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Is tolerance the holy grail for transplantation?

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FORUM
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Emerging Entities in Vascularized Composite Allotransplantation: A New Layer to Ongoing Challenges

Haizam Oubari[1]*, *Yanis Berkane*[1], *Curtis L. Cetrulo*[2] and *Alexandre G. Lellouch*[2]*

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Keywords: vascularized composite allotransplantation, VCA, whole eye transplantation, WET, swine models

A Forum discussing:

Experimental Swine Models for Vascularized Composite Allotransplantation and Immunosuppression: A Systematic Review and Case Report of a Novel Heterotopic Hemifacial Swine Model
by Knoedler L, Klimitz FJ, Huelsboemer L, Niederegger T, Schaschinger T, Knoedler S, Boroumand S, Brown S, Pomahac B and Kauke-Navarro M (2025). Transpl. Int. 38:14520. doi: 10.3389/ti.2025.14520

We read with great interest the recent article by Leonard Knoedler et al., titled *"Experimental Swine Models for Vascularized Composite Allotransplantation and Immunosuppression: A Systematic Review and Case Report of a Novel Heterotopic Hemifacial Swine Model"*, which provides a thorough overview of the current strategies for VCA studies in swine. We commend the authors for their comprehensive synthesis of recent advancements in this evolving field and their description of a novel heterotopic partial face transplant model in this species. Experimental VCA models for immunological studies must incorporate the essential components of VCA, and the innovative hemifacial model aligns well with that requirement. Of particular interest, the design conveniently includes mucosal tissue. It presents anatomical features that allow for the integration of vascularized bone marrow, an element shown to be relevant in tolerance induction studies through the establishment of mixed hematopoietic chimerism [1]. Furthermore, porcine models are especially valuable: while nonhuman primates remain a cornerstone for certain translational endpoints, their use is constrained by cost, ethical considerations, and regulatory restrictions. They are therefore most critical at the final stage of translational research, typically after compiling strong data from small animal and swine studies. Pigs offer anatomical and physiological similarities to humans, facilitating surgical refinement, preservation protocol optimization, and immunologic studies. Importantly, experimental studies in whole-eye transplantation must be ethically justified by their potential to advance vision restoration, and should adhere to established animal welfare frameworks [2] as well as recent field-specific ethical analyses [3]. At the same time, heterotopic replantation studies, although not directly assessing visual restoration, can provide critical insights into *ex vivo* preservation strategies and graft viability, which are indispensable steps toward making functional WET a clinical reality, while also informing the design of future orthotopic models that impose a higher experimental burden on the recipient animal.

Among the diverse spectrum of VCAs, a new entity has emerged: whole-eye transplantation (WET). This groundbreaking procedure was first performed by Rodriguez

Forum

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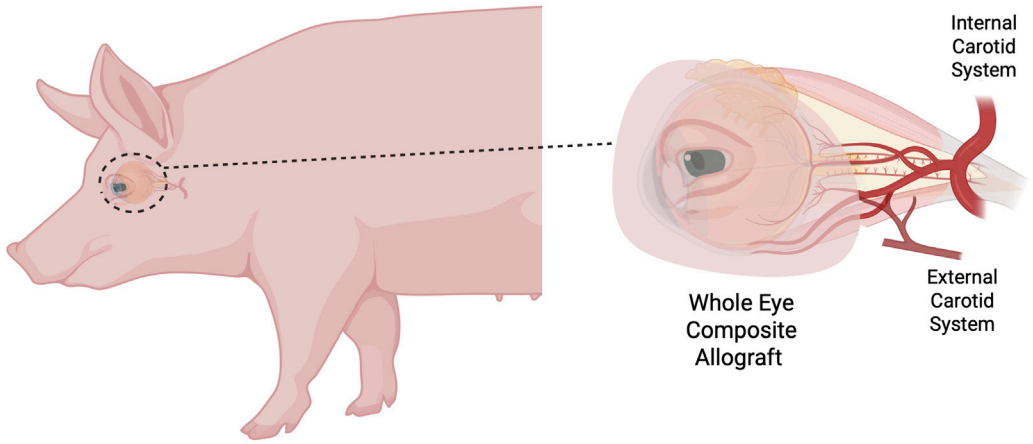

FIGURE 1 | Whole eye transplantation model in the pig.

et al. at NYU [4, 5] as part of a face VCA, aiming for morphological restoration in a patient who had sustained a severe facial injury with loss of the left eye. This groundbreaking achievement has renewed hope for patients with ocular blindness by demonstrating the technical feasibility of whole-eye transplantation, albeit without vision restoration to date. It has also underscored the need for extensive preclinical research to optimize key aspects such as graft preservation, nerve coaptation, and immunosuppressive strategies. In parallel, it has stimulated renewed interest in WET research, building on earlier work already undertaken in several animal models, including orthotopic replantation experiments in rodents [6], as well as human anatomical studies [7–9]. The porcine whole eye vascularized composite allotransplant model has been described [10, 11] and presents several distinct anatomical advantages. It includes the eyeball, palpébra, lacrimal gland, and intraorbital content. Notably, the absence of a lateral orbital wall [12] allows for a vascular configuration that is particularly favorable for procurement and experimental manipulation. The facial vein, originating from the frontal vein and forming part of the external jugular vein system, shares a communicating branch with the ophthalmic vein. On the arterial side, the ophthalmic artery maintains a direct communicating branch with the external carotid system, allowing the arterial pedicle of the WET to be dissected from the ophthalmic artery proximally to the external and common carotid arteries in the neck. This feature facilitates *ex vivo* experiments and transplantation studies, enabling WET procurement solely via the external carotid artery and jugular veins without intracranial dissection (**Figure 1**). Our group has recently refined and adapted this porcine model for *ex vivo* machine perfusion studies [13] and confirmed that these anatomical features are consistent across different pig strains, including Yucatan, Yorkshire, and common commercial breeds (unpublished data). Notably, the WET unit can also be combined with other facial components into chimeric composite flaps, including the ear and additional facial subunits.

Non–skin-bearing VCA models, such as uterine [14] and laryngeal [15] transplantation in swine, have also been developed, offering valuable insights into surgical training, preservation strategies, and immunosuppression. However, these models lie beyond the scope of the present discussion. As WET represents an even more complex and sensitive category of VCA that has only recently emerged in clinical practice, it fully fits within the VCA domain. While it holds remarkable translational promise, substantial work remains to address its unique anatomical, immunological, and neurophysiological challenges.

In conclusion, incorporating WET models into future VCA studies will be essential to tackle key hurdles, including immunological compatibility, preservation strategies, and restoration of function. Fostering close collaboration among microsurgeons, transplant immunologists, and neuroscientists will be critical to accelerating the translation of experimental advances into effective clinical protocols for WET, and VCA more broadly.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The animal study was approved by Massachusetts General Hospital IACUC. The study was conducted in accordance with the local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

HO conceptualized the manuscript, conducted the literature review, and drafted the initial version. YB contributed to manuscript drafting, critical revisions, and literature analysis. CC and AL provided expert input on vascularized composite allotransplantation models, supervised the work, and critically revised the manuscript for important intellectual content. 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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REVIEW
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Tolerance Induction Strategies in Organ Transplantation: Current Status and Future Perspectives

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Achieving donor-specific immune tolerance has the potential to eliminate the need for lifelong immunosuppression in transplant recipients, but translating this goal into clinical practice remains challenging. Unlike laboratory rodents, humans are exposed to a variety of pathogens that generate memory T cells, which can interfere with tolerance induction. Establishing full donor hematopoietic chimerism, whether spontaneous or induced, can support robust immune tolerance. However, it often relies on graft-versus-host (GvH) reactivity, which carries significant risks, including graft-versus-host disease (GVHD) and infection. Although non-myeloablative conditioning protocols have shown promise, their broader use is limited by concerns about toxicity and the need to carefully balance GvH responses. Mixed and transient chimerism represents a less toxic alternative, but its effectiveness in humans is hindered by limited durability and resistance from memory T cells. Thymus transplantation offers another strategy by promoting central tolerance through donor-specific thymic education of developing T cells. Regulatory cell therapies combined with reduced immunosuppression have emerged as a safer approach. Early clinical trials have yielded encouraging results. Innovations in IL-2 pathway modulation and genetic engineering, including CAR-redirected regulatory T cells, may further enhance the precision, durability, and safety of strategies aimed at achieving transplantation tolerance.

Keywords: transplantation, thymus, hematopoietic chimerism, immune tolerance induction, regulatory cell therapy, genetic engineering

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IMMUNE TOLERANCE

The concept of immune tolerance in transplantation refers to the immune system's inability to mount an effector response selectively against donor antigens. In experimental models, the acceptance of a second graft from the same donor in the absence of immunosuppressive therapy, contrasted with the rejection of a third-party allograft, defines donor-specific tolerance. In humans, such experimental validation is not feasible. Instead, the term operational tolerance is used to describe a state in which the graft maintains normal function and histology in the absence of immunosuppressive treatment, and the recipient shows no increased susceptibility to infections, indicating overall preservation of immune competence.

Achieving a stable and robust state of donor-specific tolerance in clinical transplantation would allow for the elimination of long-term immunosuppression and its many associated complications, notably infections and malignancies. The aim of this review is not to provide an exhaustive account of

all ongoing protocols, an effort already comprehensively undertaken in the report from the 6th International Sam Strober Workshop on Transplantation Tolerance [1], but rather to offer a critical and balanced perspective on current results and potential avenues for improvement.

CHALLENGES IN TRANSLATING TOLEROGENIC PROTOCOLS TO CLINICAL TRANSPLANTATION

Numerous immunomodulatory strategies have successfully induced tolerance to allogeneic tissues or organs in experimental models, particularly in mice [2]. However, the translation of these tolerogenic protocols to the clinical setting has often yielded disappointing or even negative results, thus limiting the translational relevance of rodent-based models [2]. It is essential to examine the reasons behind these failures in order to adapt these strategies to the specificities of the human host.

One major difference lies in the microbial exposure of humans (and other large mammals), which contrasts sharply with the controlled environments in which laboratory rodents are bred, typically under specific pathogen-free (SPF) or even more stringent conditions (SOPF) [3]. As a consequence, humans develop a substantial compartment of memory T cells [3], including donor-reactive memory T cells generated through heterologous immunity [4]. These cells contribute to a relative resistance to the induction of transplantation tolerance [5]. It is well established that laboratory mice exhibit a naïve-to-memory T cell ratio comparable to that of human neonates [3]. Remarkably, mice derived from pet stores or farms, by contrast, show a distribution of memory T cells within lymphoid organs and peripheral tissues similar to that observed in adult humans [3]. Furthermore, infection of a laboratory mouse with a single pathogenic virus can render it refractory to tolerance induction via peripheral immunomodulation, an approach otherwise highly effective in uninfected animals [6]. A dose-dependent effect has also been demonstrated: co-infection with multiple pathogens further increases resistance to tolerance induction [6].

In addition, despite numerous promising studies [7], there are still no universally validated biomarkers of tolerance in transplantation. This lack of reliable markers continues to preclude the safe and personalized tapering or withdrawal of immunosuppressive therapy [1, 8, 9].

SPONTANEOUS MIXED HEMATOPOIETIC CHIMERISM FOLLOWING SOLID ORGAN TRANSPLANTATION

In 2008, a landmark publication reported the spontaneous development of full hematopoietic chimerism in a 9-year-old girl following liver transplantation, in the absence of any myeloablative conditioning regimen [10]. This case demonstrated, first, that a transplanted liver can harbor a sufficient number of hematopoietic stem cells (HSCs) to support complete, multilineage, and durable hematopoiesis [10]. More importantly, it highlighted the capacity of graft-versus-host (GvH) reactivity, mediated by donor-derived T cells, to mimic the effects of bone marrow transplant conditioning.

This facilitating role of GvH reactivity includes two key mechanisms [1]: suppression of the host-versus-graft (HvG) immune response, and [2] clearance of hematopoietic niches via destruction of host HSCs, thereby enabling donor cell engraftment [10].

We recently reported a similar case following isolated kidney transplantation [11, 12]. Durable engraftment of HSCs derived from the renal graft was established in the recipient's bone marrow [12]. In this case as well, the induction of full chimerism was associated with robust GvH reactivity [12]. In both instances, immunosuppressive therapy was successfully discontinued without subsequent graft rejection, despite restoration of immune competence, thereby meeting the criteria for operational tolerance [10, 12].

To further elucidate the mechanisms linking GvH reactivity and hematopoietic chimerism, the group led by Megan Sykes at Columbia University investigated patients undergoing intestinal and multivisceral transplantation, in whom graft survival without rejection has been shown to correlate with the volume of transplanted tissue [13, 14]. A direct relationship was identified between the number of transplanted organs and the extent of hematopoietic chimerism observed post-transplant [15]. Notably, donor-derived T lymphocytes from visceral grafts were found to mediate GvH reactivity that supported the persistence of hematopoietic chimerism not only in the graft itself [16], but also in the recipient's peripheral blood and bone marrow [17, 18].

Collectively, these observations in solid organ transplant recipients, none of whom underwent myeloablative conditioning, underscore the critical role of GvH reactivity in the establishment and maintenance of hematopoietic chimerism.

INDUCTION OF FULL DONOR HEMATOPOIETIC CHIMERISM

The induction of stable immune tolerance associated with full donor chimerism was first achieved through sequential transplantation of hematopoietic progenitor cells and a kidney from the same HLA-incompatible donor in patients undergoing treatment for hematologic malignancies [19]. When full donor chimerism is established, donor-derived dendritic cells colonize the recipient's thymus (**Figure 1**). This allows newly developing thymocytes to undergo negative selection if they are reactive to donor or recipient antigens, presented respectively by donor dendritic cells and recipient medullary thymic epithelium (**Figure 1**). Tolerance is thus predominantly mediated through central mechanisms and requires a stable, long-term dominance or completeness of donor hematopoiesis [20].

However, this approach typically necessitates myeloablative conditioning, which carries unacceptable toxicity in patients without malignancy. In transplantation, several strategies have

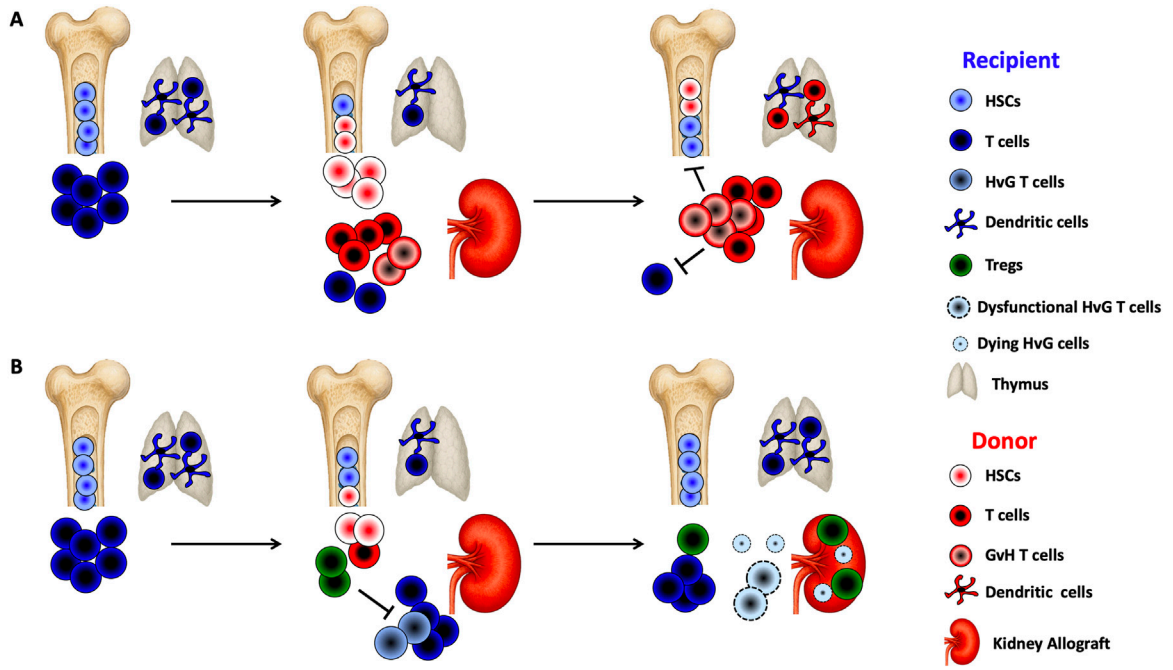

FIGURE 1 | Chimerism-based transplant tolerance **(A)** Sustained Full Chimerism: Following non-myeloablative conditioning, recipients receive a large number of donor CD34$^+$ hematopoietic stem cells (HSCs) and donor T cells along with the kidney allograft. Graft-versus-host (GvH) reactivity may promote the expansion of donor T cells, which eliminate recipient T cells and hematopoietic cells, thereby creating space in the bone marrow for donor HSCs to engraft. Once engrafted, donor HSCs continuously supply the thymus with T cell precursors and dendritic cell progenitors, promoting central donor-specific tolerance. These conditions support the establishment of sustained full chimerism. **(B)** Transient Mixed Chimerism: After non-myeloablative conditioning with T cell-depleting induction, recipients receive unfractionated donor bone marrow, including HSCs and T cells, alongside the kidney allograft. The conditioning regimen induces lymphopenia while sparing regulatory T cells (Tregs), leading to early Treg expansion. In the presence of donor antigen, this Treg-dominant environment suppresses the activation of host-versus-graft (HvG)-reactive T cells and fosters peripheral deletion of donor-reactive T cells. These mechanisms enable the development of transient mixed chimerism.

been developed to induce full chimerism, and thereby stable tolerance, without resorting to myeloablation [20].

The first such protocol, developed at Stanford University, combines total lymphoid irradiation, anti-thymocyte globulin (ATG), and infusion of a limited number of donor T cells (1×10^6/kg). This approach achieved durable chimerism and successful immunosuppression withdrawal in more than 80% (24/29) of recipients receiving combined kidney and hematopoietic stem cell transplants from HLA-identical donors [21, 22]. However, in HLA-incompatible settings, this protocol generally results in low-level and transient chimerism, even when higher doses of donor T cells are administered (up to 100×10^6/kg) [22]. Critically, loss of chimerism in this context is often rapidly followed by renal graft rejection [22].

A second strategy, developed at Northwestern University, involves a more intensive conditioning regimen [23], comprising total body irradiation, fludarabine, and cyclophosphamide administered both pre- and post-transplant, along with donor T cells (3.8×10^6/kg). Cyclophosphamide post-transplant, in combination with co-infusion of CD8$^+$ TCR$^-$ immunomodulatory "facilitator" cells (FCR001), is designed to mitigate the risk of graft-versus-host disease (GVHD) associated with the transfer of mature donor T cells [23]. Over 80% (26/32) of patients in this protocol achieved high and stable levels of chimerism, with successful discontinuation of immunosuppressive therapy in the vast majority (25/26) [24]. In this context, the establishment of full donor chimerism represents the most reliable biomarker of successful tolerance induction [25].

Nevertheless, two major adverse events have emerged as limitations to widespread implementation. Three patients experienced severe infections resulting in graft loss (n = 2) or death (n = 1) [26]. In addition, two cases of GVHD occurred, one of which was fatal, and the other developed into chronic GVHD [26]. These findings emphasize both the necessity and the inherent risk of robust GvH reactivity for maintaining high-level chimerism in the absence of myeloablation [20].

Regarding GVHD risk mitigation, Alice Bertaina and colleagues at Stanford recently reported a novel approach in three patients with Schimke immuno-osseous dysplasia, a syndrome characterized by severe combined immunodeficiency, skeletal dysplasia, and early-onset glomerular kidney failure [27]. This condition is caused by mutations in SMARCAL1, a gene involved in DNA repair, rendering patients highly vulnerable to cytoreductive treatments and increasing mortality following hematopoietic stem cell transplantation [28]. The Stanford protocol reduces this risk through the use of reduced-intensity conditioning and

grafts depleted of TCRαβ$^+$ T cells and CD19$^+$ B cells. All three patients achieved full donor hematopoietic chimerism and maintained excellent renal graft function from the same donor, in the complete and sustained absence of immunosuppressive therapy [27]. The investigators propose expanding this protocol to broader patient populations beyond those with inborn errors of immunity and hematopoiesis [27]. However, favorable outcomes with TCRαβ/CD19-depleted grafts have so far been primarily observed in patients with inborn errors of immunity [29].

Additionally, the case of a child with Schimke syndrome who spontaneously developed acute GVHD and full hematopoietic chimerism following isolated kidney transplantation illustrates the unique pathophysiological context of this condition [12]. This case highlights how host cells in this syndrome, due to their limited proliferative capacity and functional impairment, are at a competitive disadvantage, particularly under immunosuppressive therapy, which favors engraftment of donor-derived hematopoietic stem cells [29, 30].

Collectively, these pilot studies indicate that in patients without preexisting immune deficiency, achieving and maintaining high-level, durable hematopoietic chimerism in the context of HLA incompatibility and without myeloablation requires a degree of GvH reactivity that may carry life-threatening complications.

