indication for transplantation over time.

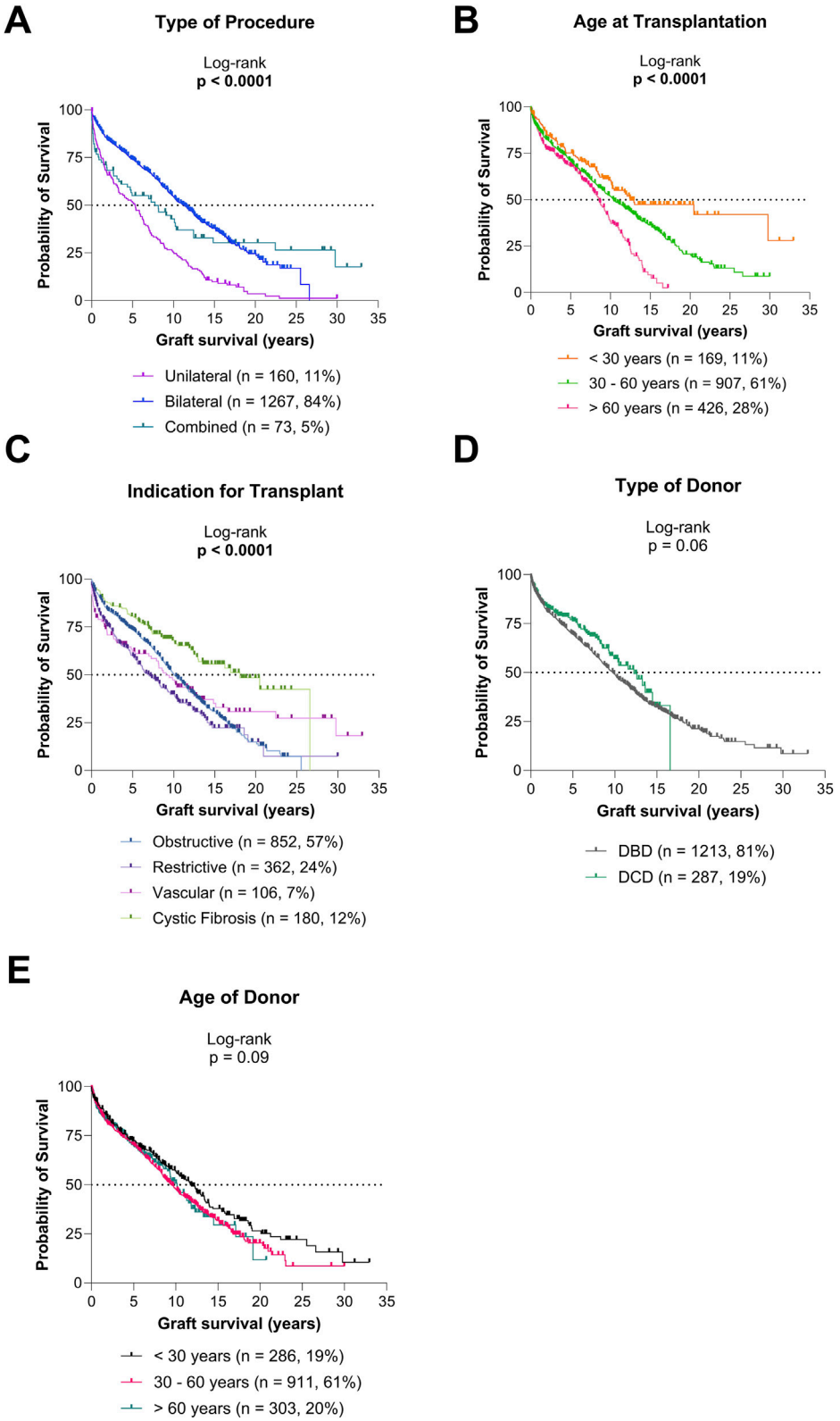


FIGURE 2 | Graft survival according to type of procedure and donor/recipient characteristics **(A)** Graft survival for diverse types of procedures. **(B)** Graft survival for diverse recipient age groups. **(C)** Graft survival for diverse indications for transplantation. **(D)** Graft survival based on type of donor. **(E)** Graft survival based on age of donor.

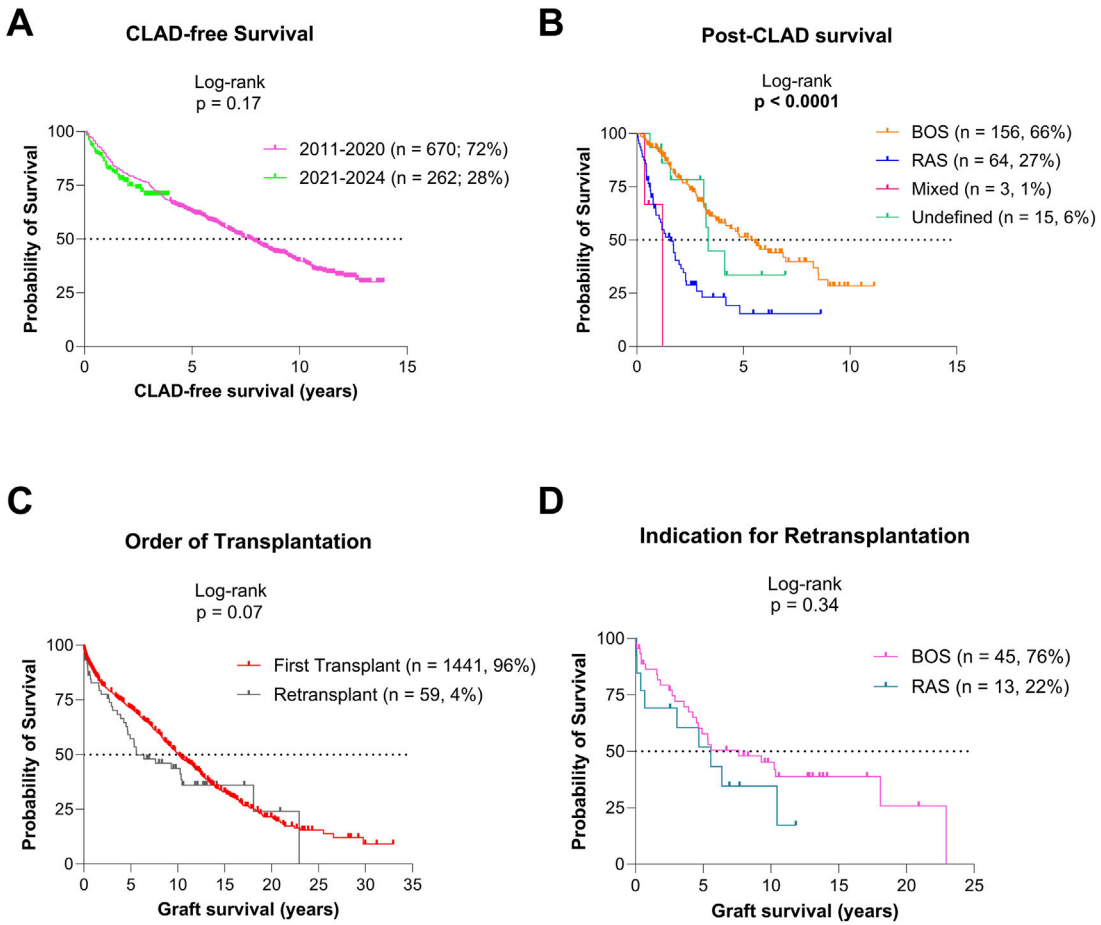


FIGURE 3 | Graft survival based on CLAD status **(A)** CLAD-free survival for the patients transplanted since 2011. **(B)** Post-CLAD survival for patients transplanted since 2011. **(C)** Graft survival for patients after primary transplantation and retransplantation. **(D)** Graft survival after retransplantation for BOS and RAS CLAD phenotypes.

MATERIALS AND METHODS

Study Population

This retrospective, single-center study analyzed all 1,500 consecutive LuTx procedures performed at University Hospitals Leuven between July 1991 and December 12, 2024. Data collected included donor demographics (age and donation type) and recipient characteristics (age at LuTx, sex, transplant indication, date of transplant, procedure type, time to CLAD, CLAD phenotype, and graft survival), with follow-up censored on 31 December 2024. Patients were categorized by transplantation era (1991–2000, 2001–2010, 2011–2020, and 2021–2024) and by procedure type: unilateral LuTx (single LuTx), bilateral LuTx (sequential single LuTx), or combined LuTx (LuTx combined with heart, liver, and/or kidney transplantation). Transplant indications were grouped into four categories: obstructive, restrictive, vascular, and CF) (**Supplementary Table S2**) for outcome analyses. For patients transplanted since 2010, CLAD phenotyping was performed according to the 2019 ISHLT consensus [12], as earlier data were insufficient for detailed classification. Institutional Ethical Review Board approval was waived for this retrospective observational study (S51577/S63978).

Statistical Analysis

Statistical analyses and visualizations were performed using GraphPad Prism 10.4.0 (San Diego, CA, United States). Categorical variables were analyzed with Fisher's exact test and Chi-square test, while continuous variables were assessed using the Kruskal-Wallis test. Survival outcomes were evaluated using log-rank tests and illustrated with Kaplan-Meier curves.

RESULTS

Patient Cohort and Graft Survival

The number of transplant procedures increased steadily over time: 8% of our cohort underwent transplantation between

1991 and 2000, 30% between 2001 and 2010, 45% between 2011 and 2020, and the remaining 17% of transplantations were performed between 2021 and 2024. Recipient and donor demographics are summarized in **Supplementary Tables S3, S4**. At the censoring date, 746 recipients (50%) were alive and followed up in our center.

Overall graft survival among all 1,500 patients was 88% at 1 year, 78% at 3 years, 70% at 5 years, 50% at 10 years, 33% at 15 years, and 22% at 20 years. Graft survival improved significantly across eras, with median survival increasing from 3.5 years (1991–2000; 95% CI 1.9–6) to 9.9 years (2001–2010; 95% CI 8.9–11.4), and 11.2 years (2011–2020; 95% CI 9.8–NA) ($p < 0.0001$; **Figure 1A**). Conditional 1-year graft survival also improved, from 7.8 years (1991–2000; 95% CI 5.5–10.6) to 11.5 years (2001–2010; 95% CI 10.4–12.6), and 12.6 years (2011–2020; 95% CI 11.44–NA) ($p = 0.003$).

Donor and Recipient Characteristics

A significant shift towards bilateral LuTx was observed, along with a significant increased use of donors after circulatory death (DCD) (both $p < 0.0001$; **Figures 1B,C**). Additionally, both donor and recipient ages rose significantly over time (both $p < 0.0001$; **Figures 1D,E**). There was a notable change in the indications for LuTx: the proportion of patients transplanted for CF declined, while those with ILD increased ($p < 0.0001$; **Figure 1F**).

Post-transplant survival varied significantly by type of LuTx, recipient age, and indication for transplantation (all $p < 0.0001$; **Figures 2A–C**). Trends toward different survival outcomes were observed by donor type ($p = 0.06$; **Figure 2D**) and donor age ($p = 0.09$; **Figure 2E**), though these did not reach statistical significance. Outcomes for each indication group (obstructive, restrictive, vascular, and CF) and single LuTx alone are shown in **Supplementary Figures S1–S5**.

CLAD and Retransplantation

For the cohort included in CLAD analysis (2011–2024, n = 989; 66%), median CLAD-free survival was 7.3 years (95% CI 6.6–8.2; **Figure 3A**). CLAD-free survival was comparable in patients transplanted in 2011–2020 vs. 2021–2024 ($p = 0.17$). Among the 238 patients (25.5%) who developed CLAD, 66% had bronchiolitis obliterans syndrome (BOS), 27% restrictive allograft syndrome (RAS), 1% mixed phenotype, and 6% undefined phenotype. Post-CLAD survival differed significantly by phenotype: 5.5 years for BOS (95% CI 3.8–8.5), 1.6 years for RAS (95% CI 1–2.2), 1.2 years for mixed (95% CI 0.37-NA), and 3.4 years for undefined phenotypes (95% CI 3.13-NA; $p < 0.0001$; **Figure 3B**).

In total, 59 lung retransplantations (reLuTx; 4%) were performed: 45 (76%) for BOS, 13 (22%) for RAS, and 1 (2%) for early postoperative pulmonary venous occlusion. Graft survival after reLuTx tended to be lower than after primary LuTx ($p = 0.07$), but survival between BOS and RAS indications was similar ($p = 0.34$; **Figures 3C,D**).

DISCUSSION

Over the course of 1,500 lung transplants in Leuven, graft survival has significantly increased from 3.5 to 11.2 years, notwithstanding major changes in procedure types, and donor and recipient profiles -trends that align with ISHLT Registry data and findings from other large cohorts [3, 28]. These improvements cannot be attributed to a single factor, but rather reflect the cumulative effect of multiple, coordinated advances in surgical techniques, perioperative management, immunosuppressive therapies, infection prophylaxis, and long-term follow-up care of recipients. These changes, combined with general improvements in medical management, complicate direct comparisons of patient cohorts across different time periods and centers. This emphasizes the importance of contemporary, near real-time outcome assessments over reliance on pooled historical registry data.

Unilateral LuTx, once predominant between 1991 and 2000, has declined steadily since 2011. This change likely reflects advances in donor management, expanding donor criteria with increase in DCD donations and broader use of older donors [29], improved graft preservation techniques, and refined surgical practices, which altogether have expanded the donor pool while reducing surgical risks and complications of bilateral transplantation, which is now the preferred procedure in most centers. Given that unilateral LuTx confers inferior long-term graft survival compared to bilateral LuTx, this may raise ethical concerns when prioritizing unilateral over bilateral LuTx, despite donor shortages and patient factors (e.g., older age) which could favor its use. Unfortunately, evidence-based guidelines for the selection of appropriate candidates for 'split' (dividing two suitable donor lungs between recipients) or 'isolated' single LuTx (where one donor lung is transplanted, and the other is declined) are still lacking [30]. In general, most centers nowadays mainly reserve unilateral LuTx for selected cases with either ILD or emphysema - in both of which conditions significant challenges may arise during long-term follow-up (i.e., infections or malignancy in the native lung, progressive fibrosis in ILD, hyperinflation in emphysema), which may compromise patient outcome.

Due to the aging LuTx population, other challenges also arise. The proportion of COPD recipients over 60 years increased from ~25% (1992–2000) to over 50% (2010–2018) per ISHLT data [31]. This is in line with evolving ISHLT candidate selection recommendations: in 2014, age >65 years was a relative contraindication, while in 2021, age 65–70 years became a risk factor only [6, 7]. However, older recipients face worse long-term outcomes [3], as also seen in our cohort, which again may raise ethical concerns when listing elderly patients. Our center's LuTx listing age limit is 65 years (67 for ILD), based on ISHLT registry data consistently demonstrating an increased risk for post-transplant mortality in patients aged ≥60 years [27]. Especially for elderly candidates, thorough comorbidity and frailty assessments, prehabilitation, and enhanced recovery protocols are essential [32–34]. Yet, optimal frailty evaluation and management remain undefined, highlighting the need for guidelines on pretransplant frailty assessment, prehabilitation, and post-transplant physiotherapy protocols along with comorbidity management.

TABLE 1 | Key areas of focus for future clinical guidelines to improve long-term outcomes.

Pretransplant care
Frailty assessment criteria
Prehabilitation strategies
Lung retransplant criteria
Peritransplant care
Donor optimization strategies
Organ preservation strategies
Immunosuppression strategies and management of immunologically sensitized recipients
Management of surgical complications, including bronchial anastomosis problems
Early recovery after surgery protocols and post-transplant revalidation strategies
Posttransplant care
Maintenance immunosuppression regimen strategies
Prevention and treatment of chronic lung allograft dysfunction
Screening and management of comorbidities
Patient reported outcomes
Advanced care planning and end-of-life management
Healthcare practitioners' involvement
Healthcare organization, including logistics, workload and budgetary management

CLAD remains one of the main factors limiting long-term survival after lung transplantation. Despite advances in graft monitoring strategies and improved recognition of CLAD and its clinical phenotypes over the past decade, little progress has been made in the treatment of this devastating complication. Consequently, the development of evidence-based guidelines for CLAD prevention and management, together with sustained translational research to elucidate its underlying mechanisms and clinical trials testing novel therapies, represents a critical and unmet need. Meanwhile, reLuTx—still the only curative option for CLAD—is becoming increasingly common worldwide, yet clear referral and listing criteria remain absent [3, 35]. Importantly, long-term use of maintenance immunosuppressive therapies–the cornerstone of transplant medicine–frequently leads to non-respiratory comorbidities (i.e., cardiovascular and renal disease, diabetes, or malignancy), which may contribute to poorer outcomes in older patients following primary LuTx, and especially after reLuTx, where the cumulative burden of immunosuppressive therapy increases substantially over time [36, 37]. Notably, reLuTx may pose significant technical challenges, especially in restrictive CLAD/RAS (i.e., pleural adhesions), which may contribute to the worse outcomes in reLuTx compared to primary LuTx [36, 37]. While previous studies reported significantly shorter post-transplant survival in reLuTx for restrictive CLAD/RAS compared to obstructive CLAD/BOS, our cohort did not fully mirror these findings [38, 39]. More strict candidate selection following recent ISHLT recommendations [6] and increased surgical experience with performing reLuTx over time [35] may have contributed to this result [6, 35]. Interestingly, the incidence of RAS as indication for reLuTx rose sharply over time in our cohort, from 6% (2001–2010) to 29% (2011–2020), and 40% (2021–2024) (**Supplementary Table S3**), likely reflecting improved recognition of this phenotype since its description in 2011 [40], as well as the worse prognosis associated with this phenotype compared to BOS, which may skew referrals towards reLuTx listing. Importantly, given the overall poor prognosis associated with CLAD, timely reLuTx evaluation in patients with CLAD—particularly at CLAD stage 4 (FEV1 ≤35% of post-transplant baseline)—is critical. Thorough multidisciplinary pre-reLuTx assessment is essential, and despite formal reLuTx criteria are currently missing, listing otherwise eligible patients could be considered when FEV1 and/or DLCO are ≤30% predicted, especially in the presence of pulmonary arterial hypertension or exertional hypoxemia.