INDUCTION OF MIXED AND TRANSIENT DONOR HEMATOPOIETIC CHIMERISM

Mixed chimerism refers to the coexistence of donor- and recipient-derived hematopoietic cells in the peripheral blood and indicates the preservation of the recipient's hematopoietic system [20]. In laboratory mice, stable mixed chimerism can be readily achieved through the administration of donor hematopoietic stem cells in combination with various tolerance-inducing regimens. Historically, the foundation for a clinically translatable strategy was laid using non-myeloablative conditioning that combined cytoreductive agents with thymic irradiation [31]. To mitigate treatment-related toxicity, cytoreduction was successfully replaced in murine models by either co-stimulatory blockade [32] or regulatory T cell-based therapy [33].

However, in humans and non-human primates, prior exposure to pathogens leads to the development of alloreactive memory T cells via heterologous immunity, which impairs the induction of mixed chimerism through immunomodulation alone [6, 34]. The first clinical protocol for tolerance induction via mixed chimerism therefore incorporated siplizumab, an anti-CD2 monoclonal antibody that effectively targets memory T cells [35]. Notably, both siplizumab and alefacept are able to inhibit the expansion of CD2^{high} CD28$^-$ pro-inflammatory T cells, which are resistant to CTLA-4-Ig [36, 37]. The development of new agents targeting memory T cells, such as OX40-specific antibodies, may ultimately restore the tolerogenic potential of co-stimulatory blockade in humans, a mechanism currently best demonstrated in murine and non-human primate models [38]. In this context, it is important to highlight the recent communication at the ESOT 2025 congress regarding the first use in humans (NCT07020156) of a monoclonal anti-OX40 antibody (OX118).

Under the leadership of the Massachusetts General Hospital (MGH) team, the mixed chimerism protocol was successfully translated to non-human primates [39] and humans [40, 41]. However, in contrast to murine models, the level and duration of donor chimerism achieved in these species were substantially lower and more transient (lasting only a few weeks). This short-lived chimerism was associated with reduced tolerance efficacy: three of the first ten patients developed *de novo* donor-specific antibodies (DSAs) or acute rejection episodes, precluding immunosuppression withdrawal. Among the remaining seven patients, three had to resume immunosuppression due to chronic rejection or recurrence of native kidney disease [26].

Several modifications have since been introduced to enhance protocol efficacy and compensate for the unavailability of specific therapeutic agents. The inclusion of four doses of rituximab helped prevent *de novo* DSA development, which had been observed in early patients [41]. More recently, the protocol was adapted to address "chimerism transition syndrome," characterized by acute kidney injury and chimerism loss during rapid immune reconstitution. The revised MGH protocol now includes fludarabine, a reduced dose of cyclophosphamide, and omits post-transplant rituximab [1]. In parallel, the PANORAMA trial (NCT04803006), led by Joshua Weiner at Columbia University, is investigating modified siplizumab dosing to enhance memory T cell depletion, with encouraging preliminary results [1].

At the Samsung Medical Center, where siplizumab is unavailable, the protocol was adapted using anti-thymocyte globulin (ATG) instead. Infectious complications, including BK virus nephritis, prompted dose reductions of both fludarabine and ATG, and a switch from tacrolimus to sirolimus at 1-month post-transplant [42]. In this Korean cohort, immunosuppression was discontinued for over 1 year in five of eight patients. However, one patient experienced T cell-mediated rejection following a respiratory infection, highlighting the fragility of the tolerogenic state [42].

Mechanistic studies have demonstrated a biphasic process in tolerance induction: initial enrichment of regulatory T cells during post-induction lymphopenia [43], followed by progressive deletion of alloreactive T cell clones over time (**Figure 1**) [44]. The renal allograft likely contributes to this functional inactivation of donor-specific responses (**Figure 1**). Indeed, patients who received hematopoietic stem cells under the same induction regimen but without a kidney transplant retained anti-donor T cell reactivity upon chimerism loss [45], unlike those with combined kidney-bone marrow transplantation [44]. This hypothesis is supported by observations in non-human primates: combined (simultaneous or sequential) heart and bone marrow transplantation from the same donor failed to induce tolerance [46]. In contrast, triple transplantation of heart, kidney, and bone marrow from the same donor, using

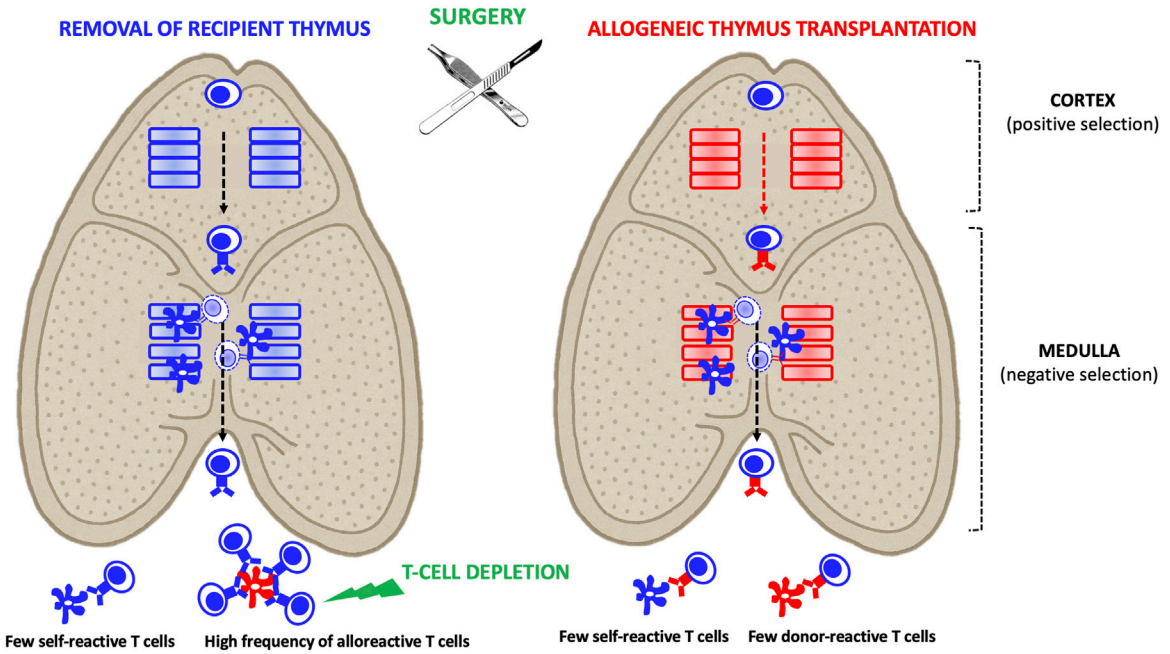

FIGURE 2 | Allogeneic Thymus Transplantation: In the recipient thymus, thymocytes derived from T cell progenitors undergo positive selection by cortical epithelial cells. This positive selection process determines the T cells' restriction to self-HLA antigens (depicted by a blue TCR) that were recognized in the cortex. Subsequently, developing thymocytes undergo negative selection in the medulla, where those that strongly react to self-antigens presented by medullary epithelial cells and dendritic cells are eliminated. As a result, mature thymocytes exiting the thymus are devoid of self-reactive T cells but may still include alloreactive T cells. In the context of allogeneic thymus transplantation, recipient-derived thymocytes are positively selected on donor HLA molecules (depicted by a red TCR). As they migrate through the medulla, they undergo negative selection, eliminating those that strongly react to recipient HLA (presented by medullary dendritic cells) or donor HLA (presented by medullary epithelial cells). Consequently, the mature thymocytes that exit the donor thymus are tolerant to both recipient and donor antigens. Combining thymus and organ transplantation from the same donor represents a potent strategy to induce immune tolerance. However, two key conditions must be met to achieve this: 1- The recipient's native thymus must be removed to eliminate a source of donor-reactive T cells. 2- Pre-existing peripheral donor-reactive T cells generated before thymus transplantation must be eliminated.

identical conditioning, resulted in higher levels of donor chimerism, prevented the formation of DSAs and anti-donor cytotoxic responses, and most importantly, enabled successful withdrawal of immunosuppression [46]. This kidney-specific protective effect was associated with an accumulation of regulatory T cells within the renal graft, suggesting their role in local suppression and potentially in the deletion of alloreactive clones [43, 46, 47].

In line with these findings, during the Sixth International Workshop on Clinical Transplantation Tolerance, several investigators reported the presence of organized infiltrates enriched in FOXP3$^+$ regulatory T cells within the grafts of operationally tolerant patients [1]. These structures are reminiscent of regulatory tertiary lymphoid organs observed in renal allografts of tolerant mice [48]. Advances in spatial transcriptomics may soon clarify the prognostic and mechanistic significance of these structures [1].

In conclusion, protocols based on mixed chimerism have yielded mixed results, with variable and often temporary efficacy in inducing tolerance. Further optimization of immunomodulatory regimens accompanying hematopoietic stem cell transplantation will be required to enhance both their clinical effectiveness and safety profile.

THYMUS TRANSPLANTATION

Thymus transplantation enables the induction of central, donor-specific immune tolerance, particularly when the donor is juvenile, provided two key conditions are met (**Figure 2**). First, the recipient must undergo thymectomy to ensure that all developing thymocytes are educated within the donor thymic microenvironment [49]. Second, profound peripheral lymphodepletion is required to eliminate pre-existing alloreactive T cells generated prior to thymus transplantation [49, 50].

In murine models, transplantation of a neonatal donor thymus under the kidney capsule of a thymectomized and lymphodepleted recipient enables long-term acceptance of a heart graft from the same donor strain without the need for ongoing immunosuppression [50]. However, the critical role of thymic vascularization in maintaining the tolerogenic function of the thymic epithelium became apparent when this approach was translated to large animal models. To address this, various surgical techniques have been developed to optimize thymic graft perfusion.

One such strategy, known as the "thymokidney" approach, involves transplanting the donor's thymus under the capsule of

one of their own kidneys several weeks prior to allogeneic transplantation [51]. This interval allows the thymus to revascularize and regain functional capacity in an autologous environment before subsequent transplantation of the composite "thymokidney" graft. This approach was notably employed by Robert Montgomery's team during the first porcine thymokidney xenotransplant into brain-dead human recipients [52]. Thymic perfusion may also be preserved through microsurgical anastomosis of donor thymic vessels [49], or via *en bloc* transplantation of combined thymic and cardiac grafts.

Nevertheless, transplantation of an intact thymus that retains mature donor-derived thymocytes carries a significant risk of GVHD, especially in immunodeficient recipients. To mitigate this risk in athymic infants, researchers at Duke University developed a strategy involving the transplantation of thymic epithelial tissue devoid of donor thymocytes. These thymocytes are eliminated by culturing thymic slices for approximately 10 days prior to implantation. This approach, now FDA-approved under the commercial name RETHYMIC® (allogeneic processed thymus tissue), has dramatically improved outcomes for children with congenital athymia [53]. Its potential to induce alloimmune tolerance has been demonstrated in a rat heart transplantation model [54] and is currently under investigation in clinical transplantation settings [55–57].

REGULATORY CELL THERAPY

The iatrogenic risks associated with hematopoietic stem cell transplantation have sparked interest in peripheral immunomodulation strategies using regulatory cell therapies, including T lymphocytes and myeloid cells such as dendritic cells and macrophages [1]. The ONE Study consortium, comprising eight European and American centers, jointly analyzed the clinical and immunological impact of distinct regulatory cell products administered to kidney transplant recipients, using a shared protocol for follow-up [58]. Combined analysis of these trials showed that, when regulatory cell therapy was paired with reduced immunosuppression, infection rates were lower and rejection rates comparable to standard immunosuppressive regimens [58].

A more specific analysis from the German cohort at Charité University Hospital demonstrated the feasibility of generating autologous $CD4^+$ regulatory T cell (Treg) products from peripheral blood collected 2 weeks prior to transplantation. Three-year kidney allograft survival reached 100% in both arms of the trial, while 73% of patients who received polyclonal Tregs were maintained on tacrolimus monotherapy [59]. A recent report indicates no graft loss among the 12 patients in the United Kingdom cohort who received polyclonal Tregs, even 7 years after transplantation [1]. Surveillance biopsies from this cohort revealed focal infiltrates enriched in B cell and regulatory gene signatures [60].

These encouraging outcomes have led to the launch of the randomized controlled TWO Study, aiming to enroll 60 patients in two arms. Initially, regulatory cell therapy was scheduled to be administered 6 months after induction with alemtuzumab [61]. Seven patients were treated under this protocol before it was suspended due to concerns about COVID-19-related risks associated with prolonged lymphodepletion [61]. The trial has since resumed with a revised protocol: one arm receives standard immunosuppression after basiliximab induction, while the other includes regulatory cell therapy on day 5 post-transplantation, followed by progressive immunosuppression minimization [62].

In liver transplantation, two clinical trials evaluating donor-specific regulatory cell therapy have yielded contrasting results [63, 64]. A Japanese study achieved complete withdrawal of immunosuppression by 18 months post-transplantation in 70% of patients, with follow-up ranging from 5.4 to 10.4 years [1, 63]. The subsequent multicenter trial (NCT04950842) showed preliminary evidence of $FOXP3^+$-enriched lymphoid infiltrates in protocol biopsies, similar to those observed in renal transplantation trials [1]. By contrast, in an American study, 4 out of 5 patients experienced acute rejection during immunosuppression tapering [64]. Notably, timing differed between the two studies: regulatory T cell therapy was administered on day 13 post-transplantation in the Japanese study, whereas in the American trial, it occurred between 2 and 7 years post-transplantation. More importantly, the Japanese protocol included a bolus of cyclophosphamide 1 week prior to Treg infusion, aimed at depleting alloreactive effector T cells that were activated and proliferating immediately following transplantation. This "debulking" effect, combined with regulatory cell therapy, shifts the immune balance in favor of tolerance.

In the American trial, deuterium-labeled cell tracking revealed rapid contraction and disappearance of infused Tregs, likely due to abrupt interleukin-2 (IL-2) withdrawal following an IL-2-rich *ex vivo* expansion phase [64]. Indeed, studies in type 1 diabetes have demonstrated enhanced Treg persistence when low-dose IL-2 is co-administered with cell therapy [65]. However, this strategy is more challenging in transplantation, where IL-2 may simultaneously stimulate effector responses. One liver transplant trial showed significant Treg expansion but also activation of $CD8^+$ T cells and NK cells, resulting in unexpectedly high rejection rates and premature trial termination [66]. To enhance IL-2 selectivity for Tregs, multiple pharmaceutical efforts are underway to develop IL-2 muteins with increased affinity for the high-affinity IL-2 receptor (CD25), while minimizing interaction with lower-affinity receptors [67, 68]. Combining regulatory cell therapy with such IL-2 muteins may further amplify therapeutic efficacy.

Finally, the development of genetically engineered regulatory cells offers highly promising new avenues (**Figure 3**). Several groups have demonstrated that chimeric antigen receptor (CAR)-redirected Tregs targeting HLA-A2 can suppress alloreactive responses in preclinical transplant models [69, 70]. CAR-Tregs display enhanced suppressive capacity compared to donor-specific Tregs generated via co-culture with donor cells [71]. The ongoing STEADFAST (NCT04817774) and LIBERATE (NCT05234190) trials are evaluating anti-HLA-A2 CAR-Tregs in renal and liver transplantation, respectively [1]. Preliminary findings suggest the presence of $FOXP3^+$ regulatory lymphoid structures within renal grafts from CAR-Treg-treated patients

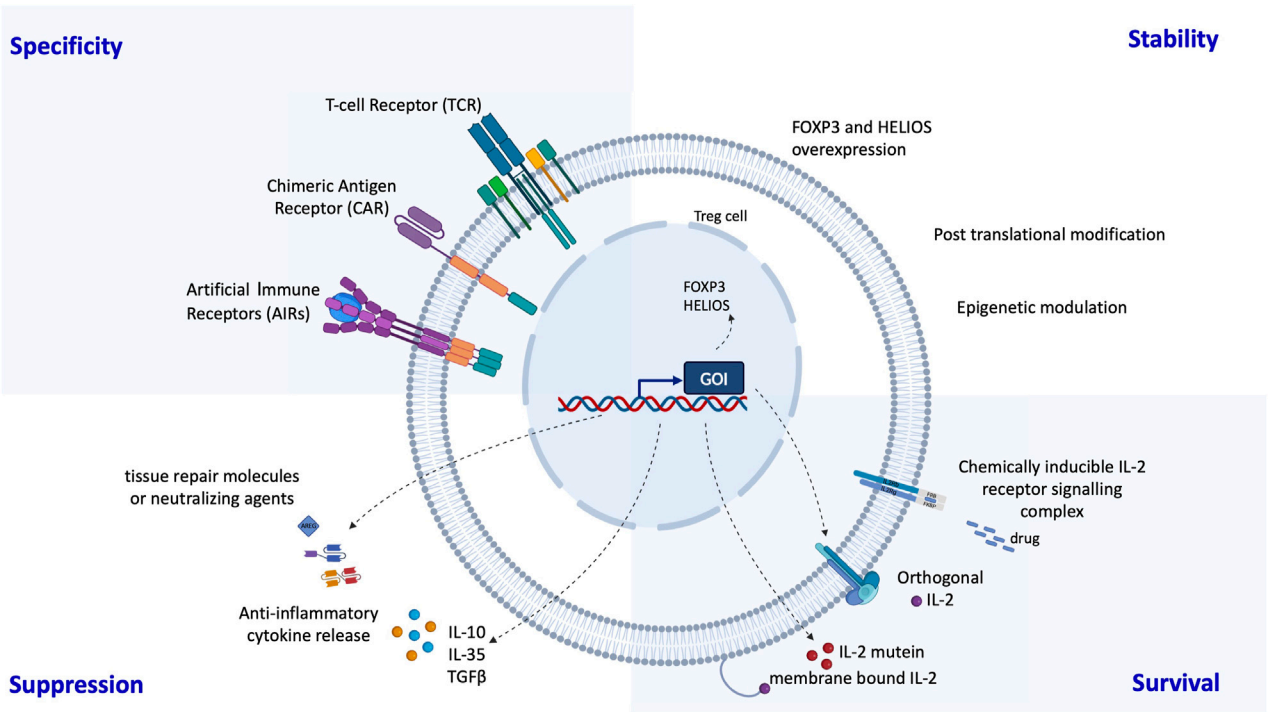

FIGURE 3 | Possibilities to enhance Treg therapies through genetic engineering: Several groups have developed genetic engineering strategies to improve the specificity, stability, survival and suppression of regulatory T cells. Specificity has been greatly enhanced by the addition of chimeric antigen receptors (CARs) or synthetic T cell receptors (TCRs). Stability can be achieved by overexpression of the transcription factors FOXP3 and HELIOS and suppression can be supported by expression of anti-inflammatory cytokines and molecules. The *in vivo* survival of regulatory T cells can be prolonged by making them self-sufficient in a Treg specific IL-2.

[1]. Additional genetic modifications have been proposed to further improve Treg efficacy and resilience. These include conferring resistance to immunosuppressants (e.g., tacrolimus, everolimus, sirolimus) by inactivating FKBP12 [1, 72], and autonomous IL-2 signaling [73]. We are also developing a strategy that harnesses the tolerogenic properties of anti-CD3 monoclonal antibodies [74], in combination with shielded CAR-Tregs that are protected from anti-CD3-mediated clearance via CRISPR-Cas9-based editing (*Blein et al. personal communication*). Additionally, the use of monoclonal antibodies currently under development - such as those targeting CD28 (FR104; NCT04837092) [75] or CD45RC [76] - in combination with targeted regulatory cell therapy, may act synergistically to shift the balance toward immune tolerance. Finally, the transgenic expression of transcription factors involved in the Treg program may help stabilize the Treg epigenetic landscape and reinforce lineage stability in inflammatory environments [77].

ORGAN ENGINEERING TO EVADE THE IMMUNE SYSTEM

An alternative to inducing immune tolerance through immunological reprogramming is the engineering of the graft itself to evade immune detection. Pregnancy provides a compelling demonstration that multiple immunomodulatory mechanisms at the placental interface can create an immunologically privileged zone that remains invisible to alloimmune responses [78]. Failure of these mechanisms can result in placental inflammation resembling transplant rejection [79, 80].

The placenta offers multiple avenues for modulating the immunogenicity of allogeneic transplants, including the epigenetic silencing of polymorphic HLA genes [81] and Th1-skewed chemokine genes CXCL9, CXCL10, and CXCL11 [82]. Additionally, the expression of FasL [83], the enzyme indoleamine 2,3-dioxygenase [84], and immune checkpoint molecules [85] can suppress T cell responses, while specific sialylation motifs on trophoblast proteins inhibit B cell activation [86].

This conceptual framework has already inspired a successful strategy in islet transplantation models in humanized mice [87], non-human primates [88], and more recently, in a first-in-human case [89]. In these studies, three genetic modifications were introduced into allogeneic pancreatic islet cells using CRISPR-Cas12-based gene editing and lentiviral transduction. These modifications involved silencing HLA class I and II molecule expression and overexpressing CD47 [89]. The absence of polymorphic HLA prevents activation of the adaptive immune response (T and B cells), while CD47 expression neutralizes the innate immune response (NK cells and myeloid cells).

The development of normothermic perfusion machines [90, 91], along with rapid advances in cell-specific targeting of viral

TABLE 1 | Pros and cons, and advancements of the different tolerogenic strategies.