While extending long-term survival and enhancing quality of life remain the primary goals of LuTx, appropriate end-of-life care is an essential component of management for all recipients. Early and proactive advance care planning is particularly important for patients who develop respiratory complications such as CLAD or who experience severe non-respiratory comorbidities. Future recommendations should address terminal-stage management, including symptom management, reduction of polypharmacy, and palliative care. Finally, with an ever-growing LuTx population requiring extended and often complex healthcare, also adequate healthcare organization—including logistical coordination, budgetary management, workload control, and physicians' well-being—requires attention. Adequate staffing to ensure state-of-the-art, life-long patients' follow-up and to avoid burnout in healthcare practitioners is challenging, yet essential for sustainable high-quality transplant care [41, 42]. **Table 1** highlights some of the essential areas for future clinical guidelines, which may be pivotal in further optimizing long-term outcomes. **Supplementary Table S5** provides a list of ISHLT-endorsed guidelines currently in development.

In conclusion, long-term outcomes post-LuTx are nowadays favorable, with median graft survival exceeding a decade in our center. However, changing donor and recipient profiles, and longer post-transplant survival conveys new challenges, of which the most important remains CLAD. Our findings may also help inform future clinical guidelines by illustrating how evolving donor and recipient characteristics, shifting indications, and changes in transplant types impact outcomes. Ongoing translational research efforts, systematic outcome assessment, and evidence-based strategies are essential to address these challenges and further improve long-term results in LuTx. Recommendations on evidence-based strategies regarding frailty assessment and management, post-transplant comorbidities, CLAD prevention and treatment, reLuTx criteria, and end-of-life care are crucial to advancing current lung transplant care.

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 robin.vos@uzleuven.be.

ETHICS STATEMENT

The requirement of ethical approval was waived by Institutional Ethical Review Board (S51577/S63978) for the studies involving humans because it is a retrospective observational study. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

AUTHOR CONTRIBUTIONS

Conceptualization, manuscript drafting, editing and finalization: AZ, LD, PD, LC, and RV. Statistical analyses: AZ and RV. Reviewing: AZ, LD, PD, LC, and RV. All authors contributed to the article and approved the submitted version.

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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.2025.15495/full#supplementary-material

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LETTER TO THE EDITOR
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Chronic Lung Allograft Dysfunction in Patients Receiving Lung Transplantation for COVID-19 ARDS

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Dear Editors,

During the COVID-19 pandemic, lung transplant eligibility criteria were expanded to include patients with COVID-associated acute respiratory distress syndrome (CARDS) and post-COVID pulmonary fibrosis (PCPF). CARDS carries high mortality and often requires prolonged extracorporeal membrane oxygenation (ECMO) support and extended intensive care [1]. We previously reported the feasibility of lung transplantation in CARDS recipients, showing early survival comparable to non-CARDS recipients despite higher primary graft dysfunction (PGD) rates [2–6].

Long-term graft assessment in CARDS is essential to guide treatment and optimize resource use. Chronic lung allograft dysfunction (CLAD)—encompassing bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), mixed, and undefined phenotypes—is the leading cause of late mortality [7]. Defined as sustained spirometric decline, CLAD affects approximately 30% of recipients within 3 years [8]. The incidence following CARDS remains unknown. This study evaluates long-term outcomes and the association between PGD and CLAD in CARDS recipients.

We conducted a single-center retrospective study of adult lung transplant recipients from January 2018 to December 2022. Patients were excluded if they died within 1 year, underwent multiorgan or repeat transplantation, or lacked sufficient spirometry (**Supplementary Figure 1**). Twenty-nine recipients which died within the first year (CARDS: 6; non-CARDS: 23) were excluded.

The primary outcome was CLAD incidence. Secondary outcomes included perioperative outcomes and multivariable CLAD predictors. PGD and CLAD were assessed by a multidisciplinary transplant team according to standard definitions [8]. CARDS transplant referrals followed our prior criteria (Supplemental Methods) [2–4].

A total of 252 patients were analyzed: 36 (14%) CARDS and 216 (86%) non-CARDS. Non-CARDS indications comprised interstitial lung disease (43%), chronic obstructive pulmonary disease (21%), pulmonary Artery Hypertension (8%), and others (28%). Compared with non-CARDS, CARDS recipients were younger (52.4 vs. 59.3 years; $p = 0.002$), less often smokers (19% vs. 53%; $p < 0.001$), more frequently bridged with venovenous (VV) ECMO use (50% vs. 4%; $p < 0.001$), had lower hemoglobin (9.1 vs. 12.0 g/dL; $p < 0.001$), and more often underwent bilateral lung transplantation (94% vs. 58%; $p < 0.001$). Median time from disease onset to listing was 104 days [IQR: 85–170]. Three-year survival was 79.8% overall and did not differ significantly between CARDS and non-CARDS (87.0% vs. 78.6%; HR 0.65, 95% CI 0.22–1.91; $p = 0.17$; **Supplementary Figure 2**) after adjustment for bilateral versus unilateral transplantation. Donor characteristics, including age, gender, and cause of death were comparable between groups and not associated with CLAD (**Table 1**).

CARDS recipients had longer operative (8.2 vs. 5.8 h; $p < 0.001$) and ischemic times (5.6 vs. 4.9 h; $p < 0.001$), more intraoperative VA-ECMO (94% vs. 56%; $p < 0.001$), greater blood transfusion ($p < 0.001$), higher PGD Grade 3 (19% vs. 7%; $p = 0.02$), and more dialysis (22% vs. 8%; $p = 0.01$). They also required

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TABLE 1 | Characteristics and outcomes of patients and multivariate cox proportional hazards regression analysis to predict CLAD.

Variable	No CARDS (n = 216)	CARDS (n = 36)	P Value
Recipient factors			
Age, years	59.3 ± 12.4	52.4 ± 10.8	0.002
Female	88 (40.7%)	16 (44.4%)	0.72
Body Mass Index, kg/m^2	25.8 ± 4.5	26.2 ± 4.6	0.56
Smoking history	116 (53.7%)	7 (19.4%)	<0.001
Hypertension	112 (51.9%)	16 (44.4%)	0.47
Diabetes	64 (29.6%)	12 (33.3%)	0.70
Chronic Kidney Disease	12 (5.6%)	0 (0%)	0.23
Pre-operative ECMO use	9 (4.2%)	18 (50.0%)	<0.001
Bilateral Transplantation	126 (58.3%)	34 (94.4%)	<0.001
Lung Allocation Score	50.3 ± 15.8	77.9 ± 16.4	<0.001
Follow-Up Days	808 [538–1,327]	1,079 [935–1,208]	0.02
Laboratory Values			
Hemoglobin, g/dL	12.0 ± 2.4	9.1 ± 1.9	<0.001
BUN, mg/dL	16.0 ± 6.0	20.3 ± 12.8	0.001
Creatinine, mg/dL	0.80 ± 0.22	0.60 ± 0.21	<0.001
PRA	85 (39.4%)	18 (50.0%)	0.27
Donor-specific antibodies	20 (9.3%)	9 (25.0%)	0.007
Donor			
Age, years	32.6 ± 11.8	30.8 ± 12.5	0.41
Female	65 (30.1%)	14 (38.9%)	0.33
Donor cause of death			
Head trauma	84 (38.9%)	17 (47.2%)	0.36
Anoxia	81 (37.5%)	16 (44.5%)	0.46
Other	51 (23.6%)	3 (8.3%)	0.05
Intra-operative outcomes			
Operative time (hours)	5.8 (4.8–7.5)	8.2 (7.4–9.5)	<0.001
Intra-op blood transfusion; pRBC	0 (0–2)	6 (2–11)	<0.001
Ischemic time (hours)	4.9 (4.1–5.8)	5.6 (5.1–6.0)	0.001
VA ECMO use	123 (56.9%)	34 (94.4%)	<0.001
VA ECMO time (hours)	1.7 (0–3.0)	3.1 (2.6–3.6)	<0.001
Postoperative outcomes – Univariate Analysis			
PGD	82 (38.0%)	21 (58.3%)	0.03
PGD Grade 3	14 (6.5%)	7 (19.4%)	0.02
Acute rejection	58 (38.9%)	2 (6.1%)	<0.001
post ECMO use	8 (3.7%)	13 (36.1%)	<0.001
Acute Kidney Injury	79 (36.6%)	18 (50.0%)	0.14
PE	7 (3.2%)	0 (0%)	0.60
Dialysis	17 (7.9%)	8 (22.2%)	0.01
CMV infection	15 (10.1%)	6 (18.2%)	0.23
ICU stay (days)	7 (5–11)	16 (10–22)	<0.001
Post-transplant ventilator (days)	2 (1–3)	4 (2–17)	<0.001
Hospital stay (days)	15 (11–27)	23 (17–37)	<0.001
Chronic Lung Allograft Dysfunction	46 (21.3%)	8 (22.2%)	1.00
BOS	36 (78.3%)	4 (50.0%)	0.18
RAS	6 (13.0%)	1 (12.5%)	1.00
Mixed	3 (6.5%)	3 (37.5%)	0.04
Undefined	1 (2.2%)	0 (0%)	1.00
Multivariable Analysis*	HR	P value	95% CI
Recipient Factors			
Body Mass Index, kg/m^2	1.07	0.03	1.01–1.14
Lung Allocation Score	0.99	0.18	0.97–1.01
Hemoglobin, g/dL	1.06	0.41	0.93–1.20

*Continuous data are shown as means ± standard deviation (SD) for age and laboratory data, and as medians and interquartile ranges [Q1-Q3] for days. *Variables with biological plausibility and a p-value <0.10 on univariate analysis were included in multivariable analysis.*

longer ventilation (median 4 vs. 2 days; $p < 0.001$), ICU stays (16 vs. 7 days; $p < 0.001$), and hospitalization (23 vs. 15 days; $p < 0.001$) (**Table 1**). CLAD incidence was similar: 22% in CARDS (8/36) and 21% in non-CARDS (46/216; $p = 1.00$). The mixed phenotype was more common in CARDS with CLAD (38% vs. 7%; $p = 0.04$, possibly reflecting distinct immune activation or airway injury patterns after severe viral ARDS. In multivariable models, only BMI predicted CLAD (HR 1.07, CI 1.01–1.14; $p = 0.03$). Donor-specific antibodies, CMV infection, acute rejection, and transplant type were not significant predictors (**Supplementary Table 1**).

Although the coronavirus pandemic has subsided, lung transplantation remains a salvage option for patients with

COVID–related respiratory failure and is currently being studied as a treatment for ARDS [9]. In this single-center case series, we report a 22% incidence of CLAD in CARDS patients undergoing lung transplantation, with an average follow-up of 1,079 days. This rate is not significantly different from the incidence in patients transplanted for other indications within our cohort (21%, p = 1.00) or from the 30% incidence reported at 1,095 days in international data [8]. These findings highlight the potential for long-term graft sustainability in this population and provide valuable single-center evidence on the feasibility of lung transplantation for ARDS in the post-COVID era.

CARDS recipients demonstrated significantly higher rates of PGD grade 3 compared to non-CARDS recipients (58.3% vs. 38.0%, p = 0.02), a key risk factor for CLAD [10]. Interpretation of this finding is complex, as the acute manifestations of CARDS—including inflammation, endothelial dysfunction, and pulmonary edema—can require prolonged ECMO support and impact PGD diagnostic criteria. Elevated PGD rates in CARDS patients may reflect acute disease severity rather than the traditional PGD pathophysiology described in lung transplant recipients with more chronic disease. Notably, only BMI was a significant predictor of CLAD in our 252-patient cohort (HR 1.07, CI 1.01–1.14, p = 0.03). Known risk factors such as PGD grade 3 was not significant [7–10]. This may reflect the limited sample size and the time-dependent nature of CLAD.

This study has several limitations, including modest sample size and mid-term follow-up, as well as a higher incidence of bilateral lung transplants in CARDS patients, which is associated with a longer time to CLAD diagnosis by a median of 150 days. In addition, 29 patients which died within the first year were excluded from the CLAD analysis. While this approach was necessary to meet the diagnostic definition of CLAD, it introduces the possibility of selection bias. We also acknowledge that death represents a competing risk when evaluating CLAD incidence, which was not formally modeled in this study. CARDS recipients in our cohort were younger and overall healthier compared with typical lung transplant candidates, which could partly explain the comparable CLAD rates observed. Although our study focused on CARDS, these findings may have implications for other acute respiratory failure syndromes, such as influenza-related ARDS; however, further research is needed before generalizing these results to other indications. In summary, our findings suggest CARDS is not associated with increased CLAD risk, and long-term outcomes remain favorable. Multi-center studies with extended follow-up are warranted.

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 Northwestern University, IRB Approval (STU00207250 and STU00213616) has been obtained for this publication. 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 because Patient consent was not required.

AUTHOR CONTRIBUTIONS

Participated in research design: BT, TK, AB, CK. Participated in the writing of the paper: BT and CK. Participated in the performance of the research: BT, TK, AC, YM, TT, AA, AB, GB, CK. Participated in data analysis: TK and TT. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPLEMENTARY MATERIAL

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ESOT | Transplant International

LETTER TO THE EDITOR
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Enhanced Recovery after Surgery in Kidney Transplantation: Shorter is Better

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Keywords: kidney transplantation, ERAS in kidney transplantation, ERAS, kidney grafts, transplantation

Dear Editors,

Peri-operative management in kidney transplantation has not evolved in years, whereas in other fields it is constantly changing and improving. The implantation of Enhanced Recovery After Surgery (ERAS) in oncological urology have significantly improved postoperative outcomes by reducing complication rates, shortening hospital stays, accelerating functional recovery, and facilitating earlier initiation of adjuvant therapies, without compromising oncological safety, and has now become a standard in perioperative care for patients [1].

We aimed to transpose this approach to kidney transplantation, which is mostly an emergency procedure, except for living donor transplants. To this end, we conducted a historical-prospective study to assess the feasibility and effectiveness of an ERAS protocol in kidney transplantation at our center, which is a pioneer in the field of renal transplantation. There are few studies in the literature on this subjet [2–5].

We retrospectively analyzed a cohort of 130 patients who underwent their first kidney transplant without ERAS protocol. After analyzing this cohort, we implemented a multidisciplinary ERAS protocol in (**Table 1**) 2023 (surgical, nephrological, anesthetic, paramedical, with explanations for patients provided through documents and a patient video) and applied it to 130 consecutive patients hospitalized for their first kidney transplant. Living Donor (LD) transplant patients were also included (16% of the population, No-ERAS Group 15% vs. ERAS Group 16%, $p = 0.86$). For deceased donor, 73% were DNC and 27% DCC.

The two cohorts did not show any statistically significant differences, except for a higher rate of grafts on perfusion machines in the ERAS group (No-ERAS Group 54% vs. ERAS Group 68%, $p = 0.027$), which correspond to the increase in the use of perfusion machine for kidney graft in recent years. Median age was 57 years (44.8–67.2).

The implementation of this ERAS protocol led to a reduction in the median hospital stay (LOS) by 2 days (Non-ERAS 7 days vs. ERAS 5 days, $p < 0.001$). This reduction of LOS was also observed in both living donor (No-ERAS 6 days vs. ERAS 5 days, $p < 0.001$) and deceased donor subgroups (Non-ERAS 7 days vs. ERAS 5 days, $p < 0.01$). The reduction of LOS has been possible, without increasing postoperative morbidity excluding transfusion (Non-ERAS 12% vs. ERAS 16%, $p = 0.37$), transfusion rate (Non-ERAS 12% vs. ERAS 18%, $p = 0.17$), surgical re-intervention rate (Non-ERAS 10% vs. ERAS 8.5%, $p = 0.67$), or the rate of re-hospitalization before day 30 (Non-ERAS 15% vs. ERAS 24%, $p = 0.086$). There was, however, a trend toward increased re-hospitalizations among ERAS patients, with the majority (60%) being due to medical causes such as renal insufficiency (7 cases), infection (6 cases) or cardiac decompensation (4 cases). This may possibly be explained by the reduced length of hospital stay, as these complications now tend to occur at home, whereas they would have previously arisen during hospitalization. Graft outcomes, including time to recovery (median of 2 days), delayed graft function (14%), and graft failure rate (4.2%, 6.2% in the non-ERAS group vs. 2.3% in the ERAS group), were comparable between the ERAS and no-ERAS groups, with no statistically significant differences observed ($p = 0.36$, $p = 0.82$, and $p = 0.12$) respectively.

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TABLE 1 | Our eras protocol.