Tolerance induction strategy	Main Mechanism	Advantages	Limitations	Currently explored new avenues	Challenges before regulatory approval
Full chimerism	Robust central tolerance via complete donor-derived hematopoiesis	– Enables successful withdrawal of IS drugs without rejection or development of DSA – Prevents post-transplant recurrence of immune-mediated nephropathies	– Conditioning-related toxicity – Risk of life-threatening GVHD – Delayed immune reconstitution – Increased risk of infections	– Approaches to reduce conditioning intensity and GVHR dependence • Use of Tregs (NCT03943238) • T- and B-cell-depleted HSC graft (NCT05508009) Delayed tolerance approaches, for patients who have already a kidney transplant • NCT03591302 • NCT01649388: terminated by sponsor	– Phase 3 CT required to demonstrate a superior benefit/risk ratio compared to standard IS therapy – • NCT03363945 (HLA-matched LD) • NCT03995901 terminated due to high GVHD rates in initial participants
Mixed chimerism	Peripheral tolerogenic mechanisms, via transient, incomplete donor-derived hematopoiesis	– Lower conditioning toxicity – No risk of GVHD – IS drugs withdrawal achieved in some patients	– Less robust tolerogenic effect (rejection or *de novo* DSA may occur upon IS tapering) – Potential recurrence of immune-mediated nephropathies – Risk of chimerism transition syndrome #	Strategies to improve efficacy and safety profile • ECP-DL infusion (NCT07083830) • Combined Treg therapy (NCT03867617) Approaches to mitigate chimerism transition syndrome • Use of fludarabine and avoidance of post-Tx rituximab (NCT04540380) • Enhanced T cell depletion (NCT04803006)	No ongoing Phase 3 CT
Thymus Tx	Central tolerance through intrathymic deletion of donor-reactive T cells	– No need of cytoreductive conditioning – Donor thymus can support immune reconstitution after recipient thymectomy	– Requires thymectomy (open-chest surgery) – Profound T cell depletion needed to eliminate preexisting donor-reactive T cells – GVHD may occur following the transplantation of an intact thymus into an immunocompromised recipient – May not promote tolerance to peripheral tissue-specific antigens (as seen in xenotransplantation models)	Combined thymus-kidney transplantation from neonatal donors in KTx recipients (NCT06715865) ##	While CTTI is approved for congenital athymia, there is currently no clinical evidence supporting its tolerogenic efficacy in solid organ transplantation
Regulatory T cell therapy	Peripheral tolerogenic effects by shifting the immune balance toward regulation	– No need of cytoreductive conditioning – No risk of GVHD – Potential to enhance Treg function through genetic engineering – May at least allow reduction of IS drug burden	– Risk of lineage instability in inflammatory environments (possible drift toward pro-inflammatory phenotypes) – Short-term persistence after administration – Unknown homing capacity to the transplanted graft – Challenge of generating sufficient cells from patients with end-stage organ failure	Approaches to improve the efficacy and robustness • Combination with donor-derived bone-marrow cells (NCT03867617) • Profound T cell depletion prior to therapy (TWO Study ISRCTN 11038572) • Use of cyclophosphamide before Treg infusion (NCT03577431; NCT03654040) Alternative regulatory T cell types • $CD8^+$ Treg cells (NCT06777719) CAR-engineered Tregs	No ongoing Phase 3 CT currently The RETIRE study is a Phase 2 RCT, comparing Treg therapy combined with reduced IS versus SOC (NCT06552169) Overcoming high manufacturing costs and standardization issues

(Continued on following page)

TABLE 1 | (*Continued*) Pros and cons, and advancements of the different tolerogenic strategies.

Tolerance induction strategy	Main Mechanism	Advantages	Limitations	Currently explored new avenues	Challenges before regulatory approval
				• In kidney transplant recipients (NCT04817774) • In liver transplant recipients (NCT05234190)	

#: Chimerism transition syndrome: characterized by acute kidney injury, fever, loss of chimerism during reconstitution of the recipient's immune system.
##: Available information does not clarify whether kidney transplant recipients in the study undergo thymectomy as part of the tolerogenic protocol.
Abbreviations: CTTI, cultured thymus tissue implantation; CT, clinical trial; DSA, donor-specific antibodies; ECP-DL, extracorporeal photopheresis donor lymphocytes; GVHR, graft-vs-host reactivity; GVHD, graft-vs-host disease; IS, immunosuppressive; LD, living donor; SOC, standard of care; Treg, regulatory T cell; Tx, transplantation.

(lentivirus, AAV) and non-viral vectors [92, 93], opens new avenues for applying these strategies to more complex, vascularized organs beyond pancreatic islets. Even before attempting to render complex organs such as the kidney immunologically privileged, it may be feasible to first engineer the graft endothelium to resist preformed donor-specific antibodies (DSA), thereby mimicking the phenomenon of accommodation [94, 95].

CURRENT CLINICAL IMPLICATIONS

To date, no tolerance induction strategy in clinical transplantation has been approved by the FDA or the EMA, nor validated in a completed phase III trial in comparison with standard-of-care immunosuppressive therapies. In other words, protocols designed to induce transplant tolerance have not yet entered routine clinical practice and remain within the realm of research. This observation raises important questions regarding the current limitations and obstacles faced by the strategies developed thus far (**Table 1**). It also underscores the need for continued research to improve both efficacy and safety (**Table 1**).

Mixed and transient chimerism protocols have shown variable success, often requiring resumed immunosuppression due to rejection or donor-specific antibodies [96]. Targeting memory T cells combined with immunomodulation may improve outcomes. Full durable chimerism offers more robust tolerance [24] but carries serious risks like GVHD and infections, limiting development [26]. Reducing conditioning intensity and GVH reactivity dependence is a key challenge. Thymus transplantation shows promise in heart and lung transplants, where thymectomy is feasible, but evidence remains limited and its use in abdominal transplants raises safety concerns due to invasive surgery. Moreover, the scientific publication of the first proof-of-concept case remains pending [57]. Polyclonal or donor-specific Treg therapies alone have not safely enabled immunosuppression withdrawal. This emphasizes the need to enhance Treg function (e.g., genetic engineering) while controlling effector immune responses to improve therapeutic success.

CONCLUSION

Hematopoietic chimerism induction protocols have demonstrated the possibility of achieving tolerance in clinical transplantation, although sometimes at the cost of excessive iatrogenic risk. The implantation of a juvenile donor thymic epithelial template in a heart transplant recipient, thymectomized during the transplantation procedure, could represent an alternative strategy for central tolerance that should be rigorously evaluated. Finally, "augmented" regulatory cell therapies, through genetic modifications, combined with a targeted strategy of effector cell depletion and immunotherapy favoring the regulatory arm of the immune response, represent very promising strategies.

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.

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REVIEW
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Simultaneous Pancreas and Kidney Transplantation in Patients With Type 2 Diabetes Mellitus

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The prevalence of diabetes is increasing exponentially, accompanied by an increase in chronic complications, including nephropathy. Kidney transplantation may offer freedom from dialysis but adding a pancreas addresses the underlying disease. Type 2 diabetes mellitus (T2DM) is often described as a condition of insulin resistance and the concurrent beta-cell loss and dysfunction is potentially underestimated. The aim of this review was to provide a critical appraisal of simultaneous pancreas and kidney (SPK) transplantation in recipients with T2DM. The primary concern with SPK transplantation in this group is insulin resistance and the impact of obesity on outcomes. Multiple studies have shown comparable graft survival (GS), patient survival and complication rates when comparing T2DM and T1DM recipients. Furthermore, patients with T2DM had significantly improved GS with SPK when compared to kidney transplantation alone. Despite these findings, SPK transplantation is only selectively used in T2DM patients. Existing literature focuses on comparing transplant outcomes between patients with T1DM and T2DM. We believe the more relevant question is whether a patient with T2DM would derive a meaningful benefit from an SPK, and whether these benefits outweigh the risks, in the context of their other co-morbidities which are not completely similar to those associated with T1DM.

Keywords: T2DM, equity, outcome predictors, SPK transplantation, review of literature

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INTRODUCTION

Diabetes mellitus represents a significant health challenge with approximately 525million individuals affected worldwide as of 2021 [1]. It is a major cause of blindness, end-stage renal disease (ESRD), cardiovascular events, cerebrovascular accidents, limb amputation and premature mortality. It exerts a substantial economic strain on healthcare systems and accounts for approximately 9% of the annual health budget spent in Europe (€149billion) [2, 3].

Abbreviations: ADA, American Diabetes Association; BMI, Body Mass Index; BMS, Bariatric and Metabolic Surgery; CIT, Cold Ischaemic Time; DBD, Donation after Brain Death; DCD, Donation after Circulatory Death; ESRD, End stage renal disease; GLP-1, Glucagon-like peptide −1; GS, Graft Survival; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; KTA, Kidney Transplant Alone; LRD, Living Related Donor; MI -Myocardial Infarction; NHS, National Health Service; PROMS, Patient Reported Outcome Measures; PTDM, Post-transplant Diabetes Mellitus; PTx, Pancreas Transplant; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors; SIDD, Severe Insulin-Deficient Diabetes; SIRD, Severe Insulin-Resistant Diabetes; SPK, Simultaneous Pancreas and Kidney Transplant; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; UNOS, United Network for Organ Sharing; QOL, Quality of Life.

Persistent hyperglycaemia leads to renal failure through inflammation, increased vascular permeability and hypertrophy of podocytes [4]. Diabetes-associated renal disease is thought to occur in 30%–50% of T2DM patients and 15%–30% of those with T1DM [5–8]. Patients with T2DM tend to present with concurrent renal disease as they have often had diabetes for years prior to diagnosis. There is, unsurprisingly, an association with progression to ESRD in patients with T2DM and concurrent co-morbidities (age and hypertension) [9]. For T2DM patients with ESRD, treatment includes dialysis, renal transplantation or, in rare cases, SPK transplantation.

The first SPK transplantation was performed in 1966 by Kelly and Lillihei [10]. Their objective was to restore kidney function and to provide an endogenous source of insulin, enhancing glucose control, eliminating the need for insulin injections, and preventing further end-organ damage secondary to hyperglycaemia. At the time, it seemed pointless to treat one condition and not the other, although this was considered very controversial with their contemporaries. Subsequent research has shown that a pancreas transplantation (PTx) can improve native kidney function, potentially reversing the pathological changes of diabetic nephropathy [11], providing further justification for a simultaneous pancreas and kidney transplantation approach.

The first SPK transplantation recipient had T1DM and, since inception, has rarely been offered to T2DM patients. It was assumed that a PTx would be less beneficial in these recipients, as the recipient's insulin resistance would prevent the new source of insulin from being effectively utilised. As a result, the treatment focus for T2DM has been on medical therapies aimed at improving insulin sensitivity, secretion and promoting glycosuria, such as thiazolidinediones, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium, glucose cotransporter-2 inhibitors (SGLT2i). These medications are increasingly being used in combination with a kidney transplant alone and have been suggested to reduce all-cause mortality and potentially HbA1c [12, 13]. There is a perception, which is reasonable, that drug treatments carry far less risk than a major surgical operation such as a PTx, even if the patient has ESRD and needs a kidney transplant, but it is often overlooked that adding a pancreas in the right patient would be more effective in the long-term.

This review aims to consolidate current literature regarding SPK transplantation outcomes in patients with T2DM, compare outcomes after transplant with alternative therapies and comment on current listing criteria.

Type 2 Diabetes

In the 1930s, clinicians identified two primary forms of diabetes: one characterised by immediate insulin dependence, typically in younger individuals, and another occurring later in life, often with obesity, where insulin therapy was not initially required for survival [14]. This distinction led to the Type 1 and Type 2 terms we are familiar with today.

Early research in T2DM largely focused on the mechanisms underlying insulin resistance, often overlooking, or in some cases completely ignoring, the role of beta cell loss, dysfunction and insulin deficiency. A study using cadaveric pancreas tissue showed obese T2DM patients had up to 60% loss of beta cell mass compared to obese patients without a diabetes diagnosis [15]. It is well appreciated for those involved in beta-cell therapy that hyperglycaemia causes glucose toxicity in the pancreas causing oxidative stress and beta cell dysfunction [16]. This results in a multiplier effect where the pancreas is less able to produce insulin, glucose levels increase and further exacerbate the glucose toxicity effects and beta-cell dysfunction.

It is clear, the initial understanding of T2DM was too simplistic and it is not a homogenous disease but a polymorphic condition with various genetic, metabolic and clinical characteristics. A deeper understanding of this heterogeneity suggests the initial binary categories do not adequately reflect the disease. Newer subtypes have been described including severe-insulin-deficient diabetes (SIDD) and severe-insulin-resistant diabetes (SIRD) [17]. This classification may represent a way to identify T2DM patients with lower insulin resistance for which there is a greater potential benefit for PTx.

In the UK, diabetes is primarily diagnosed in primary or emergency care based on clinical presentation and fasting blood glucose levels. Diabetes-related autoantibodies and C-peptide measurements are not standard practice. Management pathways diverge dependent on classification. National Health Service (NHS) guidance recommends urgent referral to an endocrinologist for those with T1DM, while T2DM patients are typically managed in primary care with National Institute for Health and Care Excellence (NICE) guidance outlining a stepwise treatment approach, beginning with lifestyle modifications, then oral agents, and eventually insulin therapy if glycaemic control remains inadequate. Many T2DM patients never undergo specialist evaluation, risking misclassification, particularly in the cohort of patients with concomitant beta-cell exhaustion who may quickly progress to insulin treatment and simply be misdiagnosed as having poorly controlled T2DM, especially if they are overweight [18–20].

A key concern with PTx in T2DM is the degree of insulin resistance, and whether the pancreas graft would be able to overcome this. It was previously thought that a PTx in a T2DM patient would be subject to overstimulation and resultant islet exhaustion and allograft failure. However, multiple studies have shown that insulin secretion and sensitivity are improved in these patients [21–24]. The gold standard technique for measuring insulin resistance is the glucose clamp technique [25]. This is a labour intensive, invasive test and simply not practical in a routine clinical setting. Predictive models may be able to quantify insulin resistance in a more accessible manner. One is the homeostatic model assessment of B-cell function and insulin resistance (HOMA-IR) [26]. A patient's fasting glucose level is compared with the models' predictions to estimate insulin resistance. The newer subtypes SIDD and SIRD use HOMA for classification.To the authors knowledge there have been no published studies looking at HOMA in the pre-operative period as a predictor of outcomes, relating to T2DM and SPK transplants. Other predictive models include QUICKI [27] and METS-IR [28]. Limitations of using predictive models include

their generic nature and lack of individual results. They also often poorly represent certain populations [29]. HOMA-IR should be used with caution in patients with low BMI [30] and women >50 years old [31]. Further research into the value of these models in the pre-transplant assessment is needed.

C-peptide has limited value for patients being considered for SPK. It is a connecting peptide cleaved during the production of insulin and has been used as a surrogate marker of insulin production [32]. It is also renally excreted and filtered during dialysis [33] complicating interpretation within the patient population who would be eligible for SPK transplant. A patient who is C peptide positive always generates debate when considering beta cell replacement therapy, but its presence is not an absolute contra-indication if the patient is insulin dependent [22]. A 2023 study by the Wisconsin group analysed the impact of pre-transplant C-peptide on SPK transplant outcomes in T2DM [34]. Patients were delineated into low (<2 ng/mL), medium (2–8 ng/mL) and high (>8 ng/mL) C-peptide levels. The group reported excellent outcomes across all groups with comparable uncensored and death-censored kidney graft failure. Adjusted C-peptide levels increased in all groups following pancreas transplant. This group advised against making clinical decisions to exclude patients from SPK transplant based on C-peptide levels, in particular high C-peptide levels.

When critically appraising the literature, it is clear the method of classification of T2DM is not standardised. Some rely on C-peptide levels [23, 35] and titres of diabetes auto antibodies, others use primarily a clinical diagnosis [36, 37]. There has even been a novel scoring system created [38]. Taken together this makes useful conclusions often difficult to judge.

Selection Criteria for SPK in Type 2 Diabetes

In the UK, eligibility for SPK transplantation follows the NHS Blood and Transplant (NHSBT) patient selection policy POL185/6 [39]. Criteria include insulin dependence and dialysis or an eGFR below 20 mL/min at the time of listing. For T2DM patients, a Body Mass Index (BMI) ≤30 kg/m^2 is required and a higher BMI considered an absolute contraindication to transplant. Current guidelines do not mandate testing for insulin resistance, glucose tolerance tests, or C-peptide levels. As an alternative, patients with T2DM are not usually eligible for an islet transplant in the UK unless they are insulin dependent and have a BMI <30, the same indications for a pancreas transplant.

The BMI limitation for T2DM patients is a point of contention. Obesity has been linked to post-operative complications such as transplant pancreatitis, graft thrombosis, and poorer wound healing [40, 41]. However, our group found a BMI >30 kg/m^2 was not associated with increased risk of complications [42]. This study also showed that whilst recipient BMI was an independent risk factor affecting graft and patient survival after PTx, the exact value at which this should become a barrier to transplant was not definable even in a very large cohort of patients. BMI is a poor surrogate for body composition and may inadequately reflect appropriateness for transplant. Alternative measurements such as body girth or hip-waist ratio, may be more relevant but again needs to be defined [43, 44].

Furthermore, patients with BMI >30 kg/m^2 who have pathological weight-loss secondary to ESRD may eventually meet BMI criteria [45] but having years of dialysis beforehand will make them more frail and less fit for transplantation, we know that pre-emptive transplantation have the best outcomes after SPK. Spain also uses a BMI <30 kg/m^2 [46] and the cut-off in the US is slightly higher at 35 kg/m^2 [47]. In the authors opinion the latter sounds more reasonable because other transplants have higher relative cut offs e.g. liver transplantation [48] is often set at 40 kg/m^2 [49, 50] as is renal transplantation.

Outcomes of SPK Transplant in T2DM

Our group have also previously reported graft and patient survival after SPK delineated by type of diabetes (n = 2,060) [36]. 3.4% (n = 94) of transplants were performed in T2DM recipients. Diabetes was pre-defined by the listing centre using clinical criteria which has scope for bias reporting in such a heterogenous group. NICE guidance uses a fasting plasma glucose >7 mmol/L and clinical features such as ketosis, rapid weight loss and autoimmune history to diagnose and distinguish T1DM from T2DM [51]. This study showed comparable patient survival at 1 year (T1DM:96.8%, T2DM:96.5%) and 3 years (T1DM:93.2%, T2DM:89.3%) regardless of diabetes type. At 5 years we saw a statistically significant decrease in T2DM patient survival (T1DM:89.4%, T2DM:79.2%), but this trend was not borne out at 10 years (T1DM:74.8%, T2DM:73.1%). Pancreas and kidney graft survival was comparable at all time points and there was no difference in complications including cardiac events and post-operative infections.

Other studies have been identified from electronic databases including Ovid MEDLINE database, PubMed and google scholar using the terms “simultaneous pancreas and kidney transplant,” “T2DM,” “SPK,” detailed in **Table 1**.

The largest (n = 6,756), utilised the United Network for Organ Sharing (UNOS) database [37]. Most patients who received an SPK (90.8%, n = 6,141) had T1DM and much fewer, (8.2%, n = 582) had T2DM. This study also showed comparable death-censored graft survival at 5 years (T1DM:85.3%, T2DM:83.0%) and patient survival was said to be comparable but exact figures were not provided. The type of diabetes in this study was again predefined by the listing centre. The American Diabetes Association (ADA) use a fasting random plasma glucose >11.1 mmol/L and a Hba1C >48 mmol/mol for diagnosis. Characteristics such as age, BMI, presence of other autoimmune diseases and history of ketoacidosis aided distinguishment between T1DM and T2DM.

There are also multiple single centre studies comparing SPK recipient outcomes delineated by type of diabetes. The Wisconsin group, (n = 323) defined T2DM using clinical judgement [38]. They demonstrated comparable pancreas graft survival (death-censored) and incidence of post-transplantation diabetes mellitus (PTDM) between recipients with T2DM (n = 39) compared with T1DM (n = 284). The patients were well matched with comparable BMI, age and sex. A novel scoring system was used to confirm diabetes type and looked at; pre-transplant

TABLE 1 | Studies pertaining to T2DM and SPK Transplant.

Study Year and Author	Type of Study	No of transplants and breakdown of type	Salient Findings
2024 Parajuli [88]	Single-centre Wisconsin, US cohort	SPK transplant only N = 183 4 groups $A^+\beta^-$, $A^-\beta^-$, $A^-\beta^+$, and $A^+\beta^+$	T2DM Diagnosis Criteria Patients were stratified by autoantibody status and pre-transplant fasting C peptide A^+ detection of ≥1 autoantibody A^- no autoantibodies detected β^- fasting C-peptide <2 ng/mL β^+ fasting C-peptide ≥2 ng/mL Those $A^-\beta^+$ would represent patients with T2DM Results Pancreas and kidney graft survival was comparable irrespective of stratification
2024 Martinez [89]	Single-centre Wisconsin, US cohort	SPK transplant only N = 345 13.6% T2DM	T2DM Diagnosis Criteria T2DM – older age at diabetes diagnosis, prior use of oral glycaemic agents, absence of auto antibodies, detectable C-peptide T1DM – younger age of diagnosis, presence of autoantibodies, absence of C-peptide Results Comparable patient, kidney-graft and pancreas-graft survival was noted when comparing patients with T1DM and T2dM Comparable rates of readmission post-transplant, comparable rates of SSI, comparable rates of major surgical complications and thrombosis
2024 Owen [36]	Multicentre UK cohort	SPK transplant only N = 2,236 3.4% T2DM	T2DM Diagnosis Criteria Type of diabetes was defined by clinical diagnosis T2DM – older age of onset, metabolic features, initial use of oral glycaemic agents T1DM – ketosis, younger age of onset, lower BMI, immediate insulin use Results Comparable graft survival at 1 year, 3 years, 5 years and 10 years Comparable patient survival at 1 year, 3 years and 10 years Statistically inferior patient survival at 5 years - trend not borne out at 10 years, nor in multivariable model No difference in complication incidence between groups
2023 Parajuli [34]	Single-centre Wisconsin, US cohort	SPK transplant only N = 76 Delineated by pre-transplant C-peptide level Low n = 14 Medium n = 47 High n = 15	T2DM Diagnosis Criteria Novel scoring system giving score from −9 to +9, a negative score correlated with T2DM and a positive score with T1DM. Results Excellent outcomes after SPK transplant for all recipients Comparable rates of uncensored and death-censored kidney graft failure irrespective of pretransplant C-peptide level Post-transplant C-peptide levels increased in all groups after SPK when adjusting for the patients renal function
2022 Amara [90]	Systematic Review	Pancreas and islet transplant Studies publishing original data from 2000 onwards	T2DM Diagnosis Criteria This review utilised studies defining T2DM with any recognised criteria including C-peptide, BMI, absence of ketoacidosis, absence of autoantibodies and age at diagnosis Results 5 studies compared patients with T2DM undergoing SPK to those with T2DM undergoing KTA. SPK was suggested to have superior outcomes in these studies 17 studies compared patients with T2DM undergoing SPK to those with T1DM undergoing SPK and found comparable outcomes (93.75% of studies)
2021 Pham [38]	Single-centre Wisconsin, US cohort	SPK transplant only N = 323 12.1% T2DM	T2DM Diagnosis Criteria Novel scoring system giving score from −9 to +9, a negative score correlated with T2DM and a positive score with T1DM. Results Comparable pancreas and patient survival No association found between BMI and post-transplant diabetes mellitus No association found between pre-transplant insulin requirements and post-transplant diabetes mellitus
2020 Hau [91]	Single-centre Lepzig, German cohort	SPK and KTA N = 127	T2DM Diagnosis Criteria: Diagnosis with either · Diagnosis age >40, no history of ketoacidosis and either a

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TABLE 1 | (*Continued*) Studies pertaining to T2DM and SPK Transplant.

Study Year and Author	Type of Study	No of transplants and breakdown of type	Salient Findings
		70.1% T1DM SPK 9.4% T2DM SPK 20.5% T2DM KTA	weight >115% ideal body weight or non-consistent insulin therapy for 2 years after diagnosis · Diagnosis age 30–39, no history of ketoacidosis, weight >115% ideal body weight and non-consistent insulin therapy for 2 years after diagnosis Results T1DM and T2DM recipients who received an SPK transplant there were comparable graft and patient survival Recipients with T2DM who received a KTA had poorer graft and patient survival when compared to SPK but it should be noted had statistically significant differences in demographics (were older and more comorbid) limiting comparison
2020 Alhamad [92]	Multicentre US cohort	SPK and KTA N = 35,849 100% T2DM 2% SPK	T2DM Diagnosis Criteria Pre-defined by the OPTN database, no further details are provided Results Statistically significantly superior kidney graft and patient survival for patients with T2DM who received an SPK when compared to KTA (deceased or living donor)
2019 Rohan [93]	Single-centre South Carolina, USA cohort	SPK, PTA, PAK SPK n = 91 41.8% T2DM	T2DM Diagnosis Criteria Detectable C-peptide level Results Note - outcomes are for all types of pancreas transplant and there was no specific SPK subgroup analysis Comparable glycaemic control post-transplant between T1DM and T2DM recipients Comparable complication rates (including infections, rejection, graft loss and patient survival) Those with T2DM had a higher incidence of BK virus nepropathy
2019 Liu [94]	Single-centre, Guangzhou, China cohort	SPK transplant only N = 63 29% T2DM	T2DM Diagnosis Criteria Not defined Results Comparable rates of complications (delayed kidney graft function, kidney rejection, pancreatitis, pancreas rejection, duodenal leak, pancreatic fistula, portal thrombosis, intestinal obstruction) Comparable pancreas graft, kidney graft and patient survival was noted
2019 Andacoglu [95]	Single-centre, Washington US cohort	SPK, PTA, PAK SPK n = 34 25% T2DM SPK	T2DM Diagnosis Criteria T2DM – detectable C-peptide, age at diagnosis, and BMI Results Comparable glycaemic control between T1DM and T2DM at 2 years post-transplant
2019 Shin [96]	Single-centre, Seoul, Korean cohort	SPK, SPLK, PAK, PTA SPK and SPLK n = 99 22% T2DM	T2DM Diagnosis Criteria: Diagnosed by either · Diabetes onset after age 40 and either weight >115% of ideal body weight or no consistent insulin use in the first 2 years after diabetes diagnosis · Diabetes onset between 30 and 40 years old and both a weight >115% of ideal body weight and no consistent insulin use in the first 2 years after diabetes diagnosis Results Comparable metabolic outcomes in patients with T1DM and T2DM after pancreas transplant (all forms and subgroup analysis of SPK only), this included HbA1c levels, C peptide levels on HOMA-IR scores
2018 Gondolesi [97]	Single-centre Buenos Aires, Argentina cohort	SPK and PTA n = 46 PTA n = 1 24.5% T2DM (All SPK)	T2DM Diagnosis Criteria T2DM - >30years/o at time of diagnosis with metabolic features T1DM - diagnosis in childhood with a high ketone levels and immediate insulin treatment Results No statistically significant difference in patient survival at 1 year or 5 years
2017 Gruessner [98]	Multi-centre, International cohort	SPK. PTA, PAK N = 1,514 100% T2DM (n = 1,317 SPK)	T2DM Diagnosis Criteria Definition provided that "the recommendations of the American Diabetes Association were used to check and correct classification of diabetes type" Results

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TABLE 1 | (*Continued*) Studies pertaining to T2DM and SPK Transplant.

Study Year and Author	Type of Study	No of transplants and breakdown of type	Salient Findings
			SPK transplant is a safe procedure in patients with T2DM with a 95% survival at 1 year
2016 Chakkera [21]	Single-centre prospective observational study, Minnesota, USA	SPK transplant only N = 16 43.8% T2DM	T2DM Diagnosis Criteria T1DM – Undetectable C-peptide (<0.1 ng/mL) on insulin therapy from the time of diagnosis. T2DM (referred to as non-T1DM in the text had a detectable C-peptide and a history or oral agents with progression to insulin Results Similar metabolic profile (determined using HOMA-IR score) between T1DM and select T2DM patients Comparable measures of glucose homeostasis at 1 year between T1DM and T2DM
2016 Jeon [99]	Two-centre, Seoul, Korean cohort	LD KTA, DD KTA, SPK, Dialysis SPK n = 48 49.6% T2DM SPK	T2DM Diagnosis Criteria T1DM defined as undetectable C-peptide (<0.8 ng/mL) and the presence of anti-pancreatic or anti-insulin autoantibodies, T2DM defined as patients not defined by the criteria above Results Patient survival was superior in patients receiving any form of transplant than dialysis alone Patient survival was statistically significantly better in those undergoing LD KTA, compared with DD KTA and SPK. It was highlighted that the waiting time for SPK in Korea is very long which may explain these results Comparable patient, kidney graft and pancreas graft survival when comparing T1DM and T2DM receiving an SPK
2013 Light [23]	Single-centre Washington, US cohort	SPK transplant only N = 173 33.5% T2DM	T2DM Diagnosis Criteria T1DM defined as undetectable C-peptide (<0.8 ng/mL), T2DM defined as detectable C-peptide (>0.8 ng/mL) Results Comparable time until first rejection in those patients that experience rejection Statistically significant poorer patient survival in recipients with a detectable c-peptide
2013 Margreiter [35]	Single-centre Innsbruck, Austria cohort	SPK and KTA N = 248 78.6% T1DM SPK 12.9% T2DM SPK 8.5% KTA	T2DM Diagnosis Criteria T1DM diagnoses as early onset, immediate insulin requirement, presence of autoantibodies and C-peptide negativity. T2DM diagnosed with C-peptide level Results No statistically significant difference in pancreas graft survival Poorer patient survival in recipients with T2DM receiving an SPKT compared with T1DM recipients (univariate), not borne out in multivariable model This dataset also compared T2DM receiving KTA compared with T1DM & T2DM receiving SPK. Those receiving KTA had inferior 5-year graft ($p < 0.001$) and patient ($p < 0.0001$) survival
2012 Park [100]	Single-centre Seoul, Korean cohort	SPK, PTA, PAK SPK n = 91 17.5% T2DM	T2DM Diagnosis Criteria Not defined in the text Results No statistically significant difference in pancreas graft survival
2011 Sampaio [37]	Multicentre US cohort, OPTN/UNOS data	SPK transplant only N = 6,756 8.6% T2DM	T2DM Diagnosis Criteria Serum C-peptide >0.8 ng/mL Results Delayed kidney graft function and primary non function rates were statistically higher in T2DM recipients Pancreas complication rates were comparable Death censored kidney graft survival was poorer in patients with T2DM ($p = 0.04$) Comparable patient survival Comparable pancreas graft survival
2010 Chakkera [21]	Single centre Minnesota, US cohort	SPK transplant only N = 80 12.5% T2DM	T2DM Diagnosis Criteria Defined patients as T2DM if they had detectable C-peptide, negative GAD65 Antibody, absence of diabetic ketoacidosis and the use of oral hypoglycaemics Results

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TABLE 1 | (*Continued*) Studies pertaining to T2DM and SPK Transplant.

Study Year and Author	Type of Study	No of transplants and breakdown of type	Salient Findings
			Comparable graft and patient survival between recipients with T1DM and T2DM
2005 Nath [101]	Single centre Minnesota, US retrospective observational analysis	SPK, PTA and PAK N = 17 7 (41%) SPK 100% T2DM, no comparison with T1DM	T2DM Diagnosis Criteria: Diagnosed by either · Diabetes onset after age 40 and either weight >115% of ideal body weight or no consistent insulin use in the first 2 years after diabetes diagnosis · Diabetes onset between 30 and 40 years old and both a weight >115% of ideal body weight and no consistent insulin use in the first 2 years after diabetes diagnosis Results 1 year patient and graft survival rate was 94%, and all surviving patients were euglycemic at 1 year

KTA: Kidney Transplant Alone, LD: Living Donor, PAK: Pancreas After Kidney, PTA: Pancreas Transplant Alone, SLPK: Simultaneous deceased donor pancreas and Living donor Kidney transplant, SPK: Simultaneous Pancreas and Kidney transplant, T1DM: Type 1 Diabetes Mellitus, T2DM: Type 2 Diabetes Mellitus, UNOS: United Network for Organ Sharing.

insulin requirement, pre-transplant fasting c-peptide levels (assigning a score of +2 if C-peptide <0.5 ng/L, −1 if 0.5–2 ng/L and −2 if >2 ng/L), family history and the presence of diabetes-associated antibodies. A score from −9 to +9 was created for each recipient, and a negative score defined as T2DM and a positive score with T1DM. Again, this showed comparable patient or graft survival. It would also be interesting to better understand the reclassification rate—i.e., how many patients had their diabetes type changed after applying the novel scoring system. This information was not provided but would be especially relevant given the joint consensus statement by the ADA and the European Association for the Study of Diabetes (EASD), noting that up to 40% of those diagnosed with T1DM after age 30 were initially misclassified as T2DM [52].

A smaller single centre study was reported in 2013 by an Austrian group (n = 248) comparing T1DM undergoing SPK transplant (n = 195) with T2DM SPK (n = 21) and also with T2DM receiving a kidney transplant alone (KTA) (n = 32) [35]. They defined T2DM using detectable C-peptide levels. They also ensured a minimum of 6 months oral therapy prior to being started on insulin in their diagnosis and had a BMI cut off >32 kg/m^2. Comparable rates of pancreas graft survival between T1DM and T2DM recipients undergoing SPK were described. A statistically significant poorer patient survival (PS) was seen in univariate analysis when comparing T2DM recipients who had an SPK with T2DM recipients who had a KTA and with T1DM recipients who had an SPK at 1 year (T2-SPK: 90.5% T2-KTA:87.1%, T1-SPK:96.9%) and 5 years (T2-SPK:80.1% T2-KTA:54.2%, T1-SPK:91.6%). A multivariable analysis was performed adjusting for donor and recipient age, BMI, Cold Ischaemic Time (CIT) and patient survival was no longer statistically significantly different. This univariate finding contrasts with the other literature discussed. It is also important to note this paper does not differentiate KTA by donor brain death (DBD), donor circulatory death (DCD) or living related donor (LRD) which can makes accurate analysis difficult.

From 2004 to 2019, only 3.4% of SPK transplants in the UK were performed in patients with T2DM [36]. Other countries have comparable proportions of patients with T2DM; 91% in USA [53], 90%–95% in Germany [54] and 90% in the Netherlands [55]. In 2010 the International Pancreas Transplant Registry, IPTR (which receives data from both UNOS and Eurotransplant) showed 8% of SPK's were performed in T2DM patients [56]. The 2024 Annual report of OPTN/SRTR showed almost a quarter of SPK transplants were performed in patients with T2DM [57], suggesting the UK is more stringent in accepting patients with T2DM for SPK. However, a positive trend in the UK is noted with an increase in the percentage of total SPK's being performed in patients with T2DM each year (2% 2005, 4.3% 2009, 5.8% 2018) [36]. Reasons explaining the relatively lower numbers are not entirely clear.

Graft and patient survival are not the only metrics of success, and it is imperative to look further at post-transplant glycaemic control after transplant, renal function, and quality of life. A Chinese study assessed renal function and HbA1C after KTA and SPK in recipients with T2DM, using propensity score matching [58]. This study found that 2 years post-transplant, those who had an SPK transplant had a statistically significantly greater decrease in HbA1C (HR:1.05, 95% CI: 0.7–10.4, p = 0.005), decreased fasting blood glucose (HR:2.49 95%CI: 1.81–3.17, p < 0.001), decreased triglyceride levels (HR:0.65, 95%CI: 0.39–0.91, p = 0.0015) and a higher eGFR (HR:-14.5, 95% CI −18.6–−10.4, p < 0.001) than those who had a KTA.

There are no studies looking specifically at quality-of-life or patient reported outcomes (PROMS) after SPK in T2DM, and these should be a focus for further research. An American study (n = 54) compared T1DM recipients who underwent KTA compared to SPK [59]. They found improved diabetes-related quality of life (QOL) scores (using the Diabetes QOL questionnaire [60]) in SPK recipients and equivalent mental health and wellbeing scores utilising the Medical Outcome Health Survey Short Form-36.

Comparison of SPK With Alternative Therapies for Patients With T2DM

When considering SPK transplant, alternatives should always be evaluated, including remaining on dialysis, kidney transplant alone with wearable technologies.

Dialysis

Dialysis provides a method of filtration and excretion. However, dialysis has significant morbidity long-term including peritoneal infections and fistula complications. For those on haemodialysis, it often prevents patients being a part of the workforce and being economically inactive is associated with low self-esteem and poor mental health [61, 62].

Kidney Transplant Alone

A KTA has a well-established survival and quality of life advantage over dialysis and is an option for patients with T2DM and end stage renal failure [63]. However, this will not address the primary issue of hyperglycaemia and as such nephropathy may later occur in the donated kidney [64, 65]. It should be noted that as medical management of hyperglycaemia improves, the benefit of the addition of a pancreas, may reduce.

A Taiwanese group recently published a propensity matched study assessing the use of SGLT2i inhibitors after kidney transplantation in diabetic recipients [12]. This landmark study showed a significant improvement in all-cause mortality, (2.08% in the SGLT2i user compared to 9.54% in the non-user group at 3.4 years - their median follow-up time), a reduction in major adverse cardiac events (SGLT2i: 4.44% compared to non-SGLT2i: 13.87%, HR 0.48) and a reduction in major adverse kidney events (SGLT2i: 8.93% compared with non-SGLT2i: 22.54%, HR 0.52). They noted that only 6.5% of kidney transplant recipients with diabetes utilise a SGLT2i and so there is significant scope for implementation.

A US trial (the FLOW trial) evaluated the impact of Semaglutide use in patients with T2DM and an eGFR between 25 and 75 mL/min/1.73 m^2 [66]. The use of this GLP-1 receptor agonist was seen to slow the decline of renal function, as reduced the risk of cardiovascular events and death. It should be noted that the effect of Semaglutide on these outcomes was thought not to be relate to changes in body weight, but to a potential of decreasing inflammation, oxidative stress and fibrosis in the kidney. A further study was performed assessing the use of GLP-1 agonists in kidney transplant recipients and also found improved graft and patient survival with the use of a GLP-1 agonist [67].

The other consideration is the additional risk that presents with the addition of a pancreas transplant. Recipients undergoing SPK have more episodes of rejection than those with a KTA and so are treated with more aggressive immunosuppression regimes [68]. These patients also have higher rates of wound infections and urinary tract infections [69]. Pancreas grafts can have enteric leaks, bleeding, and small bowel obstruction, all leading to higher morbidity and mortality in these patients [70].

Wearable Insulin Technologies

Wearable insulin sensors and pumps have revolutionized diabetes management, enabling personalised insulin regimes and reducing needlestick burden [71, 72]. NICE guidance was changed in 2023 to allow adults with T2DM to be offered continuous glucose monitoring, prior to this they were excluded [73]. We hope these technologies will have a significant impact on diabetic complications in future but there is limited data demonstrating benefit in transplant patients. This is one area that needs urgent attention. Given the challenges that immunosuppression brings to managing blood glucose [74, 75], it is imperative that these technologies are prioritised for transplant patients.

Challenges for SPK Transplant for Patients With T2DM

BMI and Obesity as Barriers to SPK in T2DM

Pre-transplant weight loss strategies include diet, exercise, bariatric surgery and GLP1-inhibitors.

Diet and exercise regimens may be challenging for patients with renal failure due to electrolyte imbalances associated with fruit, vegetable and protein intake [76]. Exercise regimens may also be difficult secondary to fatigue often present in chronic illness. A US study followed 376 patients who were BMI >30 kg/m^2 and asked to lose weight prior to being listed for transplant. Only 10% of patients lost any weight at all and a meagre 5% reached their target weight [44]. This challenges the efficacy of these programmes and raises ethical concerns about delaying listing for transplantation when success is limited.

Bariatric and metabolic surgery (BMS) may be an option [77]. A recent meta-analysis found that BMS (gastric bypass, sleeve gastrectomy, gastric banding and duodenal switch) was both safe and efficacious, with a combined mortality rate for patients who underwent both BMS and KTA of 4% which is not much different in non-obese patients having KTA or even SPK transplantation in expert centres [78]. They recommended that it formed part of the transplantation work-up process to enable hard-to-list obese patients to be considered. A smaller Minnesotan study followed 17 patients who underwent bariatric surgery prior to PTx (11 gastric bypass, 5 sleeve gastrectomy and one gastroplasty). Post-operatively the median BMI decreased from 37.4 kg/m^2 to 26.4 kg/m^2 and the median time from bariatric surgery to transplant was 2.4 years. These patients were compared with control matched patients and had comparable length of stay, graft thrombosis and incidence of rejection. At the 4-year follow up time, graft and patient survival was 100%, suggesting that in the right patients it should be considered [79]. It is important to note that whilst bariatric surgery may facilitate transplant it also has the potential to negate the need for SPK transplant. Multiple studies have shown that BMS improves glucose haemostasis and could lead to diabetes remission [80, 81].

Obese patients with T2DM may benefit from the use of GLP-1/GIP analogues such as Semaglutide or Tirzepatide to lose weight [82, 83]. These analogues enhance insulin secretion, inhibits glucagon release, slows gastric emptying, and promotes satiety, which leads to weight loss and improved insulin sensitivity. Weight loss may also decrease anaesthetic risks, particularly around intubation and cardiovascular events. In the post-operative period weight reduction may improve wound healing. However, it is important to note that GLP-1/GIP analogues should be used with caution and careful monitoring, as it can have gastrointestinal side effects such as nausea (53.3%) and vomiting (30.3%), which could lead to dehydration [83]. There are case reports suggesting

Semaglutide may cause pancreatitis which could be catastrophic in the context of a transplanted pancreas graft [84, 85]. However, a recent meta-analysis showed no increased risk [86]. The other concern is the predisposition for muscle loss [87]. In the renal failure population, already at risk of sarcopenia, GLP-1/GIP analogues use would need to be delivered with considerable dietician oversight.