Pre-operative	Peri-operative	Post-operative
Oral and written information about kidney transplantation	Pre-surgery	Early oral intake of fluids then solids after surgery according to protocol
Oral, written and video information about ERAS protocol	Pre-operative preparation of surgery site	Early mobilization
Regular physical activity	Carbohydrate loading till 6 h before surgery	- POD 0: Edge of bed
Cessation of smoking and alcohol intake is recommended	Oral fluids loading till 2 h before surgery	- POD 1: First step
Risk stratification (Lee index, assessment of functional capacity, ASA score)	Anesthesia	- POD 2: Walk and armchair
Management of anemia	Standard anesthesic protocol and depth of anesthesia monitoring (bispectral index, BIS)	- Mobilization exercise (according to protocol)
Stabilization of chronical disease	Multimodal analgesia including systematic TAP Block before or after surgery	Early recovery of normal bowel function
	Neuromuscular blockade, monitoring and reversing	- Chewing-gum
	Perioperative haemodynamic management (ballanced cristalloids, +/- minimally or non invasive cardiac output monitor *based on pulse contour analysis)*	- Limitation of opioid analgesia
	Preventing and treating postoperative nausea and vomiting	- Early mobilization
	Preventing intraoperative hypothermia (active warming device)	- Early oral intake of fluids then solids after surgery according to protocol
	Intraoperative glycaemic control	Own dress as soon as possible
	No nasogastric intubation	Multimodal opioid-sparing analgesia
	Anesthesic induction is performed via a peripheral venous cathter	Early removal of intravenous infusion and treatment
	Central venous catheter is inserted if:	Early removal of surgical drainage
	- Induction with thymoglobulin >48 h and absence of arterio-veinous fistula	- POD 2 if < 50 mL
	- Poor venous capital, even if induction with thymoglobulin <48 h	- Follow surgical instructions
	Surgery	Early removal of bladder catheter
	Systematic bladder catheterization before surgery	- Women: POD 2
	Systematic ureteral stenting	- Men: POD 4
	No systematic surgical drainage, and less drainage as possible	- Follow surgical instructions
		Patient education about drugs (immunosuppression, analgesia . . .)
		Removal of ureteral stenting at 4–6 weeks in consultation
		Call of the patient at first day of discharge and nephrologic consultation at three-days then once a week

Thus, our ERAS protocol in kidney transplantation led to a reduction in hospital stay without increasing postoperative morbidity or early re-hospitalization rates. These positive results have allowed us to expand this protocol to all our kidney transplant patients, and will become our new standard in kidney transplantation care. There are still areas for improvement in kidney transplantation, as recently demonstrated by an American unit, with an awake kidney transplantation, with discharge on the next day.[1] Although this is not yet published, this encouraging outcome may represent a potentiel future direction.

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 Groupe Nantais d'Ethique dans le Domaine de la Santé (GNEDS). 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 When patients are admitted to the Nantes University Hospital, they are given a document informing them of the possibility of having their data used anonymously in clinical studies.

AUTHOR CONTRIBUTIONS

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 authors declare that the research 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) declare that no Generative AI was used in the creation of this manuscript.

[1]https://www.nm.org/healthbeat/medical-advances/new-therapies-and-drug-trials/Awake-Kidney-Transplantation-A-Revolution-in-Renal-Care

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LETTER TO THE EDITOR
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Increased Treg in Kidney Transplant Recipients With Erythrocytosis

Carolina Bigatti[1,2], Sadia Mustofa[3], Dana Korogodsky[1], Yorg Azzi[3], Elie Salloum[4], Andrea Angeletti[1,2], Enver Akalin[3], Maria Ajaimy[3] and Paolo Cravedi[1]**

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Keywords: PTE, regulatory T cells, monocytes, EPO, erythropoietin

Dear Editors,

Erythropoietin (EPO) is a glycoprotein hormone produced predominantly by the kidney in response to hypoxia. While widely known for its hematopoietic role, EPO also exerts immune-modulating effects. In murine transplant models, administration of exogenous EPO prolongs allograft survival by increasing the frequency of regulatory T cell (Treg) and by promoting macrophage polarization towards an anti-inflammatory phenotype [1]. Consistent with these preclinical findings, clinical studies have demonstrated that recombinant EPO administration at the doses normally used to correct anemia in humans enhances both the number and suppressive capabilities of circulating Tregs [2, 3].

The immune-modulating effects of endogenous EPO in kidney transplant recipients are less clearly defined. Mice that are EPO deficient are prone to the development of autoimmunity. Patients with chronic kidney disease (CKD) often show intrarenal immune infiltrates, which may be due, at least in part, to the reduced EPO production associated with impaired kidney function. However, CKD patients exhibit multiple inflammatory sources, complicating any direct causal relationship between reduced endogenous EPO levels and intrarenal inflammation.

To more rigorously investigate endogenous EPO's immunological impact in humans, we focused on kidney transplant recipients with post-transplant erythrocytosis (PTE), a complication affecting approximately 10%–20% of patients, typically within the first 2 years post-transplant. PTE is characterized by persistently elevated hematocrit levels without ongoing blood loss, hypoxia, or exogenous EPO therapy [4]. We hypothesized that kidney transplant recipients (KTRs) with PTE have high EPO levels and exhibit a distinct immunological profile, characterized by increased circulating Tregs and monocytes with an anti-inflammatory profile.

We conducted a cross-sectional study of 14 KTRs with PTE (hematocrit ≥50%) and 19 matched controls without PTE. Using flow cytometry, we quantified circulating immune subsets, including regulatory T cells (Tregs), T cells, B cells, and monocytes. Cytokine levels were assessed by ELISA (see **Supplementary Material**).

Patients with PTE and controls were similar in terms of age (52.9 ± 11.5 vs. 52.1 ± 10.5 years, p = 0.8), time since transplantation (4.1 ± 2.6 vs. 5.6 ± 1.9 years, p = 0.08), and kidney function (creatinine 1.4 ± 0.4 vs. 1.4 ± 0.5 mg/dL, p = 0.8). Consistent with prior reports [5], the PTE group had a significantly higher proportion of male patients (92.9% vs. 52.6%, p = 0.02). No significant differences were observed in induction therapy, donor-specific antibodies (DSA), or prior rejection episodes. The distribution of race/ethnicity and underlying kidney disease was comparable between groups (**Supplementary Table S1**). The use of RAS inhibitors (Renin-Angiotensin system inhibitors) was comparable between PTE patients and controls. Secondary causes of erythrocytosis, including renal artery stenosis and renal tumors, were ruled out in PTE patients. Additional cancer screening was not performed when PTE diagnosis occurred shortly after transplantation, considering the limited time for malignancy development. Patients with PTE had significantly higher serum EPO levels compared to controls (10.5 ± 5.9 vs. 6.8 ± 2.5 mIU/mL, p = 0.02) (**Supplementary Figure S1A**).

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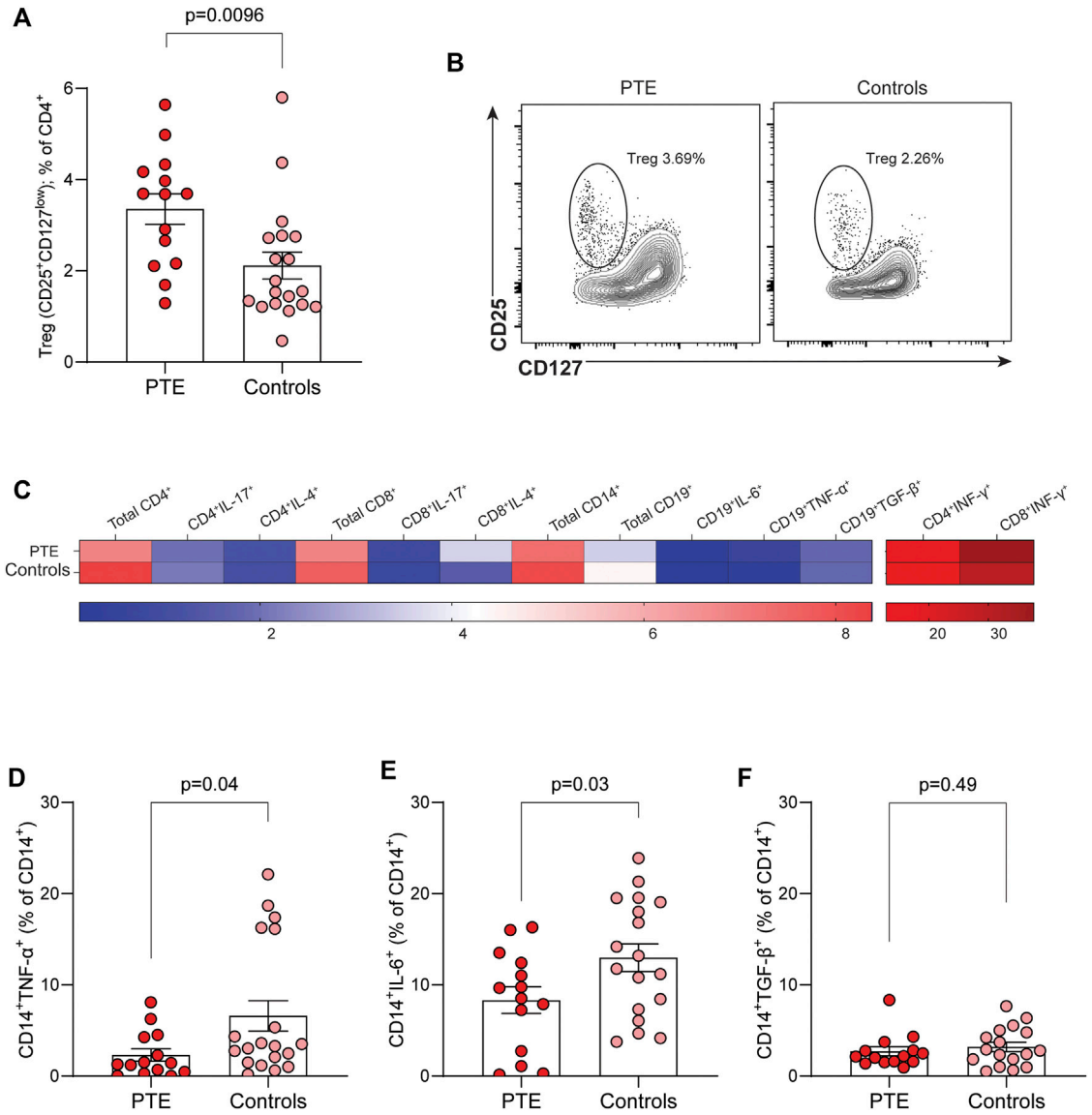