Post-Transplant Complications

Renal failure and suboptimal glucose control are well-documented risk factors for myocardial infarction (MI) and impaired wound healing. These risks, however, are not unique to T2DM patients and are similarly observed in individuals with T1DM. Our analysis, consistent with prior studies, revealed no significant difference in the incidence of postoperative complications between T2DM and T1DM recipients undergoing SPK transplant [36].

CONCLUSION

SPK transplantation is a complex procedure requiring careful patient selection to ensure benefits outweigh risks. It offers freedom from dialysis, insulin independence and improved quality of life. At present, patients with T2DM show improved HbA1c after transplant and superior kidney graft survival when compared to a KTA. Improvements in medical management of hyperglycaemia may reduce the benefit of the additional pancreas when compared to KTA and should be re-evaluated regularly. QOL outcomes remain unexplored in this cohort. Predictive models (such as HOMA-IR) may identify T2DM patients with low insulin resistance who could benefit from SPK transplant.

Most literature focuses on comparing outcomes with patients with T1DM. We hypothesise that there is much greater overlap in the pathophysiology of T1DM and T2DM and many complications and comorbidities are similar. We believe the more appropriate questions should be, is there a recipient with T2DM that would benefit from a SPK transplant? Are the risks acceptable? Then, if the benefits outweigh the risks, listing is justified.

There is a desire for clearer guidelines as to which recipients with T2DM should receive an SPK if more patients were to be accepted for transplant. The data is limited by the smaller number of SPK transplants performed in T2DM patients, and most studies are underpowered to provide statistical confidence. Our group would support the cautious expansion of SPK transplant to patients with T2DM using the current listing criteria as outcomes after transplant remain satisfactory.

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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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Mapping and Handling Conflicts of Interest in Deceased Organ Donation: How to Handle Ethical Issues and Build Trust in the Healthcare Team

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It has been suggested that there is a significant conflict of interest between providing best care for the dying patient and a subsidiary role in facilitating the donation process. Should healthcare professionals who are involved in a patient's care and determination of death also be involved in discussing donation with families? If they are involved, should they disclose this potential conflict of interest? In this paper we address the issue of conflicts of interest in organ donation by examining current best practice in four European countries (Sweden, Netherlands, the United Kingdom and Spain) and discuss whether having clear separation of roles in order to avoid conflicts is preferable to having the same physician (or team) handle both the dying process and donation. We also analyse the benefits and burdens of disclosing such potential conflicts.

Keywords: ethics, conflicts, organ donation, policy, law

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INTRODUCTION

A conflict of interest is any motivation or circumstance that might bias a professional's decision-making in a particular situation. Perhaps the classic example is where a researcher receives substantial payment linked to results from a pharmaceutical company whilst conducting a clinical trial involving their product: the financial contribution can constitute a significant conflict of interest that could bias the objectivity of the research endeavour.

At first glance, deceased organ donation might not seem like a particularly likely context for conflicts of interest in staff caring for a potential organ donor; as they often see no benefit to themselves or the patients under their direct care from any subsequent transplant. However conflicts or tensions in role responsibilities can arise between the different professional duties of healthcare professionals.

In normal medical practice, if a patient is ill, the doctor's job is to help them get better; if a patient is dying and can no longer be saved, it is the doctor's job to reduce their suffering; if a patient wants to become an organ donor at the end of life, it is the doctor's job to facilitate that goal wherever possible–this is regarded as a normal part of end-of-life care in many countries [1, 2]. However, a potential conflict of interest can arise if the same healthcare professional is deciding that a patient can

no longer be saved, determining that a patient will die, and also raising the issue of organ donation with the patient's family. If the doctor is perceived as "pushing" donation, whatever their motivations, it might appear that he or she might not have made the maximum possible effort to save the patient's life. Some fear that this is particularly the case with donation after circulatory determination of death (DCD), where there are less formal criteria (compared to neurological criteria for death) for deciding to instigate end-of-life care and remove mechanical ventilation [3]. While this fear may only represent the risk of a *perceived* potential conflict of interest, rather than a genuine conflict of interest, it would be unfortunate if any family ever got this impression.

In a position paper issued by various American medical associations, it is stated that "If real or perceived conflicts arise between the goals of providing optimal end-of-life care and the goals of procuring organs, delivery of quality end-of-life care should take priority." [4] It is true that end-of-life care should not be subordinated to "organ procurement" (itself an unfortunate, transactional term that betrays other biases; for which we will use the term "recovering"), but it can also be argued that organ donation is a key part of end-of-life care. Particularly if a patient has made clear that they want to be a donor and save lives. It is this very fact–that organ donation is so closely linked to, and is sometimes part of, end-of-life care and that recipients are in desperate need for a lifesaving transplant–that makes conflicts of interest an important ethical issue.

As authors, we reject the claim that organ donation is in competition with optimal end-of-life care, and thus that a conflict always exists between the duty to preserve life and reduce suffering, and the possibility of organ donation. We consider, like others, that organ donation can and should be an integral part or end-of-life care for patients who have an autonomous wish to become donors. Facilitating organ donation does not mean that the care given to the patient will in any way be sub-optimal, indeed there is much to suggest it will be superior [5].

The question this paper explores concerns conflicts of interest related to role responsibility and disclosure. Given the risk of conflicts of interest, real or perceived, should it be the same healthcare professional or team who handles the decision that further treatment is futile *and* the initiation of the organ donation process and dialogue with the family? The stakes are high for everyone involved. Dying patients, their families, recipients, transplant teams are at the sharp end of these conflicts can be those caring for a potential donor.

Different countries and donation systems have different approaches to this issue.

THE ORGAN DONATION FAMILY APPROACH: FOUR EUROPEAN EXAMPLES

To inform our analysis of conflicts of interest, it will be helpful to describe how the donation process unfolds and interacts with other aspects of end-of-life care in different countries: Sweden, the Netherlands, the United Kingdom and Spain (all four of which have both DBD and DCD donation). Each of these countries has a different process, with some favouring greater separation of roles than the others. The descriptions here are based on the expertise of the authors of this paper in clinical practice in their respective countries, and their knowledge of the applicable guidance. From the outset, it should be noted that the end of life and organ donation healthcare team involves not only doctors, but a multi-disciplinary team. For readability, we will often shorthand the multi-disciplinary team to doctors, who in the countries we outline, are typically the senior healthcare decision maker.

In Sweden, the conversation about donation is normally initiated by the intensive care unit (ICU) doctor and ICU nurse, who should also be available to discuss the topic later in the process and answer any questions that the family might have [6]. In some regions of Sweden a donation specialist nurse (DOSS) is also involved. The organ donor register is consulted after a "breakpoint decision" (that further treatment is futile) or after the declaration of death. The decisions about end-of-life care as well as donation are made by the intensivists [7]. It is not considered to be a conflict of interest that the treating doctor in the ICU raises the issue of organ donation with the family. Instead, it is seen as one conversation among others with families. The perception from intensivists (ICU doctors) is that it would be a "betrayal" to hand over this conversation to someone else because of the existing bond of trust between intensivist and family; it might arouse suspicion on the part of the family if the doctor they have collaborated with suddenly distances him/herself in these scenarios where organ donation becomes a possibility.

In Sweden, ICOD refers to organ-preserving treatment initiated outside the ICU after an end-of-life decision, solely to assess the possibility of organ donation. Swedish legislation formally recognizes these measures as *organ-preserving treatment*. Following changes to the Transplantation Act 1995: 831 in 2022, such treatment may not only continue after it is clear the patient will not survive but may also begin specifically to evaluate donation potential [8]. An end-of-life decision ("breakpoint decision") must be made by two licensed physicians and documented according to national regulations. Once this decision is made, care transitions to palliative care and organ-preserving treatment, which may include interventions like intubation—even before the patient's wish to donate are known. These preferences should be clarified as soon as possible, with respect to the next of kin.

Healthcare providers are required to promote organ donation and identify potential donors, even outside the ICU. If a possible donor is found, an ICU physician must assess donation feasibility, often in consultation with a transplant coordinator in organ donation.

Organ-preserving treatment for donation assessment is mainly considered for patients with severe acute brain injuries, where total brain infarction is expected within a short time. Treatment may be provided for up to 72 h after the end-of-life decision.

In the Netherlands there is a strict separation between medical professionals involved in organ donation or in transplantation [9]. This separation also extends to decisions about continuing or

ending treatment. It is unlawful to continue with medical treatment after further treatment has been deemed futile. After it is decided that further treatment is futile, typically this is before death determination even in donation after brain death (DBD), the ICU doctor and ICU nurse will (as in Sweden) approach the donor family for organ donation, after consultation of the Donor Register. If consent is given, by the donor via the Register or the family, the organ donor coordinator (ODC) will come to the hospital to organize the donor procedure. In this sense, there is a potential conflict of interest, because the treating physician is also the one who will inform the family about the patient's imminent death and initiate the conversation before donation. Nonetheless, many doctors see it as their role to discuss donation with the family. Additionally, in cases where the intensive care doctor works in a transplant center they will have potential or current recipients of organs on their ward, so discussing donation with the family is sometimes regarded as a particular conflict of interest. However, in the Netherlands the law on organ donation strictly separates roles after consent: "Before an organ is removed, death is determined by a doctor who may not be involved in the removal or implantation of the organ."

In 2022–23 the Netherlands ran a one-year pilot during which the treating physician was asked to have early contact with the ODC, before the bad news was shared with the family. In practice, this meant that as soon as the treating physician consulted the Donor Register, the ODC was requested to get in contact with the doctor. During this first moment of contact the ODC gave information using a checklist on four topics; medical suitability for donation, legal framework, planning and logistics, and preparing the donor conversation. This last topic included the possibility for the physician to invite the ODC to approach the donor family together. This collaborative approach was not performed very often, as there was some hesitation from both the doctors and the ODC's. The few times an ODC was involved in the donation conversation, this was perceived positively by the physician. One of the reasons for this was that a collaborative approach avoids a potential conflict of interest, as perceived by the doctor: the division of roles means that the ODC could be the one who raised donation while the physician could concentrate on the end-of-life care decision.

In the Netherlands, ICOD started with a pilot study in 6 hospitals in 2018; after the success of this study the protocol was implemented nationally according as described here:

> "The roles of the emergency physician, neurosurgeon, and neurologist were clearly defined and entailed the identification of potential organ donors within their patients with acute brain injury that had a futile prognosis. These physicians then had to consult the Donor Registry (DR) after identification of a potential organ donor in the ED. Once a patient met the criteria, and if the intensivist was not already part of the decision-making in the ED, the emergency physician, neurosurgeon, or neurologist would contact the intensivist for consultation about the possibility of organ donation and ICU admission. If family members were present, they would be informed about the futility of treatment by the neurologist, neurosurgeon, and emergency physician. Whether or not organ donation was concurrently discussed in the ED or would be deferred to a later moment (ie, if families were too emotional), was left to the clinical judgment of the physician. As per protocol, the possibility was open to transfer these patients to the ICU in order to give the family more time to grieve, discuss organ donation, and start end-of-life care" [10].

In the United Kingdom two senior doctors must agree on the decision to withdraw life-sustaining treatment before potential organ donation. National Institute for Health and Care Excellence (NICE) guidance states that "a multidisciplinary team (MDT) should be responsible for planning the approach and discussing organ donation with those close to the patient" [11]. It is explicitly stated that the MDT should include a Specialist Nurse for Organ Donation (SNOD). SNODs are employed by NHS Blood and Transplant (NHSBT) but are linked to each ICU or attend on a regional on-call basis. The most recent national guidelines for provision of intensive care services refers to the clinician handing over to the SNOD for the donation conversation:

> Where organ donation can potentially be offered for a patient, it would be common for the intensive care consultant, intensive care nurse and SNOD to meet the family together. The consultant would lead on breaking bad news before handing over to the SNOD when it is clear that the family have accepted the inevitability of their loss and are ready to consider what may happen next. Involvement of the SNOD in this way provides timely information and support for the family, and significantly increases the consent rate [12].

A 2022 multi-professional endorsed guidance, known as the Donations Action Framework, states that "The individual leading the approach to the family for organ donation must be suitably trained and qualified, have the time to support the family and have sufficient knowledge and skill to sensitively answer any questions." The Human Tissue Authority, which regulates organ donation in the UK, is of the opinion that specialist nurses are the most suitable persons to lead a donation discussion with the family, working in collaboration with the treating clinical team [13].

A historic area of concern in UK practice was how to introduce the SNOD into the conversation, potentially before transitioning care to palliation had been raised with the family and certainly before donation had been raised by the healthcare team treating the patient. NHSBT guidance suggests the SNOD is introduced as a "specialist nurse that we work with on the unit and who helps support families at this time." [14] The UK Donation Ethics Committee considered there is no conflict between early involvement of the SNOD with the treating team or the patient's family but there would be a conflict of interest if the

SNODs were to provide medical care to potential donors whilst they are still alive [15].

The UK does not practice ICOD. Non-therapeutic elective ventilation for the purpose of organ donation is currently considered to be against current national guidance (Reference Donation Actions Framework). In the UK patients who are mechanically ventilated in the emergency department with devastating brain injury are admitted to the ICU for the primary purpose of neuro-prognostication not organ donation, even if organ donation is a likely possibility in time [16].

In Spain, decisions regarding the withdrawal of life-sustaining treatment and end-of-life care are made by a multidisciplinary team, which includes all senior intensivists of the unit where the patient is admitted and other specialists (from other hospital units that have taken part in patient care) at dedicated sessions. In Spain unlike the other countries discussed the donor coordinator DC is often a doctor. If the DC is working as an intensive care doctor in the unit where the patient is admitted, he or she refrains from taking part in the WLST decision. The clinical discussion will be led by another member of the treating team. However, this does not preclude them from performing their duties as intensivists, providing optimal care for their patients. The decision to discuss treatment futility and the possibility of WLST is made collectively by the medical team—including multiple intensivists and specialists from other services—along with the patient's family. At this stage, the DC remains uninvolved to preserve the integrity of the decision-making process.

These mandates are part of the recommendations issued by the Spanish Intensive care society (SEMICYUC) [17], the national protocol of DCD [18] and the national guidelines on intensive care to facilitate organ donation (ICOD) [19]. The latter scenario is nuanced, as the family approach is made before the patient is dead (early interview). Donor coordinators are specifically trained to request consent for admitting patients that typically have a devastating brain injury and fatal prognosis in ICU to preserve the option of organ donation [20]. The maintenance and assessment may end up with a brain death donation process (DNDD) or a DCD if the patient does not evolve to brain death or the family request to finalise the maintenance at any stage of the admission. If the patient was admitted in the ICU, not to preserve organ donation but to attain curative goals and the multidisciplinary team decides to withdraw treatment, the treating physician will explain the prognosis to the family and share the decision with them. Only when the family agrees upon WLST and the shift from active treatment to palliative care, will the DC approach the family to discuss donation opportunities. Notification/referral of the possible donor to the DC must be done in a timely and early fashion according to national guidance, for the DC to assess medical eligibility and properly plan the family approach. In addition, if the patient is not a medically suitable organ donor, but their family asks for information about organ donation or voices that the patient wished to be an OD, the DC will always have a conversation with them.

In Spain, timing to refer the possible donor to the donor coordinator is more flexible. For example; if the family announces the patient's wishes to donate, the intensivist will notify the case to the coordinator and subsequently leave them to have a conversation about organ donation options; or if the intensivist wants to consult the coordinator to establish whether the patient's disease (e.g. patients with a rare disease or history of cancer) means that donation is not feasible. In the latter case, the coordinator will have time to study the disease and learn about the specific evaluation approach. Thus, when the coordinator approaches the family, they can ask about details of the medical history, provide information about the diagnostic test that may be needed to assess each organ suitability or to give good reasons to rule out organ or tissue donation.

The legislation states that healthcare professionals must consult the advanced directives registry and learn from the family if organ donation was consistent with the wishes and values of the person. National recommendations establish that conversations about deceased organ donation should always be led by the DC (regulation established in the national donation protocol) [15]. Key to the Spanish approach is the fundamental point that intensivists will spell out the patient's prognosis and the treatment options to the family but the option of organ donation is usually presented by the donor coordinator.

ETHICAL ANALYSIS

Separation of Roles or Continuity of Care?

As is clear from these descriptions from practice in the different countries, there are a variety of approaches to the family conversation donation process, and thus different attitudes regarding the importance of potential conflicts of interest in this context. In Sweden, it is simply not seen as a conflict of interest for the treating healthcare team to also be involved in donation; indeed, it would seem odd or even unethical for them not to be involved. In the Netherlands, there is a potential perceived conflict but it is standard for the treating doctor to discuss donation with the family before handing over to an organ donor coordinator (though many physicians regard it as their role to discuss donation and are not keen to hand over). In the United Kingdom, there has emerged over time a relatively clear separation of roles. Working collaboratively, the treating doctors will discuss the determination of death or end of life decision with the family with the specialist nurse present; the nurse then handles the donation conversation. Finally, in Spain the treating team is not involved in presenting the option of organ donation but another intensive care doctor, who is the donor coordinator, will raise the topic of donation.

Another important factor to consider is the system of consent for donation that is in place and how that relates to potential conflicts of interest. All of our example countries have opt-out systems in place. It might be assumed that lesser separation of roles would make sense in jurisdictions that have adopted a presumed consent (opt-out) system, where the default is that donation is desired unless an objection is registered. One of the purported positives of presumed consent or opt-out systems is that they normalise donation and make it a normal part of end-of-life care rather than a special, out-of-the-ordinary event that

necessitates special treatment. If donation is in this way more of a routine part of end-of-life care it would indeed seem strange to delegate it to somebody else rather than having the intensivist also handle the donation discussion with the family. However, while that logic might seem superficially appealing, we should bear in mind the core potential conflict of interest that concerns us here: the role responsibilities and disclosure between the doctors and nurses providing the best possible care to the patient in order to save his or her life, and discussing organ donation with a dying patient's family. It is precisely *because* presumed consent can be seen as normalising donation to some extent that greater care may need to be taken within healthcare systems that have implemented this consent modality. If donation becomes seen as routine, that might make it more, rather than less likely that a conflict could be perceived as arising between donation and providing the best possible care for the patient.

The Importance of Trust in the Team

In fact, this initial analysis reveals that providing an objective, overall ethical analysis of conflicts of interest in this context is very difficult due to the socially and institutionally embedded nature of the ethical norms in each of the different countries. While it might be concluded in the abstract that conflicts of interest should always be avoided via a rigid separation of roles, or that continuity of care including donation is more important in all cases, that would be to ignore the particularities of each individual jurisdiction, health service and institution.

Given that healthcare professionals work within legal, ethical and professional frameworks' and are subject to numerous procedures designed to prevent any conflict affecting their clinical decision-making, the key point here concerns perception. If a conflict of interest is perceived by families, that could call into question (from their perspective) the integrity of the end-of-life care (and organ donation) process. But *whether* a conflict of interest is likely to be perceived depends entirely on the particular institutional and team set-up. If a family feels at ease with their relative's clinical care, they are unlikely to be uncomfortable either with a new person discussing donation or with the same person doing so [21].

In this sense, potential conflicts of interests are best handled by promoting trustworthiness in the healthcare team and system for patients and their families. Trust is recognised as being extremely important to organ donation processes [22]. If an institution and healthcare team are trusted because they have rigorous, trustworthy systems in place, it will make little difference whether the same person or a different one conducts the donation conversation. This reliance on trust might be taken as pointing towards maintaining continuity of care with the same person starting the donation discussion, because a relationship of trust already exists in that context, and in some hospitals and countries that might well be the case. However, it may be that wider trust in the entire healthcare team and institution is at least as valuable, or even more so. Handing over the 'baton of trust' between sequential members of the healthcare team, including to the SNOD, is a frequent metaphor used in NHSBT education and training. In some healthcare systems, trust may best be built and maintained by clear separation of roles; in others, trust is best served by continuity of end-of-life care, including organ donation, and in other systems a hybrid of both.

Donation Physicians–A Special Case

In the Netherlands, Sweden and the UK some doctors have dual paid roles as both donation physician and intensive care doctor. In these countries the donation physician role is typically involved responsibility for strategic leadership and management in championing donation rather than direct donor coordination of an actual donor's care. In Spain the donation physician is the donor coordinator but not at the same moment in time. The UK Donation Actions Framework states that "the role of [donation physicians] is a managerial rather than a clinical responsibility. . . should not be considered, simply by nature of their role, to have any specific conflict of interest." [23].

Even so, can the desire to promote donation by these employed donation physicians be a conflict of interest that should be disclosed to the family when the doctor is leading end-of-life care in their capacity as the duty intensive care doctor for patient treatment that day.

Again, at first glance, disclosure seems a robust mechanism that minimises and makes transparent potential conflicts of interest. However, disclosure puts the onus on judging the importance of the information disclosed, onto the receiver. In donation approaches it asks the family to determine whether a role disclosure represents a conflict of interest and whether they should be concerned about this [24]. Given the grief and stress the family is already under, this is likely to be counterproductive, and risks increasing mistrust. Declaring a conflict where none was previously perceived is likely to confuse families and patients, as recognised by the Canadian Medical Association's "Ethics Guide Recommendations for Organ-Donation–Focused Physicians":

> Disclosure is context specific and depends on the donation physician's role, the circumstances, and the relationship with the patient and family. Disclosure is not necessary if it has no bearing on the situation or the relationship with the family. If the physician, as most responsible physician (MRP), has been treating the patient, he/she should disclose his/her role as a donation physician once donation conversations begin with the family. The disclosure should be made regardless of whether the donation physician role is clinical or administrative [25].

There is also potential for inter-professional issues regarding conflicts of interest. This is because some staff might see a conflict of interest between a doctor's dual role in providing end-of-life care and being a donation physician. In terms of the family, the most important aspect of any such issues is that they are resolved in a way that does not without-merit lessen family trust in the process. Relatedly, some members of staff might themselves have a personal conflict with particular aspects of care, such as donation after circulatory determination of death; in such cases, the staff member can invoke conscientious objection to avoid participation [26].

The Canadian guidance also mentions that "Donation physicians should build institutional trust by openly engaging with staff about their role" – but we would suggest that building institutional trust–and particularly "trust in the team" - among families of potential donors (and patients generally) is even more important. Trust can be built in different ways, but fundamentally important for trust of the family is that the professional making the request is well trained, open to family questions and good at communication.

Other Potential Conflicts

An important but more specific conflict concerns the timing of disclosure to the family that donation might be a possibility, in relation to when a donation coordinator is notified. The key issue is whether to notify coordinators of the potential for donation before discussing with family. It could be perceived as a potential conflict of interest if the first step towards donation is taken without first consulting the family (even if there is not really a conflict because the decision to stop treatment was already made independently). Again, local practices on this issue vary. The UK Donation Ethics Committee took a strong position on this topic, stating that:

> Contact between the clinical team treating the potential donor and the SN- OD before the decision has been made to withdraw life-sustaining treatment is ethically acceptable. Advantages include identifying patients who are not suitable donors, and avoiding distressing delays to the family if the SN-OD has to travel some distance to get to the unit [13].

Thus, the protection for the patient is that the decision for withdrawal of life-sustaining treatment is independent of the SNOD or considerations of organ donation.

Another potential clinical conflict of interest occurs in occasional cases where the potential recipient of an organ is on the same ward as a potential donor. This is a common occurrence in heart and liver transplant units and particularly in paediatrics, where the sickest children in the country are often cohorted in the largest paediatric intensive care units, typically which are also paediatric transplant centres. Independent and transparent allocation rules are vital to minimise either a real or perceived conflict of interest. While it does not change the nature of the conflict between doing one's best for the dying patient and seeking to facilitate donation, this reduction of moral distance from the recipient could make more members of staff subject to potential conflicts. (It should also be considered whether the degree of trust that families will have in healthcare systems and institutions could also be affected by whether they are public or private. It is possible that the potential for conflicts of interest to arise is likely to be higher in private, for-profit institutions.)

Finally, it should also be acknowledged that family member's decision-making can itself be affected by quite severe conflicts of interest. The classic example of this is the "family overrule" or override where the patient is a registered organ donor and one or more family members want to prevent donation. Here, the conflict is an emotional one: they have just lost a loved one and their emotions are in conflict with the wish to respect the dying wish of the patient. Healthcare professionals can help resolve this conflict with careful counselling and discussion [27].

CONCLUSION

It is clear from the description of how donation is handled in four different countries and from the ethical analysis above that there is no universal prescription for how best to handle the donation process with respect to role responsibilities. Insisting on separation of roles could lead to discontinuity of care for families who prefer the same trusted healthcare professional to be involved; equally, some families might be distrustful if they perceive an interest in donation potentially compromising end-of-life care. Instead of seeking a "golden bullet" solution–like disclosure, it will be more productive for healthcare professionals to recognise that the essence of managing conflicts of interest in donation is to build and maintain trust in the healthcare team and system among patients and their families.

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cDCDD and Heart Procurement: Challenges from a French Critical Care Perspective

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Controlled donation after the circulatory determination of death (cDCDD) is currently one of the most promising ways to increase organ availability. In France, a national cDCDD protocol requiring abdominal normothermic regional perfusion (A-NRP) has been in place since 2015. The recent consideration of heart procurement from cDCDD donors has reignited clinical and ethical debates within the critical care community. This position paper, endorsed by the two French intensive care societies, provides a critical care perspective on this evolving practice. Two key challenges are identified. First, heart procurement may require the withdrawal of life-sustaining measures (WLSM) to occur in or near the operating room, in contrast with French current practice where WLSM mostly takes place in the ICU. Intensivists strongly advocate maintaining ICU-based WLSM whenever possible, and ensuring continuity of care and end-of-life support when relocation is unavoidable. Second, the use of NRP raises concerns about the permanence of death and compliance with the dead donor rule. These concerns can be addressed through targeted biomedical research and a robust ethical framework affirming that death is declared prior to NRP and that no return to life is possible thereafter. Transparent engagement with these challenges is essential to sustain trust in the cDCDD pathway.

Keywords: controlled donation after circulatory death, end-of-life care, normothermic regional perfusion, dead donor rule, heart procurement

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INTRODUCTION

Heart procurement from donors after controlled donation following the circulatory determination of death (cDCDD) is currently under active consideration in France. Since the national implementation of cDCDD in 2015, a single standardized protocol mandating the use of abdominal normothermic regional perfusion (A-NRP) has been applied [1–3]. The potential extension of this program to include heart procurement–currently under review by the French regulatory authority (*Agence de la Biomédecine*) - opens a new chapter in the ongoing development of cDCDD in the country.

A central point of debate in the French context concerns the choice of surgical strategy for heart procurement in cDCDD donors. Two main approaches are currently under consideration: 1- direct heart procurement followed by *ex vivo* machine perfusion of the heart, in combination with A-NRP; and 2- thoraco-abdominal NRP (TA-NRP) with *in situ* restoration of cardiac activity prior to heart procurement [4–13]. Regardless of the strategy ultimately adopted, there is a strong national commitment to preserve the systematic use of A-NRP - given its proven benefits in terms of graft viability and post-transplant outcomes [14–19] - and to maintain a single standardized national protocol [2]. The choice between these two techniques requires careful consideration of multiple factors: their impact on recipients, including the viability and quality of both thoracic (heart and lungs) and abdominal grafts; the safety and feasibility of the procurement procedure itself; and the implications for donors, particularly regarding end-of-life care and compliance with the dead donor rule. In addition, broader technical, logistical, and financial aspects must also be carefully assessed when evaluating each approach.

However, this paper does aim to promote one surgical technique over another. At the time of writing, no definitive national decision has been made, and both strategies remain under review. Instead, this position paper - endorsed by the two French intensive care societies (*Société Française d'Anesthésie-Réanimation-SFAR, and Société de Réanimation de Langue Française-SRLF*) - aims to explore how the potential introduction of heart procurement in cDCDD has reopened two major issues already inherent to the cDCDD pathway: first, the potential impact of organ donation on end-of-life care; second, the debate surrounding the permanence of death and the compliance with dead donor rule when using NRP.

IMPACT OF HEART PROCUREMENT ON END-OF-LIFE CARE

In the current French cDCDD protocol, the systematic use of A-NRP enables to withdraw life-sustaining measures (WLSM) within the intensive care unit (ICU), an environment familiar for both the patient and their relatives, prior to any post-mortem transfer to the operating room for organ procurement. Two exceptions to this practice have been observed: 1- in some centers, when lung retrieval is planned, WLSM may exceptionally occur in or near the operating room to meet the ischemic constraints of lung grafts; 2- when families explicitly expressed the wish not to be present at the WLSM time, some teams may opt for operating room to facilitate procedural logistics and optimize conditions for the installation of A-NRP and subsequent organ procurement. Nevertheless, more than 85% of WLSM in French cDCDD donors currently occur within the ICU. This is a major strength of the French protocol. It allows end-of-life care to be delivered in the patient's usual care setting, ensuring relational continuity, geographical stability and the sustained involvement of the ICU caregivers that accompanied the patient and their family throughout their hospitalization. Within this model, organ donation minimally disrupts the dying process, therefore preserving the integrity of end-of-life care and supporting a patient-centered approach until death [20].

The introduction of heart procurement in French cDCDD donors will have a major impact on this current end-of-life care model. Regardless the technical approach used (direct procurement with A-NRP or TA-NRP), heart procurement requires that LSM be withdrawn in or near the operating room to meet the strict time constraints associated with the ischemic constraints of heart grafts (less than 30 min). Several challenges arise from this relocation. First, the physical environment of the operating room is inherently technical and not designed to support the emotional needs for the patient's families during the dying process. The presence and involvement of relatives becomes difficult, if not impossible. Second, the ability of ICU caregivers–particularly nurses–to accompany the patient is considerably reduced. Finally, this relocation risks reinforcing a technical and time-driven approach to dying, in which organ donation take precedence over a patient centered end-of-life care.

The potential introduction of heart procurement in French cDCDD donors has reaffirmed the position of intensivists regarding the appropriate location for WLSM. From the perspective of ICU caregivers, WLSM should, whenever possible, take place in the ICU. The only acceptable reason for relocating this step in or near the operating room is the need to meet ischemic constraints specific to certain grafts, particularly the heart and lung. Conversely, the absence of relatives at the time of WLSM should not, in our view, justify such relocation. Even in their absence, the ICU provides a more supportive environment for dying, ensuring continuity of care and the presence of familiar caregivers, particularly nursing staff.

Although relocation to the operating room may occasionally be necessary, the associated challenges can be addressed through targeted organizational and training strategies. Dedicated spaces adjacent to the operating room should be created to enable the presence of relatives and ICU caregivers. Furthermore, all healthcare professionals involved, including anesthesia and surgical teams, should receive trainings to maintain the quality of end-of-life care, facilitate the presence of relatives when appropriate, and foster effective collaboration with ICU teams.

IMPACT OF HEART PROCUREMENT IN CDCDD DONORS ON THE PERMANENCE OF DEATH AND ON THE DEAD DONOR RULE

The permanence of death and compliance to the dead donor rule when using NRP represent central clinical and ethical challenges in the development of cDCDD. These issues have been widely explored in the international literature [4, 21–25]. The following section summarizes the main dimensions of this debate before exploring how these questions are addressed from a French critical care perspective.

There is currently a broad international scientific and medical consensus that defines death as the permanent loss of brain function, that is the complete absence of consciousness brainstem reflexes, including the ability to breathe spontaneously [26, 27]. This definition has its origin in the concept of brain death, developed in the 1960s, which enabled both the possibility of withdrawing LSM in ICU patients in an "irreversible coma," and the possibility of organ donation from donors with a beating heart [28–31]. Importantly, this definition is based on the notion of *permanence,* rather than *irreversibility*. Brain function is considered permanently lost if it will not return spontaneously and will not be restored by intervention. In

contrast, irreversibility implies that brain function cannot be restored even if an intervention were performed [32, 33]. In addition, this definition emphasizes the loss of brain *function* rather than the cessation of cerebral *circulation* [30, 31]. Two pathways of dying are considered. In the circulatory sequence, the permanent cessation of peripheral circulation leads to the permanent cessation of cerebral circulation, which the results to the permanent loss of brain function. In the neurological sequence, a devastating brain injury leads to the permanent cessation of cerebral circulation due to intracranial hypertension, resulting in the loss of brain function [27]. The dead donor rule is a fundamental ethical principle in organ donation. It is based on two core requirements: first, that organs may only be retrieved from patients who have been declared dead using accepted medical criteria; and second, that organ procurement must not cause the patient's death [34–38].

However, this physiological and ethical framework is challenged by the use of NRP in cDCDD, both in A-NRP, which is currently used in France, and in TA-NRP, a technique that may be selected for introducing heart procurement into the French cDCDD protocol. In the French protocol, as in other international cDCDD protocols, death is declared after a clearly defined sequence [2]. Following the WLSM, circulatory arrest is confirmed by the absence of arterial pulsatility. This leads to the cessation of cerebral circulation and the complete loss of brain function. After a five minutes no-touch period, the loss of brain function is considered permanent, and death is declared [39, 40]. In the current French cDCDD protocol, A-NRP is then initiated to restore circulation to abdominal organs to improve graft viability and function. To prevent any restoration of cerebral circulation, an intra-aortic balloon is used to maintain the permanence of brain function loss and, therefore, the validity of death determination.

While this sequence is clearly described, its integrity can be challenged. When using A-NRP or TA-NRP, several technical and anatomical factors may compromise the exclusion of cerebral circulation. Intra-aortic balloons may be insufficiently occlusive, allowing the restoration of coronary circulation, which may in turn lead to the resumption of cardiac activity, followed by the restoration of peripheral and cerebral circulation, and ultimately the restoration of brain function–a function that was deemed permanently, but not yet irreversibly, lost. In some cases, cerebral circulation may be restored more directly, even in the absence of cardiac activity restoration. Furthermore, collateral circulation between the thoracoabdominal aorta and the posterior cerebral circulation, as well as anatomical variants, may allow blood to bypass the occlusion created by balloons or vascular clamps. This can lead at least a partial restoration of posterior cerebral circulation, and therefore of brain function, particularly the brainstem function [4]. Such scenarios directly challenge the first requirement of the dead donor rule–namely that organs can only be retrieved from patients who have been declared dead. Moreover, the use of intra-aortic balloon or vascular clamps raises ethical concerns regarding the second requirement of the dead donor rule - namely that organ donation process must not cause death. By actively preventing the potential restoration of cerebral circulation, the technique may be perceived as ensuring that death occurs, rather than simply confirming that it has taken place [41].

The perspective of introducing heart procurement from cDCDD donors has recently triggered renewed debate in France regarding the permanence of death when using NRP. Interestingly, this issue has attracted little attention at the time of the initial implementation of the French national cDCDD protocol in 2015, despite the protocol mandating the systematic use of A-NRP. At that time, the French critical care community was primarily focused on other critical aspects of the protocol, particularly the potential impact of organ donation on end-of-life decision-making [42, 43]. In this new phase, however, the potential introduction of TA-NRP as part of heart procurement protocol has brought to highlighted medical and ethical concerns regarding the permanence of death when using NRP in cDCDD donors. In response, French intensivist, supported by the two French intensive care societies, advocate for a combined approach based on both biomedical evidence and ethical deliberation. This has involved both a critical review of the medical literature in accordance with evidence-based medicine, and the facilitation of structured spaced for interdisciplinary discussion involving ethicists.

From a biomedical perspective, several research strategies are currently being explored to provide evidence of the permanence of brain function loss when using NRP [24]. The first strategy seeks to identify technical solutions that would completely prevent any restoration of the cerebral circulation. However, this remains limited, as collateral circulations and anatomical variants, may still permit some degree of cerebral circulation. The second strategy aims to determine the point at which brain function loss becomes irreversible, either by establishing a time threshold beyond which recovery is impossible, or through the development of neurological monitoring tools. The third strategy focuses on identifying the minimal level of cerebral blood flow, in terms of flow or perfusion pressure, below which the permanent (though not yet irreversible) loss of brain function cannot be restored. This physiological threshold remains poorly understood and is likely patient-specific. The fourth strategy seeks to demonstrate the permanence of the complete loss of brain function during NRP despite a possible partial restoration of cerebral circulation, particularly posterior circulation. This approach, however, is limited by current monitoring tools and by the systematic use in France of continuous and deep sedation maintained until death, a confounding factor in the assessment of brain function [44, 45].

Although complex, this biomedical agenda is seen as necessary, and research is ongoing. Available data are rather reassuring [4, 46–50]. One particularly informative study directly monitored pressures at different anatomical sites during NRP, including the radial artery (reflecting thoracic pressure), the femoral artery (abdominal pressure), and the intracranial arterial pressure at the circle of Willis. In two TA-NRP procedures performed with median sternotomy, ligation of the three arch vessels, and venting of the cephalad ends to the atmosphere, no measurable intracranial pressure was detected when NRP was initiated, despite restoration of thoracic circulation and return of cardiac activity [48]. These results support the hypothesis that appropriate surgical techniques can effectively prevent cerebral reperfusion during NRP, thereby helping to address ethical concerns related to the dead donor rule and supporting the expansion of cDCDD programs.

Nevertheless, important gaps in our physiological knowledge remains. First, the temporal sequence linking circulatory arrest, the permanent loss of brain function, and its irreversibility is still not fully understood. Second, the precise thresholds - whether in terms of cerebral blood flow or perfusion pressure - below which brain function becomes permanently and irreversibly lost have yet to be clearly defined and are likely to vary between individuals. Far from being a limitation, these challenges represent a major opportunity to strengthen the scientific foundations of cDCDD and improve the safety and acceptability of its protocols. Continued interdisciplinary research is therefore both necessary and promising.

The issue related to the permanence of death when using NRP must also be assessed from an ethical perspective [21, 22, 51–54]. While some have argued that NRP *de facto* violates the dead donor rule, the ethical approach, in our view, must follow a completely different path, based on two key considerations. First, the decision to withdraw LSM has been made solely in the best interests of the patient, independently of any consideration for organ donation. The dying process is therefore initiated for clinical and ethical reasons unrelated to transplantation. Second, the potential cDCDD donor is, in our view, indeed dead at the time of organ procurement, despite the limitations previously discussed. This position is based on a carefully defined sequence of events. After the withdrawal of LSM, the cessation of peripheral circulation, and therefore cerebral circulation, is observed leading to the loss of brain function. This state is maintained for five minutes before death is officially declared. In current French practice, however, the absence of circulation persists for approximately twenty minutes before A-NRP is initiated [3]. At the point NRP is initiated, the patient could not re-enter a trajectory of life. Before initiating NRP, targeted interventions are used to prevent or minimize any restoration of cerebral circulation, keeping any residual blood flow well below the thresholds that could allow for any recovery of brain function. The possibility of minimal restoration of the posterior cerebral circulation does not, in our view, undermine the determination of death. Under no circumstances could such marginal flow in the posterior cerebral circulation restore hemispheric function or consciousness. To suggest that this potential low-level cerebral reperfusion compromise the ethical validity of the dying process, the outcome of death as the best outcome for this patient, or the status of the donor as deceased appears to us ethically and clinically unfounded.

Building on the precedent analysis, the following section outlines a set of practical recommendations aims at ensuring that the use of NRP in cDCDD remains consistent with both ethical and clinical best practices [1]. All the technical strategies intended to prevent any restoration of cerebral circulation should be implemented prior to the NRP initiation. For A-NRP, this includes intra-aortic balloon occlusion; for TA-NRP, clamping the supra-aortic trunks and drainage of the cephalad ends into the thorax are required [2]. Throughout the NRP procedure, the absence of pressure in the left radial artery should be continuously monitored as an indicator of the effectiveness of the techniques implemented to exclude the cerebral circulation [3]. In parallel, to ensure that brainstem function loss remains permanent, specific clinical parameter should be observed, including the absence of pupillary reactivity - assessed either clinically or by pupillometry every 30 min - and the absence of diaphragmatic activity, at least until the administration of neuromuscular blockers used to facilitate organ procurement [4]. If objective signs of posterior cerebral function are detected during NRP–namely reactivity and/or diaphragmatic movements - corrective measures must be immediately undertaken to eliminate any restoration of cerebral circulation. This may include repositioning the intra-aortic balloon occlusion or checking the vascular clamps. Should these corrective measures fail, with persistence of signs of cerebral function–however partial, the organ procurement should be discontinued.

CONCLUSION

The development of cDCDD - and more specifically the use of NRP- raises complex technical and ethical challenges. These issues deserve to be addressed with caution, as they have the potential to undermine the trust of stakeholders upon which deceased donation and transplantation systems fundamentally rely. In France, the perspective of heart procurement in cDCDD donors has prompted a renewed clinical and ethical reflection. Combining biomedical research and ethical deliberation, the French critical care community aims to ensure that this evolution in practice remains consistent with both scientific rigor, ethical clarity and end-of-life care.

DATA AVAILABILITY STATEMENT

This work is a conceptual and ethical analysis; it does not include or rely on any original research data. Therefore, no data are available.

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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.

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SYSTEMATIC REVIEW AND META-ANALYSIS
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Quality of Measurement Properties in Patient Reported Outcomes Used in Adult Liver Transplant Candidates and Recipients: a Systematic Review

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Objective: Patient Reported Outcome Measures (PROMs) are increasingly recognized in liver transplant (LT)-patients, yet recent evaluations of their quality are lacking. This systematic review gives a comprehensive overview of available PROMs in adults awaiting or undergoing LT and their measurement properties.

Method: A systematic search in MEDLINE, EMBASE, PubMed, and COCHRANE (01/2010–08/2023) included studies involving adult LT-candidates and/or recipients utilizing PROMs with original evaluations of measurement properties. The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) was used to ascertain the quality of measurement properties.

Results: In total, 23 studies encompassing 35 PROMs were identified, including nine disease-specific and 26 generic PROMs. The *(Short-form) Liver Disease Quality of Life* ((SF-)LDQoL), *Transplant Effects Questionnaire* (TxEQ) and *Post-Liver Transplant Quality of Life* (pLTQ) were the most utilized disease-specific PROMs. Most studies demonstrated low-quality evidence for measurement properties. *pLTQ* demonstrated high-quality evidence for internal consistency, reliability, and responsiveness; the generic *Hospital Anxiety and Depression Scale (HADS)* showed strong evidence for internal consistency and construct validity.