FIGURE 1 | Immune profile in PTE and control kidney transplant recipients. **(A)** Frequency of Treg ($CD4^+CD25^+CD127^{low}$) among $CD4^+$ T cells in the two study groups. **(B)** Representative flow cytometry plots. **(C)** Heatmap showing mean frequencies of total and cytokine-expressing $CD4^+$, $CD8^+$ T cells, monocytes ($CD14^+$), and B cells ($CD19^+$) in PTE patients (n = 14) and controls (n = 19), expressed as percentage of parent population. Frequencies of TNF-α^+ **(D)**, IL-6^+ **(E)**, and TGF-β^+ **(F)** monocytes ($CD14^+$) following *ex vivo* LPS stimulation. Data are shown as mean ± SEM. Statistical comparisons were performed using unpaired, two-tailed t-tests.

Tregs, defined phenotypically as $CD4^+CD25^+CD127^{low}$ cells, were significantly higher in patients with PTE compared to controls (3.4% ± 1.3% vs. 2.1% ± 1.3, respectively; $p = 0.0096$) (**Figures 1A,B**). We did not observe significant differences in the overall percentages of $CD4^+$ and $CD8^+$ T cells, or B cells, between PTE patients and controls (**Figure 1C**). Intracellular cytokine analysis of $CD4^+$, $CD8^+$ T cells (including IL-17, IL-4, IFN-γ) and B cells did not reveal significant differences between the two groups.

Monocyte percentages did not differ between PTE patients and controls (**Figure 1C**), but functional analyses revealed that, upon stimulation with LPS (5 ng/mL), the percentages of monocytes producing TNF-α (2.3% ± 2.5% vs. 6.6% ± 7.3, respectively; $p = 0.043$) and IL-6 (8.3% ± 5.5% vs. 12.9% ± 6.4, respectively; $p = 0.038$) were significantly lower in PTE patients compared to controls. TGF-β production in monocytes did not differ between the two study groups (**Figures 1D–F**).

Plasma levels of TNF-α (22.11 vs. 22.56 pg/mL; p = 0.92) and IL-6 (10.79 vs. 12.65 pg/mL; p = 0.69) were comparable between PTE patients and controls (**Supplementary Figures S1B, C**).

In summary, we found that elevated EPO levels in KTRs with PTE are associated with increased frequency of circulating Treg and a reduced proinflammatory activation profile in monocytes,

despite comparable systemic levels of TNF-α and IL-6. These findings suggest that elevated endogenous EPO may promote a more tolerogenic immune environment after kidney transplantation.

Published data by our group and others indicate that EPO promotes the release of active TGF-β by monocytes/macrophages, promoting conversion of naive $CD4^+$ T cells into functional Treg [1, 6]. We also showed that EPO induces an anti-inflammatory program in macrophages, although the molecular mechanisms are not fully clear.

The combination of increased Tregs and reduced monocyte-derived inflammation in PTE patients raises the intriguing possibility that this cohort of patients may be at lower risk of acute rejection due to the immune-regulatory effects of EPO [7]. On the other hand, the recent evidence that tumors producing EPO have lower chances to be cleared by the anti-tumor immune response [8], supports studies testing the neoplastic risk of these patients.

We also observed a lower rate of DSA in PTE patients (7% vs. 31% in controls). Although this difference did not reach statistical significance, this trend may be biologically relevant, suggesting a possible protective role of EPO against alloimmune sensitization, as we previously reported in mice [9].

Our study has several limitations, including its relatively small sample size and cross-sectional design, which limit the ability to infer causality. Additional prospective studies with larger cohorts are required to confirm our findings, elucidate the precise mechanisms by which endogenous EPO modulates immune responses in humans, and determine the long-term implications for graft outcomes.

In conclusion, consistent with animal studies and previous clinical data involving recombinant EPO, our findings suggest that elevated endogenous EPO levels in kidney transplant recipients with PTE promote an anti-inflammatory immune environment under stable immunosuppression. This evidence could be leveraged to test the hypothesis that, in this patient population, lower levels of immunosuppression are needed to prevent rejection. On this line, an ongoing prospective study is testing the hypothesis that EPO administration allows safe immunosuppression withdrawal in stable liver transplant recipients (NCT06832189).

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 Montefiore Medical Center, Albert Einstein College of Medicine A, Bronx, NY, USA. 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

PC and MA contributed to the conception and design. SM, YA, ES, EA, and MA enrolled patients and processed samples. CB, DK, and AA performed assays and data analysis. CB drafted the manuscript under PC and MA guidance. All the authors contributed to data interpretation and manuscript revisions. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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LETTER TO THE EDITOR
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The Impact of Hyperbaric Oxygen Therapy in Liver Donors Before Controlled Circulatory Death on Graft Function Recovery: A Pilot Study

Morgan Caplan[1], Juliette Philipon[2], Sébastien Dharancy[3], Emmanuel Boleslawski[4], Guillaume Strecker[5], Bruno Mourvillier[1], Erika Parmentier-Decrucq[2] and Vincent Dupont[6]†*

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Keywords: liver transplantation, hyperbaric oxygen therapy, ischemia reperfusion injury, donation after circulatory death, early allograft dysfunction

Dear Editors,

Hyperbaric oxygen therapy (HBO) is a specialized treatment modality that involves the administration of 100% oxygen at pressures exceeding atmospheric levels (ATA) [1]. Currently, there is no data on the impact of HBO prior to organ donation on graft function recovery. However, the combination of elevated oxygen levels and increased pressure may influence liver function, especially in the context of ischemia-reperfusion (IR) injury.

The objective of this study was to evaluate graft function recovery in liver transplant recipients from donors who received HBO before organ procurement compared to recipients from untreated donors.

We conducted a retrospective study at a high transplant-volume university center in Lille, France, where HBO therapy is commonly used in life-threatening hanging cases, occasionally leading to controlled donation after circulatory death (DCD) procedures. We included all liver transplantations (LT) from DCD donors over the period 1 January 2018, to 31 December 2023, and excluded donors/recipients aged <18 years or with missing data.

Recipient outcomes were analyzed based on the HBO treatment performed before the liver donation procedure. Each HBO session involved a 15-min pressure rise from 1 to 2.5 ATA, maintaining this pressure for 90 min with an inspired oxygen fraction of 100%, followed by a 15-min decompression period [1].

The French national protocol for DCD includes systematic normothermic regional perfusion (NRP). Transaminase kinetics and maximum values recorded during NRP are considered markers of indirect viability of the liver graft. Graft biopsy was systematically performed. All LT procedures used standardized anesthetic and surgical protocols with the side-to-side cavocaval technique. The institutional immunosuppression protocol consists of an initial triple-immunosuppressive regimen (calcineurin inhibitors, corticosteroids, and anti-metabolites).

Donor and recipient characteristics were collected from medical records by a member of the intensive care unit (ICU) and a hepatologist, respectively, then anonymized before analysis.

Abbreviations: ATA, Atmospheric pressure; DCD, Donation after circulatory death; EAD, Early allograft dysfunction; HBO, Hyperbaric oxygen therapy; ICU, Intensive care unit; IR, Ischemia-reperfusion; LT, Liver transplantation; MEAF, Model of early allograft function; MELD, Model for end-stage liver disease score; NRP, Normothermic regional perfusion; POD, Post-operative days.

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TABLE 1 | Donors and recipients' characteristics.