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Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CD-RISK, Connor Davidson Resilience Scale; CES-D, Center of Epidemiological Studies Depression Scale; CISS-SF, Coping Inventory for Stressful Situations; COSMIN, COnsensus-based Standards for the selection of health Measurement Instruments; EQ-5D, EuroQol-5 Dimension; FACT-G, The Functional Assessment of Cancer Therapy – General; FSI, Fatigue Symptom Inventory; GAD-7, Generalized anxiety disorder screener; HADS, Hospital Anxiety and Depression Score LPA-SQUASH: Light-intensity Physical Activity Short Questionnaire to Assess Health-Enhancing Physicial Activity LT, Liver Transplantation PHQ-9, Patient Health Questionnaire depression scale pLTQ, Post-Liver Transplant Quality of Life PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis PROM, Patient Reported Outcome Measures PSSS, Perceived Social Support Scale PTGI, Post-Traumatic Growth Inventory QoL, Quality of Life; QUALIOST, Quality of Life Questionnaire in Osteopororis (SF-)LDQoL, Short Form Liver Disease Quality of Life SF-36, Short-Form 36 SOC-L9, Sense of Coherence scale by Antonovsky SSS, Medical Outcomes Study Social Support Survey STAI-6, State-Trait Anxiety Inventory TxEQ, Transplant Effects Questionnaire WHO-5, World Health Organisation – Five Wellbeing Index.

Conclusion: Measurement properties in LT-patients remains of low-quality. *pLTQ* stands out for its superior methodological quality among disease-specific PROMs. For future studies, there is a strong recommendation to focus more on patients' subjective measures and their measurement properties.

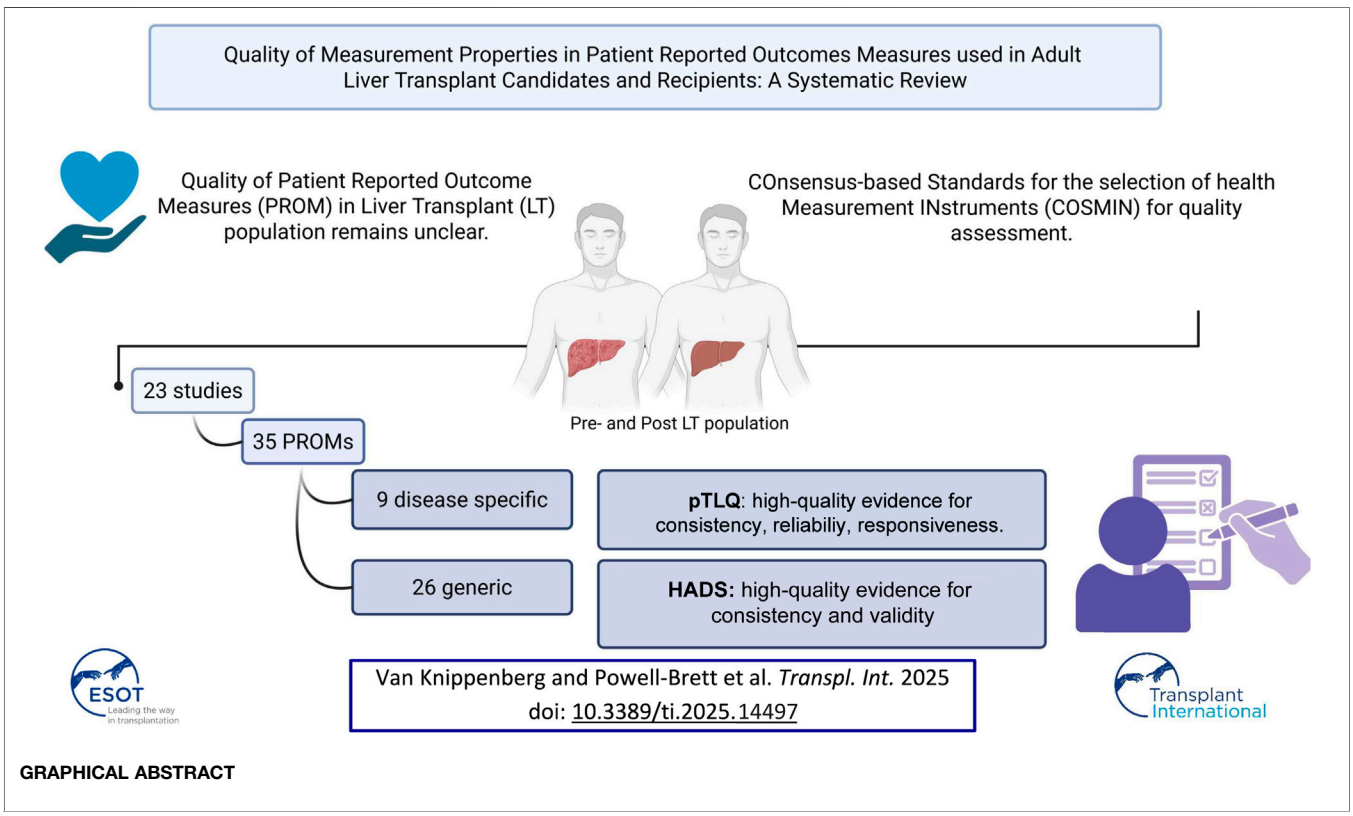
Keywords: patient reported outcome measures, liver transplantation, quality of life, measurement properties, surgery

INTRODUCTION

The field of liver transplantation (LT) is rapidly evolving. Over the last 10 years, more than 8,000 liver transplants have been performed in the United Kingdom with excellent long-term outcomes. In the United Kingdom, elective transplant procedures exhibit respective one- and 5-year survival rates of 94% and 81%, while urgent transplant cases demonstrate corresponding survival rates of 90% and 81% over the same time periods [1].

With increasing numbers and improving survival rates, there is a growing population of long-term survivors following LT. This results in a shift of focus towards subjective patient outcomes, including quality of life (QoL), anxiety and depressive symptoms. Survival is easily quantifiable; patients' subjective outcomes however are not. The last 20 years have seen the advent of a multitude of generic and disease-specific tools for measuring these patient-reported outcome measures (PROMs). Despite the increased recognition of the importance of PROMs and the growing number of tools, a standardized methodology for their application among patients undergoing LT has yet to be established.

The use of PROMs in the LT population is an invaluable tool to target improvements in clinical care, develop benchmarking standards and assess hospital performance [2]. Given the breadth of available tools (both generic and specific), it is difficult to select one that is most likely to deliver meaningful results and effect the most benefit in this cohort. Ultimately, the integration of a PROM into routine care of LT patients requires careful consideration at an early stage. Two systematic reviews by Jay et al. and Cleemput et al. reported on QoL instruments used in the LT population [3, 4]. However, both articles are over 10 years old and there have been significant methodological improvements since. Considering the above, a full, up to date systematic review is required. The aim of this systematic review is to provide a comprehensive overview of PROMs currently available for use in adults undergoing LT and their measurement properties.



GRAPHICAL ABSTRACT

TABLE 1 | Description of the domains used to evaluate the risk of bias and quality of the measurement properties for each PROM.

Domain	Description
Reliability	
Internal consistency	The degree of the interrelatedness among the items of the PROM, as long as the items together form a unidimensional scale. Most of the times, the Cronbach's alpha is measured. If the Cronbach's alpha is >0.70, the internal consistency can be deemed "sufficient"
Reliability	The proportion of the total variance in the measurements which is due to "true" differences between patients. There must be evidence that the patients are stable at the time of the PROM assessment. If the intra class correlation coefficient is > 0.70, the reliability is deemed "sufficient"
Measurement error	The systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured. The smallest detectable change should be smaller than the minimal important change, to deem the measurement property "sufficient"
Validity	
Content validity	The degree to which the content of a PROM is an adequate reflection of the construct to be Measured. Content validity is considered the most important measurement property, because the items of the used PROM should be relevant, comprehensive and comprehensible for the patient population in which the PROM is used
Contruct validity	The degree to which the scores of a PROM are consistent with hypotheses based on the assumption that the PROM validly measures the construct to be measured Construct validity is divided into structural validity, hypotheses testing and cross-cultural validity *Structural validity* refers to the degree to which the scores of a PROM are an adequate reflection of the dimensionality of the construct to be measured and is usually assessed by factor analysis *Hypotheses testing for construct validity* refers to the degree to which the scores of a PROM are consistent with hypotheses *Cross-cultural validity* refers to the degree to which the performance of the items on a translated or culturally adapted instrument are an adequate reflection of the performance of the items of the original version of the instrument. Therefore, this measurement has to be assessed by at least two different groups
Criterion validity	The degree to which the scores of a PROM are an adequate reflection of a 'gold standard', deemed 'sufficient' if the correlation with this gold standard is ≥0.70 or has an Area Under the Curve of ≥0.70
Responsiveness	The ability of a PROM to detect change over time in the construct to be measured. The results should be in accordance with the hypotheses or have an Area Under the Curve of ≥0.70
Interpretability	Interpretability is the degree to which one can assign qualitative meaning - that is, clinical or commonly understood connotations – to a PROM's quantitative scores or change in scores

METHODS

Design

An initial scoping search was undertaken to identify relevant studies on this topic. This systematic review was conducted and written in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and report in PROSPERO (PROSPERO registration number: CRD42021251533) [5].

Search

A systematic search was conducted of MEDLINE, EMBASE, PubMed and COCHRANE to identify all studies including patients undergoing LT from January 2010 until August 2023. To report the screening process, the PRISMA flow diagram was used. Studies were included if they used a PROM to measure subjective insight of LT candidates and/or LT recipients, inclusive of QoL, anxiety, depressive symptoms, pain, mobility and liver failure symptoms. Included studies had to report either the development or evaluation of one or more measurement properties of their chosen PROM. Studies with non-original evaluations of the measurement properties were excluded. *In vitro* studies, studies only covering patients under 16 years of age or those reporting on living donors were excluded. Systematic literature reviews were excluded but were used to cross check included studies and identify additional references. Additionally, the reference list of included studies was reviewed to identify additional eligible studies. The complete search strategy is described in **Supplementary Table S1**.

Screening Process

EndNote X7 (Clarivate Analytics, Pennsylvania, US) was used to collate the search results and exports of all citations were sent to the review software Rayyan (Qatar Computing Research Institute, Doha, Qatar) where duplicates were removed. After duplicate removal, four independent reviewers (SvK, SP, KJ, VW) screened by title and abstract and then by full text review. Abstracts that did not report enough information for an inclusion/exclusion decision underwent full text review. Disputes were resolved by the senior author (HH).

Data Extraction

Data extraction elements were defined in advance and included: study population, demographics (age, sex, pre-/post-LT), the PROM tools (title, scoring system, number of items, domains) and measurement properties of the PROM. Some studies described measurement properties with different

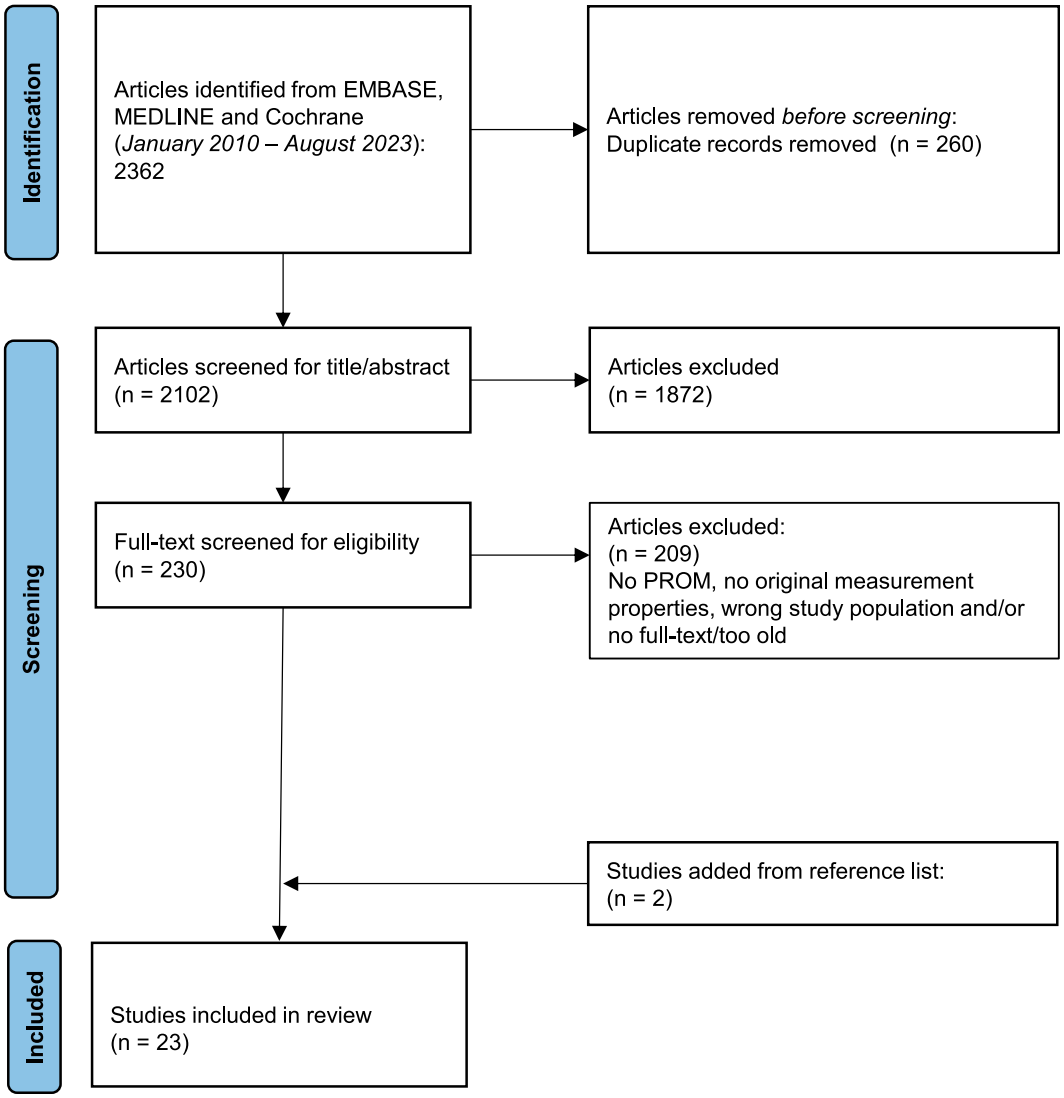


FIGURE 1 | Flow diagram.

definitions. The COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) was used to ascertain which measurement properties were evaluated by the studies [6].

Quality Assessment of Included Studies and Measurement Properties

Two authors (SvK, VW) first independently assessed the methodological quality of different domains of the studies using the COSMIN Risk of Bias checklist [7]. This employs a four-point rating system ("very good," "adequate," "doubtful" or "inadequate") and the overall quality rating of each study is based on "the worst score counts" principle, i.e., the lowest rating of any standard. **Table 1** presents information on the domains used to evaluate the risk of bias and quality of the measurement properties for each PROM.

Data Synthesis

Subsequently, the quality of the measurement properties was assessed by the updated criteria for good measurement properties (based on Terwee et al, and Prinsen et al) as outlined by the COSMIN guideline for systematic reviews [6, 7].

Measurement properties were assessed using the following principles: content validity, structural validity, internal consistency, cross-cultural validity, reliability, measurement error, criterion validity, hypothesis testing for construct validity and responsiveness. The quality of the measurement properties were scored using a four-point rating system ("+"= sufficient, "?" = indeterminate, "–" = insufficients "±" = inconsistent). When the measurement properties of a PROM were not reported in any of the included articles, no score was assigned.

The criteria for good measurement properties were then applied to the results per measurement property per PROM, and the quality of the evidence (using the GRADE approach) was analyzed.

TABLE 2 | Study and patient characteristics, categorized per Patient Reported Outcome Measurements (PROMs).

PROM	Author	Country	Publication year	Study population	Gender (male (%))	Age (mean (SD))	Mode of administration	Number of items	Response rate (%)	Target population	Patient population (pre-/post LT)
Disease-specific PROMs											
Short Form Liver Disease Quality of Life ((SF-)LDQOL)	Kanwal F (SF-LDQOL) [9]	USA	2008	156	54.8	53.9 (11)	Questionnaire	36			Pre
	Gralnek I.M [10].	USA	2000	221	64.3	52.2		111	86.6		Pre
Transplant Effects Questionnaire (TxEQ)	Pérez-San-Gregorio, MÁ [11]	Spain	2018	240				21			Post
	Annema, C [12].	Netherlands	2018	116	65.5	50.8 (11.4)	Questionnaire		75.8		Both
Post-Liver Transplant Quality of Life (pLTQ)	Molski, C [13].	Brazil	2016	160		56.9 (10.4)	Questionnaire	32			Post
	Saab, S [14].	USA	2011	196	59.7	53.1 (12.6)		32	93.8		Post
Self-made questionnaire	Parsa Yekta, Z [15].	Iran	2013	250	63.3	37.5 (12)	Questionnaire administered by hospital receptionist	40			Post
Self-made questionnaire	Lasker, J. N. (social QoL) [16]	USA	2011	100	0	58.5	Questionnaire via mail, online and interview		Response to items ranged from 93% to 100%	women with PBC on waiting list (WL) and post-transplant (PT)	Both
Self-made questionnaire	Franciosi, M. (ITaLi-Q) [17]	Italy	2011	177	71.8	57.2	Questionnaire, self-administered and anonymous	37	100% first questionairre, 49/177 the retest	Patients requiring HBV prophylaxis after LT	Post
Self-made questionnaire	Chen, X. (Post-LiverTransplant Symptom Experience Questionnaire) [18]	China	2021	265 (reliability tested on 30 patients in pilot study)	80		Questionnaire	40	96.1		Post
Self-management Questionnaire for LT recipients	Xing L [19].	China	2015	124				45			Post
Quality of Life Questionnaire in Osteopororis (QUALIOST)	Atamaz, F [20].	Turkey	2013	38 LT patients, 42 controls	81.6	42 (11.6)		24	ND		Post
Generic PROMs											
Short-form 36 (SF-36)	Fernandez, A. C [21].	USA	2016	125	60.8	56.1		36	96		Pre
	Miller-Matero, L. R [22].	USA	2014	84	66.8	SRD 53.96 (7.11) and HRD 55.87 (6.89)	Semi-structured interview	36	66.7		Both (prospective study)
	Pelgur H [23].	Turkey	2009	64	67			14	ND		Post

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TABLE 2 | (*Continued*) Study and patient characteristics, categorized per Patient Reported Outcome Measurements (PROMs).

PROM	Author	Country	Publication year	Study population	Gender (male (%))	Age (mean (SD))	Mode of administration	Number of items	Response rate (%)	Target population	Patient population (pre-/ post LT)
Hospital Anxiety and Depression Score (HADS)							Face-to-face interview, Questionnaire administered by researcher			patients who had undergone liver transplantation at least 1 month prior and were attending clinic for follow-up	
	Miller-Matero, L. R [22].	USA	2014	84	66.8	SRD 53.96 (7.11) and HRD 55.87 (6.89)	Semi-structured interview	14	66.7		Both (prospective study)
	Lin. X [24]	China	2017	285	75.8	53.3 (10.2)	Questionnaire	14	95		Post
World Health Organisation – Five Wellbeing Index (WHO-5)	Fernandez, A. C [21].	USA	2016	125	60.8	56.1 (8.64)	"	5	56		Pre
	Weber S [25].	Germany	2021	79	64.6	58.2	Questionnaire	5	ND		Post
WHOQOL-BREF	Annema, C [12].	Netherlands	2018	116	65.5	50.8 (11.4)	Questionnaire	24	75.8		Both
	Molski, C [13].	Brazil	2016	160		56.9 (10.4)	Questionnaire				Post
Post-Traumatic Growth Inventory (PTGI)	Gangeri, L [26].	Italy	2018	233	84	61	Questionnaire send to patients	21	76		Post
	Scrignaro M [30].	Italy	2016	100	15	59.88		21	58		Post
The Functional Assessment of Cancer Therapy - General (FACT-G)	Gangeri, L [26].	Italy	2018	233	84	61	Questionnaire send to patients	27	76	"	Post
Connor Davidson resilience scale (CD-RISC)	Fernandez, A. C [21].	USA	2016	125	60.8	56.1 (8.64)		25	56		Pre
Beck Depression Inventory (BDI)	Fernandez, A. C [21].	USA	2016	125	60.8	56.1 (8.64)		21	56		Pre
Beck Anxiety Inventory (BAI)	Fernandez, A. C [21].	USA	2016	125	60.8	56.1 (8.64)		21	56		Pre
Medical Outcomes Study Social Support Survey (SSS)	Fernandez, A. C [21].	USA	2016	125	60.8	56.1 (8.64)		20	56		Pre
State-Trait Anxiety Inventory (STAI-6)	Annema, C [12].	Netherlands	2018	116	65.5	50.8 (11.4)	Questionnaire	6	75.8		Both
Center of Epidemiological Studies Depression Scale (CES-D)	Annema, C [12].	Netherlands	2018	116	65.5	50.8 (11.4)	Questionnaire	20	75.8		Both

(Continued on following page)

TABLE 2 | (*Continued*) Study and patient characteristics, categorized per Patient Reported Outcome Measurements (PROMs).