Variables[a]	HBO - (n = 34)	HBO + (n = 25)	Univariate analysis
			P value
Donors' baseline characteristics			
Age, *years*	56 (47–66)	44 (31–50)	**<0.001**
Male, *n (%)*	26 (76.5)	22 (88)	0.33
BMI, *kg/m²*	28 (25–30)	24 (22–27)	**0.001**
Smoke, *n (%)*	14 (41.2)	11 (44)	1
Alcohol, *n (%)*	7 (20.6)	9 (36)	0.31
Hypertension, *n (%)*	12 (35.3)	4 (16)	0.14
Diabetes, *n (%)*	4 (11.8)	0 (0)	0.13
Cause of admission			
Suicide by hanging *n (%)*	1 (2.9)	25 (100)	**<0.001**
Stroke, *n (%)*	8 (23.5)	0 (0)	**0.02**
SAPSII score	55 (47–65)	55 (47–61)	0.90
Cardiac arrest, *n (%)*	20 (58.8)	24 (96)	**0.002**
No flow, *min*	5 (0–7)	20 (15–30)	**<0.001**
Low flow, *min*	23 (19–30)	20 (12–24)	**0.03**
Electric shock, *n (%)*	12 (35.3)	2 (8)	**0.03**
Adrenaline, *mg*	2 (1–4)	1 (0–2)	**0.01**
Admission lactate level, *mmol/L*	6.3 (3.6–7.3)	4 (2.9–6.8)	0.10
Biological parameters before circulatory arrest			
PT, %	79 (70–83)	84 (71–96)	0.19
Total bilirubin, umol/L	5 (4–7)	5 (3–7)	0.40
AST, UI/L	52 (30–79)	58 (42–82)	0.35
ALT, UI/L	41 (23–74)	62 (37–101)	**0.04**
Maastricht 3 procedure characteristics			
Circulatory arrest time, *min*	18 (15–22)	17 (15–19)	0.52
Total WIT, *min*	32 (27–42)	28 (25–34)	0.11
Functional WIT, *min*	22 (20–29)	20 (18–25)	0.08
Biological parameters during NRP			
AST peak, UI/L	55 (30–101)	65 (50–85)	0.18
ALT peak, UI/L	35 (23–86)	53 (41–95)	**0.02**
Macrovacuolar steatosis >5%, *n (%)*	20 (58.8)	11 (44)	0.61
Recipients' baseline characteristics			
Age, *years*	59 (54–61)	57 (49–61)	0.56
Male, *n (%)*	24 (66.7)	20 (74.1)	0.55
BMI, *kg/m²*	28 (25–30)	28 (25–32)	0.69
Causal liver disease			
Alcoholic, *n (%)*	21 (58.3)	21 (77.8)	0.08
Viral, *n (%)*	5 (13.9)	5 (18.5)	0.73
Child pugh score	6 (5–8)	7 (5–9	0.40
MELD score	10 (7–14)	11 (8–16)	0.33
Cold ischemia time, *min*	278 (241–329)	265 (225–291)	0.22
Liver recipients and early graft outcomes			
AST or ALT >2000UI/L within the first 7 POD, *n (%)*	6 (17.6)	3 (12)	0.52
Bilirubin ≥10 mg/dL on POD 7, *n (%)*	15 (44.1)	7 (28)	0.19
INR ≥1.6 on POD 7, *n (%)*	0 (0)	0 (0)	1
Early graft dysfunction (olthoff), *n (%)*	20 (58.8)	9 (36)	0.08
MEAF score	5.1 (4.2–6.0)	5.0 (3.6–5.4)	0.36
ICU stay, *days*	9 (7–12)	10 (8–12)	0.34
Hospital stay, *days*	13 (10–17)	13 (10–16)	0.97
New liver transplantation within 1 year, *n (%)*	2 (5.9)	1 (4)	1
Death within 1 year, *n (%)*	2 (5.9)	2 (8)	1

[a]*Data are reported as numbers (percentages) or medians (interquartile ranges). HBO, hyperbaric oxygen therapy; BMI, body mass index; SAPSII, simplified acute physiologic score II; PT, prothrombin time; WIT, warm ischemia time; NRP, normothermic regional perfusion; AST, aspartate aminotransferase; ALT, alanine aminotransferase; POD, post operative day; MEAF, model for early allograft function; MELD, model for end-stage liver disease; INR, international normalized ratio.*
Bold values indicate statistically significant p-values (p < 0.05).

The primary outcome was the occurrence of early allograft dysfunction (EAD) according to the Olthoff definition based on the occurrence of at least one of the following criteria: bilirubin concentration ≥10 mg/dL on post-operative day (POD) 7, INR value ≥1.6 POD, and AST or ALT >2.000 U/L within the first seven POD [2]. We also studied the model of early allograft function (MEAF), which allows a quantitative assessment of allograft function within the first three POD.

This study was conducted in accordance with current French legislation (CNIL and MR004).

Data were graphed and statistics were calculated using GraphPad Prism, version 9.5.1 (GraphPad Software). Quantitative and qualitative data were compared using the Mann–Whitney test and Fisher exact test or χ^2 test with Yates correction, respectively. The Benjamini-Hochberg procedure was applied to account for multiplicity. Statistical significance was set at $P < 0.05$.

During the study period, 554 LTs were performed including 68 donors with DCD. Among the latter, 5 and 4 LT were excluded due to missing recipient and donor data (organs retrieved or transplanted in a different center). Thus, we included 59 LT in our study, of which 25 (42.3%) involved donors exposed to HBO before donation (**Table 1**). All HBO-treated donors underwent a total of five sessions within the first 48 h of ICU stay, with a median time between the last HBO session and donation procedure of 6 (5–8) days.

The causes of death differed between the two groups and reflected local practices (as HBO is performed in cases of suicide by hanging). Donors from the HBO group had a lower BMI than the controls. Admission severity was similar between the two groups. Compared with controls, recipients from the HBO donor group showed higher prothrombin time from POD 2 to 14 as well as lower bilirubin values on POD 14 and 1 month after LT.

To our knowledge, this is the first study to assess HBO as a preconditioning intervention for liver graft outcomes. Our primary finding was that HBO treatment did not adversely affect the graft or recipient outcomes. These results suggest the feasibility and safety of HBO administration in ICU patients who later become organ donors. Interestingly, despite the limited sample size, we observed a trend toward reduced EAD occurrence in recipients from HBO-treated donors compared to controls, alongside a significant improvement in prothrombin time and bilirubin levels post-LT. Furthermore, this trend toward improved hepatic recovery was observed when HBO was not intentionally used as a preconditioning therapy [1], which led to a significant delay between HBO treatment and the procurement procedure.

From a mechanistic perspective, HBO may exert its effects through the reduction of ischemia-reperfusion injury, attenuation of oxidative stress, and modulation of inflammatory pathways, as previously suggested in experimental models [3–5]. In addition, HBO has been shown to promote hepatocyte regeneration and improve microcirculatory function, which could explain the favorable trends we observed in graft function recovery. Further mechanistic studies are warranted to delineate these potential pathways in the clinical transplantation setting.

This study had several limitations. First, its small sample size and retrospective design hindered the feasibility of multivariate analysis to account for confounding variables. Hence, the substantial baseline differences between the two groups of donors restrict the strength of our conclusions. Accordingly, our results should be interpreted as exploratory and hypothesis-generating, providing a rationale for larger prospective multicenter studies. Second, there were notable differences in donor characteristics between the two groups, though the similar admission severity score strengthens the observed trends. Finally, the study design did not allow us to differentiate whether the potential benefits of HBO on early graft function were due to post-exposure effects following cardiac arrest or a preconditioning effect before organ procurement.

Taken together, our results primarily support the feasibility and safety of hyperbaric oxygen therapy in potential liver donors. Rather than demonstrating a proven benefit, these preliminary findings should be regarded as hypothesis-generating and provide a rationale for future prospective and multicenter investigations.

Overall, our findings highlight favorable trends in post-transplant hepatic function and support the feasibility and safety of HBO in this donor population, while underscoring the need for larger, prospective studies to confirm these preliminary observations.

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 this study was conducted in accordance with French current legislation (CNIL and MR004). 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

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

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LETTER TO THE EDITOR
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Protocol for the ELISPOT-TC Trial: A Randomized Controlled Study Evaluating CMV-Specific Cellular Immune Monitoring in Heart Transplant Recipients

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Keywords: cytomegalovirus (CMV), cellular immune response, heart transplantation, ELISpot, enzyme-linked immunosorbent spot

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Dear Editors,

Human cytomegalovirus (CMV) is the most frequent opportunistic infection in the early months after heart transplantation with reported DNAemia in up to 40%–50% of high risk recipients and CMV disease in 10%–15% within the first year post-transplantation. CMV continues to exert a major negative impact, contributing to acute rejection, opportunistic infections, coronary allograft vasculopathy, graft dysfunction and increased healthcare costs [1].

Post-transplant risk stratification is based on donor–recipient serostatus (D+/R–as high risk, R+ as intermediate, and D–/R–as low); paradoxically CMV transmission and infection may still occur even in settings where immunity or prophylaxis should confer protection, reflecting organ-specific variability in transmission risk and indicating that serology alone does not reliably reflect protective immunity, thereby highlighting the need for additional immune biomarkers [2].

Memory/effector T cells help control CMV through responses to IE-1 and pp65 antigens and the IFN-γ ELISpot assay enables the detection of CMV-reactive T cells and prediction of infection risk [3]. CMV-specific cellular immunity (CMI) can identify higher-risk kidney transplant recipients who are more likely to develop CMV infection, while preserved CMV-CMI responses confer protection against post-transplant replication and disease [4, 5]. Recent multicenter trials have further supported the role of immunoguided prophylaxis in solid-organ transplantation. In kidney and liver transplant recipients, immune monitoring based on CMV-specific T-cell responses safely

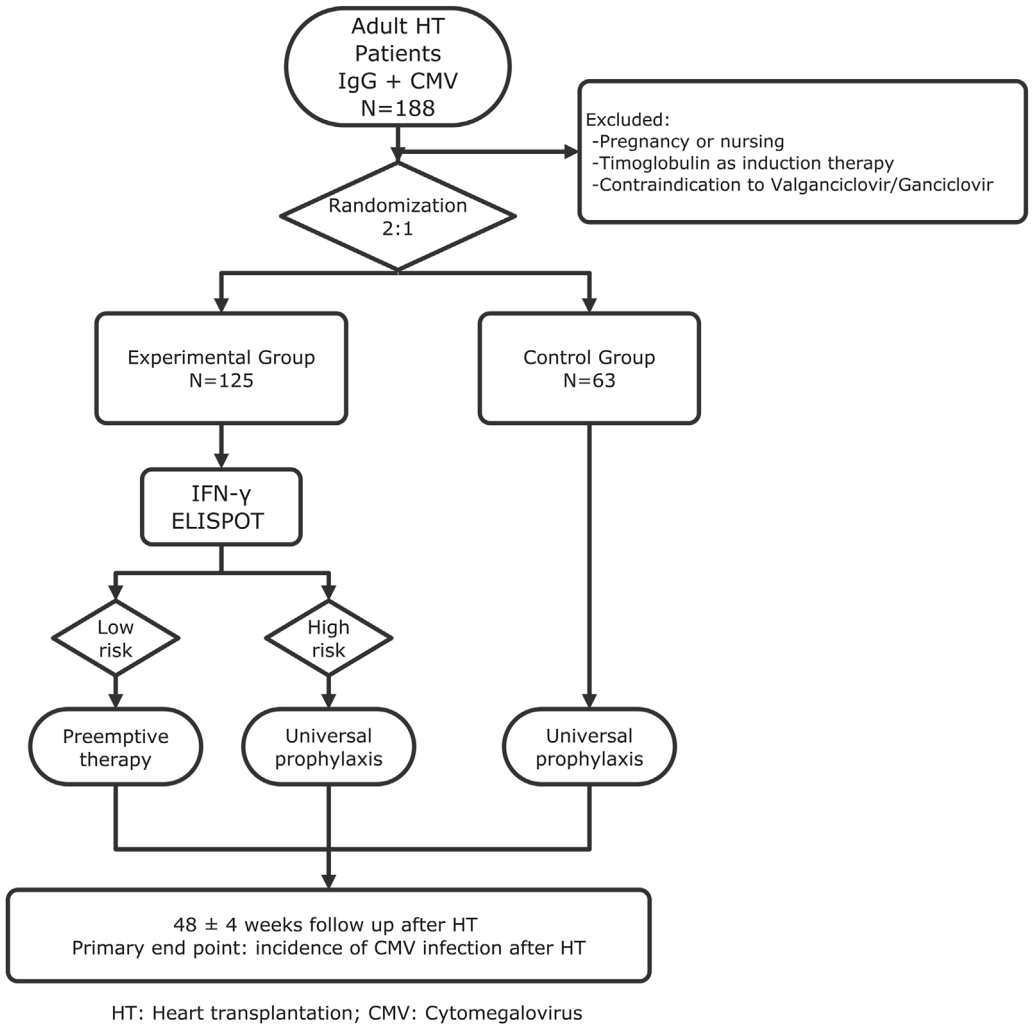

FIGURE 1 | Flowchart of the trial.

reduced antiviral exposure without increasing infection rates [6], whereas in lung transplantation, CMV-CMI–guided prophylaxis proved non-inferior to standard strategies while minimizing antiviral toxicity and adverse events [7].

However, most studies assessing CMV-specific cellular immunity have been conducted in kidney transplantation, and their findings may not be fully extrapolable to heart transplant recipients, who face higher perioperative morbidity and mortality [5].

Current Spanish and international guidelines for heart transplantation provide only low-level evidence, and CMV-CMI monitoring is still recommended based solely on expert opinion, particularly in seropositive (R+) recipients [8, 9].

Preventive strategies currently rely on universal prophylaxis with valganciclovir or PCR-guided preemptive therapy. While effective, both have limitations such as toxicity, late-onset infections, and viral resistance [8, 10].

The ELISPOT-TC trial will address this gap by evaluating whether prophylaxis guided by CMV-specific CMI, assessed by IFN-γ ELISpot (T-SPOT.CMV), is non-inferior to universal valganciclovir prophylaxis in seropositive heart transplant recipients.

It will be a phase IV, multicenter, open-label, randomized (2:1), non-inferiority clinical trial conducted across 11 Spanish transplant centers. A total of 188 adult CMV-seropositive recipients will be enrolled (125 experimental, 63 control) as shown in **Figure 1**.

Patients will be randomly assigned by a centralized computer system to either:

- Group 1: CMI-guided prevention based on T-SPOT.CMV results, or
- Group 2: Standard universal valganciclovir prophylaxis for 3 months.

Randomized will be centralized and stratified by center. The assigned preventive strategy will not be masked to investigators or participants.

Eligible participants will be adult (≥18 years) CMV-seropositive recipients able to provide informed consent. All patients will undergo T-SPOT. CMV testing at day 10 and at month 3 post-transplant,Viral load monitoring by quantitative nucleic acid testing (QNAT) will be performed throughout follow-up according to a standardized schedule.

In the experimental arm, T-SPOT. CMV testing at day 10 post-transplant will classify patients as high or low risk, guiding either initiation of antiviral prophylaxis in those without CMV-specific cellular immunity (high-risk) or a pre-emptive strategy in those with preserved immunity (low-risk).

Patients will be followed for 48 weeks with scheduled visits to monitor outcomes.

The primary endpoint will be the cumulative incidence of CMV infection at 1 year. Secondary endpoints will include the classification of CMV infection into clinically significant and no-clinically significant categories (according to standardized, consensus-based viral load thresholds uniformly applied across centers and the presence of CMV-related symptoms or disease) as well as CMV disease, graft rejection, opportunistic infections, hematological adverse events, mortality, and cost-effectiveness.

Analysis is planned both per-protocol and by intention-to-treat. Comparisons between groups will use standard tests for continuous and categorical variables, Cox proportional hazards models for time-to-event analyses, and Kaplan-Meier survival curves. Non-inferiority will be assessed with a 10% margin. The trial will comply with the Declaration of Helsinki and Spanish legislation and has received approval from the national regulatory authority and local ethics committees. It has been registered at ClinicalTrials.gov (NCT04278547).

This study will represent the first randomized multicenter trial in heart transplantation to use a validated and commercially available IFN-γ ELISpot assay (T-SPOT.CMV) for guiding CMV prevention. As a randomized clinical trial, the study design will ensure strong internal validity and methodological robustness, while stratification by center will enhance the generalizability of the results across diverse clinical settings. By prospectively integrating immunological monitoring into a clinical decision algorithm, this trial takes an essential step toward individualized prevention.

The trial will not only examines efficacy and safety but will also address the economic impact, including both direct antiviral costs and indirect healthcare-related costs.

Universal valganciclovir prophylaxis is effective but costly and associated with frequent adverse events such as leukopenia and neutropenia. A CMI-guided approach has the potential to reduce unnecessary drug exposure, minimize toxicity, and lower costs while maintaining protection. This aligns with the broader movement toward precision medicine in transplantation [8, 9].

Certain limitations should be acknowledged: variability among participating laboratories may influence CMV DNAemia quantification despite standardized procedures; the exact proportion of patients who will ultimately receive valganciclovir prophylaxis versus preemptive therapy cannot be determined in advance; and the 48-week follow-up period will be insufficient to fully assess indirect CMV effects such as cardiac allograft vasculopathy, which has traditionally been one of the main arguments supporting universal prophylaxis.

Despite these challenges, the ELISPOT-TC trial could support a paradigm shift in CMV prevention. Instead of exposing all patients to antiviral prophylaxis, immune monitoring could allow for targeted use of therapy, reducing adverse events and improving cost-effectiveness. The ELISPOT-TC trial thus represents a landmark step toward personalized prevention strategies in transplantation [9].

Detailed methods, inclusion criteria, statistical analyses, and full CONSORT checklist will be provided in the **Supplementary Material**.

Sincerely,

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 Bellvitge University Hospital Ethics Committee, Barcelona, Spain. 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

Conceptualization/Design: EG-R, CD-L, DK, VD, MG-C, CO-B, FH-P, DC-M, FG-V, LF-G, LL-L, AG-T, MG-M, PC, LH, LR, SI, NS, JC-C, OB, and JG-C. Methodology/Investigation: All authors. Writing – Original Draft and Review: EG-R, CD-L, DK, VD, MG-C, CO-B, FH-P, DC-M, FG-V, LF-G, LL-L, AG-T, MG-M, PC, LH, NS, JC-C, OB, and JG-C. Resources/Analytic Tools: DK, LD, and OB. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research 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.2025.15565/full#supplementary-material

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