PROM	Author	Country	Publication year	Study population	Gender (male (%))	Age (mean (SD))	Mode of administration	Number of items	Response rate (%)	Target population	Patient population (pre-/post LT)
Pearlin-Scooler Mastery Scale	Annema, C [12].	Netherlands	2018	116	65.5	50.8 (11.4)	Questionnaire	7	75.8		Both
Coping Inventory for Stressful Situations (CISS-SF)	Annema, C [12].	Netherlands	2018	116	65.5	50.8 (11.4)	Questionnaire	21	75.8		Both
Perceived Social Support Scale (PSSS)	Lin, X [24].	China	2017	285	75.8	53.3 (10.2)	Questionnaire	14	95		Post
General Comfort Questionnaire	Demir B [29].	Turkey	2021	148	81.8%	ND	Interview	28	ND		Post
Fatigue Symptom Inventory (FSI)	Lin, X [24].	China	2017	285	75.8	53.3 (10.2)	Questionnaire	13	95		Post
Patient Health Questionnaire depression scale (PHQ-9)	Gronewold N [27].	Germany	2022	544	63.1	51.95 (9.84)	Questionnaire	9	ND		Pre
Generalized anxiety disorder screener (GAD-7)	Gronewold N [27].	Germany	2022	544	63.1	51.95 (9.84)	Questionnaire	7	ND		Pre
Perceived social support questionnaire	Gronewold N [27].	Germany	2022	544	63.1	51.95 (9.84)	Questionnaire	14	ND		Pre
Sense of Coherence Scale by Antonovsky	Gronewold N [27].	Germany	2022	544	63.1	51.95 (9.84)	Questionnaire	9	ND		Pre
General Self-Efficacy Short Scale	Gronewold N [27].	Germany	2022	544	63.1	51.95 (9.84)	Questionnaire	3	ND		Pre
German Body Image	Gronewold N [27].	Germany	2022	544	63.1	51.95 (9.84)	Questionnaire	20	ND		Pre
Short Questionnaire to Assess Health-Enhancing Physicial Activity (SQUASH)	Ushio M [28].	Japan	2023	173	47.4	ND	Questionnaire	13	ND		Post
UCLA Loneliness Scale Utility Measure	Weber S [25].	Germany	2021	79	64.6	58.2	Questionnaire	20	ND		Post
EQ-5D	Russell R.T [8].	USA	2009	285	64	53.3		5			Both

Abbreviation: ND = not described.

TABLE 3 | Risk of Bias using the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) Risk of Bias checklist.

PROM	Author	Content valicity	Structural validity	Internal valdity (Cronbach's alpha)	Cross-cultural validity	Reliability	Measurement error (test-retest)	Criterion validity	Hypothesis testing for construct validity	Responsiveness
Disease specific N = 9										
(SF-)LDQOL	Kanwal F (SF-LDQOL)		Inadequate	very good			adequate	very good	very good	very good
	Gralnek I.M.	Very good	Inadequate	very good			inadequate		very good	
TxEQ	Pérez-San-Gregorio, MÁ			very good	very good					
	Annema, C		inadequate	very good	inadequate					
pLTQ	Molski, C			very good	very good	very good				very good
	Saab, S		very good	very good			very good	very good		
Self-made questionnaire	Parsa Yekta, Z	very good	Inadequate	very good		adequate				
Self-made questionnaire	Lasker, J. N. (social QoL)			very good		inadequate	inadequate		doubtful	
Self-made questionnaire	Franciosi, M. (ITaLi-Q)			very good		doubtful	very good	very good	very good	
Self-made questionnaire	Chen, X. (Post-LiverTransplant Symptom Experience Questionnaire)		Inadequate	Very good					inadequate	
Self-management Questionnaire for LT recipients	Xing L			very good						
QUALIOST	Atamaz, F		NA	Very good	Doubtful	doubtful		Very good		
Generic N = 26										
Short-form 36 (SF-36)	Fernandez, A. C			Very good		Inadequate			Very good	
	Miller-Matero, L. R			very good		very good			very good	
Hospital Anxiety and	Pelgur H			very good						
Depression Score (HADS)	Miller-Matero, L. R			very good		very good			very good	
	Lin. X			Very good						
World Health Organisation – Five Wellbeing Index (WHO-5)	Fernandez, A. C			Inadequate/ Doubtful						
	Weber S			Doubtful						
WHOQOL-BREF	Annema, C			very good	inadequate					
	Molski, C									
Post-Traumatic Growth	Gangeri, L			very good	doubtful		very good		Doubtful	very good
Inventory (PTGI)	Scrignaro M			Very good		Inadequate	Inadequate		Very good	
The Functional Assessment of Cancer Therapy - General (FACT-G)	Gangeri, L			very good	doubtful		very good		Doubtful	very good
Connor Davidson resilience scale (CD-RISC)	Fernandez, A. C		inadequate	very good		adequate			very good	
Beck Depression Inventory (BDI)	Fernandez, A. C			Inadequate/ Doubtful						
Beck Anxiety Inventory (BAI)	Fernandez, A. C			Inadequate/ Doubtful						
Medical Outcomes Study Social Support Survey (SSS)	Fernandez, A. C			Inadequate/ Doubtful						
State-Trait Anxiety Inventory (STAI-6)	Annema, C			Inadequate/ Doubtful						
	Annema, C									

(Continued on following page)

TABLE 3 | (*Continued*) Risk of Bias using the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) Risk of Bias checklist.

PROM	Author	Content valicity	Structural validity	Internal valdity (Cronbach's alpha)	Cross-cultural validity	Reliability	Measurement error (test-retest)	Criterion validity	Hypothesis testing for construct validity	Responsiveness
Center of Epidemiological Studies Depression Scale (CES-D)				Inadequate/ Doubtful						
Pearlin-Scooler Mastery Scale	Annema, C			Inadequate/ Doubtful						
Coping Inventory for Stressful Situations (CISS-SF)	Annema, C			very good						
Perceived Social Support Scale (PSSS)	Lin. X			Very good						
General Comfort Questionnaire	Demir B			Doubtful	Inadequate					
Fatigue Symptom Inventory (FSI)	Lin. X			Very good						
Patient Health Questionnaire depression scale (PHQ-9)	Gronewold N			Doubtful						
Generalized anxiety deisorder screener (GAD-7)	Gronewold N			Doubtful						
Perceived social support questionnaire	Gronewold N			Doubtful						
Sense of coherence scale by Antonovsky	Gronewold N			Doubtful						
general self-efficacy short scale	Gronewold N			Doubtful						
German body image	Gronewold N			Very good						
Short Questionnaire to Assess Health-Enhancing Physicial Activity (SQUASH)	Ushio M					Adequate	adequate	Very good		
UCLA loniless scale	Weber S			Doubtful						
Utility measures N = 1										
EQ-5D	Russell R.T.					Doubtful	inadequate	very good	very good	

TABLE 4 | Quality Assessment of the Patient Reported Outcome Measures (PROMs) using the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) guideline.

PROM	Author	Content Validity	Structural validity	Internal valdity	Cross-cultural validity	Reliability	Measurement error	Criterion validity	Hypothesis testing for construct validity	Responsiveness
Disease specific N = 9										
(SF-)LDQOL	Kanwal F (SF-LDQOL)		?	-				?	+	+
	Gralnek I.M.		?	-					+	
TxEQ	Pérez-San-Gregorio, MÁ			+	+					
	Annema, C.			-	?					
pLTQ	Molski, C.			+	?	+				+
	Saab, S.		?	+			-	?		
Self-made questionnaire	Parsa Yekta, Z.		?	+		?				
Self-made questionnaire	Lasker, J. N. (social QoL)		?	-		?	?		?	
Self-made questionnaire	Franciosi, M. (ITaLi-Q)		?/-	+		?		+	?	
Self-made questionnaire	Chen, X. (Post-LiverTransplant Symptom Experience Questionnaire)		?	+						
Self-management Questionnaire for LT recipients	Xing L.			+						
QUALIOST	Atamaz, F.			+	+	+		-		
Generic N = 26										
Short-form 36 (SF-36)	Fernandez, A. C.			+		?			+	
	Miller-Matero, L. R.			+					+	
Hospital Anxiety and Depression	Pelgur H.			+						
Score (HADS)	Miller-Matero, L. R.			+					+	
	Lin. X			+						
World Health Organisation – Five	Fernandez, A. C			+						
Wellbeing Index (WHO-5)	Weber S.			+						
WHOQOL-BREF	Annema, C.			-						
	Molski, C.									
Post-Traumatic Growth Inventory	Gangeri, L.			+			?		?	+
(PTGI)	Scrignaro M.			+		?	?		+	
The Functional Assessment of Cancer Therapy - General (FACT-G)	Gangeri, L.			+			?		?	+
Connor Davidson resilience scale (CD-RISC)	Fernandez, A. C.			+					?	
Beck Depression Inventory (BDI)	Fernandez, A. C.			+						
Beck Anxiety Inventory (BAI)	Fernandez, A. C.			+						
Medical Outcomes Study Social Support Survey (SSS)	Fernandez, A. C.			+						
State-Trait Anxiety Inventory (STAI-6)	Annema, C.			+						
Center of Epidemiological Studies Depression Scale (CES-D)	Annema, C.			+						
Pearlin-Scooler Mastery Scale	Annema, C			+						
Coping Inventory for Stressful Situations (CISS-SF)	Annema, C			+						

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TABLE 4 | (*Continued*) Quality Assessment of the Patient Reported Outcome Measures (PROMs) using the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) guideline.

PROM	Author	Content Validity	Structural validity	Internal valdity	Cross-cultural validity	Reliability	Measurement error	Criterion validity	Hypothesis testing for construct validity	Responsiveness
Perceived Social Support Scale (PSSS)	Lin. X			+						
General Comfort Questionnaire	Demir B			+	?					
Fatigue Symptom Inventory (FSI)	Lin. X			+						
Patient Health Questionnaire depression scale (PHQ-9)	Gronewold N			+						
Generalized anxiety disorder screener (GAD-7)	Gronewold N			+						
Perceived social support questionnaire	Gronewold N			+						
Sense of coherence scale by Antonovsky	Gronewold N			+						
General self-efficacy short scale	Gronewold N			+						
German body image	Gronewold N			+						
Short Questionnaire to Assess Health-Enhancing Physicial Activity (SQUASH)	Ushio M					-	?	?		
UCLA loniless scale	Weber S			+						
Utility measures N = 1										
EQ-5D	Russell R.T.						?	-	+	

Abbreviations: + = positive rating; ? = indeterminate rating; – = negative rating.

RESULTS

The search strategy retrieved a total of 2,362 titles/abstracts. After 260 duplicates were removed, 2,102 abstracts were screened, and 210 full-text articles were retrieved for further review. Following reference list and citation searching, two more articles were retrieved. After further review, a total number of 23 studies were included (**Figure 1**).

In total, 35 PROMs were used, with a minimum of one, and a maximum of six PROMs per study. PROMs could be divided in two categories: generic and disease-specific PROMs, and PROMs used for pre- and post-LT populations. Seven PROMs were disease-specific for liver disease and/or LT. Additionally, two PROMs addressed osteoporotic symptoms [Quality of Life Questionnaire in Osteoporosis (QUALIOST)] and emotional responses of organ transplant recipients [*the Transplant Effects Quesstionnaire (TxEQ)*], and were also categorized as disease-specific PROMs. 25 PROMs used in the studies were generic. One PROM was categorized under "utility measures," providing utilities or values regarding health, that can be used for cost-utility analyses or interventions [8].

A total of eleven PROMs were applied to the pre-LT population, while thirteen were used for post-LT population. Additionally, eleven PROMs were used for both the pre- and post-LT population. Detailed study characteristics are described in **Table 2**, and a brief description of the PROMs evaluated is presented in **Supplementary Table S2**.

The risk of bias and methodological qualities of the PROMs used and described in the selected studies are described in **Tables 3**, **4**, respectively. Overall, the evidence for the measurement properties was limited and the methodological quality was insufficient or inconsistent. None of the studies evaluated all measurement properties of the COSMIN system. Internal consistency was the most evaluated measurement property.

Disease-Specific PROMs

A total of twelve articles described the measurement properties of the nine disease-specific PROMs [9–20]. Of these PROMs, one was used in a pre-LT population, six in the post-LT population and two in both the pre- and post-LT population.

Only the (*Short-form) Liver Disease Quality of Life* [(SF-) LDQOL] (two studies), *TxEQ* (two studies) and *Post-Liver Transplant Quality of Life* (pLTQ) (two studies) were employed by multiple studies, each with their own measurement properties of the utilized PROMs. The *pLTQ* scored a high evidence level for internal validity, reliability and responsiveness.

The *ITaLi-Q*, the *self-made questionnaires* by Parsa Yekta et al. and Chen et al., the *self-management questionnaire for LT-recipients* by Xing et al. and the *QUALIOST* were all graded with a high evidence level for adequate internal validity [15, 18, 19].

The *QUALIOST* reported a high level of evidence for cross-cultural validity and reliability. The *(SF-)LDQOL* reported a high level of evidence on hypothesis testing for construct validity and responsiveness.

Generic PROMs

A total of fourteen articles described the measurement properties of 26 generic PROMs [12, 13, 21–30]. Of these PROMs, ten were used in a pre-LT population, and eight in the post-LT population. Furthermore, eight PROMs were utilized in both the pre- and post-LT population. The *EQ-5D*, graded as a 'utility measure', used in both pre- and post-LT population.

The most utilized PROMs were the *Hospital Anxiety and Depression Score* (HADS) (three studies), the *Short-form 36* (SF-36) (two studies), the *World Health Organisation – Five Wellbeing index* (WHO-5) (two studies), the *WHOQOL-BREF* (two studies) and the *Post-Traumatic Growth Inventory* (PTGI). All other PROMs were used by one study only.

There was moderate evidence for the internal validity in most studies; the *HADS* and *SF-36* both scored a high level of evidence in internal validity and hypothesis testing for construct validity. The *Short-Questionnaire to Assess Health-Enhancing Physical Activity* showed a low level of evidence for reliability. The *EQ-5D* showed a low level of evidence for criterion validity.

DISCUSSION

This systematic review is the first study to evaluate the methodological quality of PROMs utilized in the pre- and post-LT population, using the COSMIN-guidelines. In total, 23 articles employed nine disease-specific PROMs for the pre- and post-LT population, while 25 general PROMs and one utility measure were included. The (SF-)LDQOL, TxEQ and pLTQ were the most commonly used disease-specific PROMs. PLTQ showed high quality evidence of Internal validity, reliability and responsiveness. HADS was the most frequently used general PROM, and showed high-quality evidence for internal consistency and hypothesis testing for construct validity.

The methodological quality of most general and disease-specific PROMs was found to be limited, as the majority of the studies failed to adequately evaluate the measurement properties of the utilized PROMs, a trend observed in other similar reviews [31–33]. Within this review, most studies merely described the internal validity, while other essential measurement properties either lacked a description or exhibited inadequate methodological quality. Furthermore, there was inconsistency in scores for different measurement properties between different studies. For example, internal validity of the PROM *TxEQ* demonstrated sufficient quality in one study, but insufficient quality in another study, while both studies utilized the same PROM within the post-LT patient population. This discrepancy aligns with finding from the study by Elberts et al., who evaluated the quality of measurement properties in patients with neurological diseases [32]. Variations in measurement properties between studies can be in part attributed to differences in patient demographics and socio-economic characteristics. McHorney et al. found that SF-36 scores were generally lower among the elderly, those with less than a high school education and those in poverty [34]. Therefore, socio-economic backgrounds and diverse patient populations must be considered when implementing a PROM.

The limited use of PROMs in this patient population made it challenging to effectively synthesize and summarize the data. Most PROMs were reported in only one study, with only thirteen studies evaluating the same PROMs [9, 10, 14]. This lack of quality assessment is also reflected in reviews evaluating PROMs in other medical subpopulations [32, 33]. Aiyegbus et al. reviewed the measurement properties of PROMs used in kidney transplantation patients [31]. Despite a greater quantity of studies including a quality assessment of PROMs, the evidence was still of poor quality, with significant gaps in information. Chiarotto et al. evaluated the quality of measurement properties in PROMs for patients with lower back pain – including the *SF-36, SF-12, EQ-5D-3L, EQ-5D-5L, Nottingham Health Profile* and the *PROMIS-GH-10*, and found similar scarcities of high-quality evidence in their patient population [35].

The lack of robust quality assessment of PROMs can be attributed to their relatively recent rise in prominence in clinical research. However, PROMs are of the upmost importance for individual patients, as they reflect what matters to patients at a personal level, transcending the broader context of population-level survival. Therefore, identifying high quality, high level of evidence measures that can be standardized across patient populations is of paramount importance.

Assessing subjective patient measurements remain complex due to variability in individual values. Individuals prioritize different aspects of their live, posing a challenge in developing a universally applicable tool. While general tools like the SF-36 and HADS offer a broad applicability, they lack assessment of disease-specific burden. Disease-specific PROMs are therefore more suitable for subpopulations, facilitating accurate detection of burden in subjective measurements.

An additional consideration when selecting a PROM is its original intended purpose. For example, the EuroQol-5 Dimension (EQ-5D) was not originally conceived for the evaluation of QoL in medical research but rather to facilitate cost-effectiveness assessments, rendering it particularly valuable in economic studies. Poor definitions within PROMs also pose a problem, for example, the definition of HRQoL is not always clear [36].

This review extends beyond PROMs simply assessing QoL, to encompass an overview of all PROMs used in pre- and post-LT population. There is not a clear single best option and the choice of a PROM should be made with careful deliberation, considering the particular objectives of the study. Over the last decade, the use of PROMs has increased, including the use of web questionnaires [37]. The integration of PROMs into research and clinical practice enables more accurate assessment of patient symptoms and supports more efficient allocation of healthcare resources. In the context of LT, evaluating changes in symptoms before and after the procedure is particularly relevant, as it could reflects treatment effectiveness. Disease-specific PROMs are therefore generally more appropriate for assessing disease-related symptoms with greater sensitivity. In contrast, generic PROMs are more appropriate to compare across different diseases and populations, and preferred in health technology assessment [38]. Nonetheless, the use of both generic and disease-specific PROMs requires careful consideration. When clinicians or researchers select existing PROMs or developing new ones, several critical aspects must be addressed, including cross-cultural validation, the intended purpose (clinical or research), and patient acceptability and feasibility [31].

There are limitations to this review. Firstly, the populations of the included studies are heterogenous, conducted across many different countries and languages. Cultural nuances play a pivotal role in shaping perception, and the translation of PROMs into different languages may introduce variations in interpretation. Cross-cultural validation represents one approach addressing this problem. However, most of the studies did not provide a comprehensive report on this measurement property. Furthermore, the pre- and post-LT populations have different considerations, including underlying liver disease, the severity of the disease, time after transplantation and the current symptoms of the patient. All these aspects influence patient's subjective feelings and therefore the outcome of the PROM utilized. However, since there was a lack of strong evidence studies, these sub-analyses could not be performed.

In summary, this review identified the *(SF-)LDQOL, TxEQ and pLTQ* as the most commonly used disease-specific PROMs, and the *HADS* was the most frequently used general PROM. For disease-specific PROMs in both pre- and post-LT patients, the *pLTQ* emerges as the PROM of choice based on its superior methodological quality. However, the limited number of studies assessing the quality of the same PROMs and the low quality of evidence surrounding these instruments highlight the necessity of further investigation. Further studies are needed to carefully evaluate both the appropriateness of the PROM selection for their target population, and the evidence regarding the measurement properties of these instruments, either through rigorous assessment or validation.

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

SK, SP-B, KJ, and VW conducted the search, selected the studies and wrote the manuscript. HH supervised and reviewed the manuscript. 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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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.2025.14497/full#supplementary-material

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Early Post-Transplant Urinary EGF as a Potential Predictor of Long-Term Allograft Loss in Kidney Transplant Recipients

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Improved biomarkers are needed to enhance prognostication in kidney transplantation. We evaluated urinary Epidermal Growth Factor (uEGF) as a predictor of long-term allograft loss. We conducted a prospective, single-center cohort study of 290 adult kidney transplant recipients with uEGF measured 3 months post-transplant. The primary outcome was allograft loss, defined as return to dialysis or pre-emptive re-transplantation. Multivariable cause-specific Cox models assessed the independent association between uEGF and allograft loss. Model performance was compared to the iBox prediction model using 7-year time-dependent AUC and Akaike Information Criterion (AIC), with internal validation *via* bootstrap resampling. Temporal validation was performed in an independent cohort of 203 patients. uEGF correlated with markers of chronic injury, including eGFR, donor age, and interstitial fibrosis. After a median 8.8-year follow-up, lower uEGF was independently associated with allograft loss (adjusted HR 0.19; 95% CI, 0.11–0.32). Adding uEGF to the iBox improved discrimination (AUC 0.72 vs. 0.63) and reduced AIC (383 vs. 394). While results were robust to internal validation, temporal validation did not show an independent association of uEGF with allograft loss. These findings suggest uEGF may provide independent prognostic value, but further studies in larger and more diverse cohorts are needed to confirm its clinical utility.

Keywords: fibrosis, kidney transplant failure, allograft dysfunction, survival analysis, epidermal growth factor receptor

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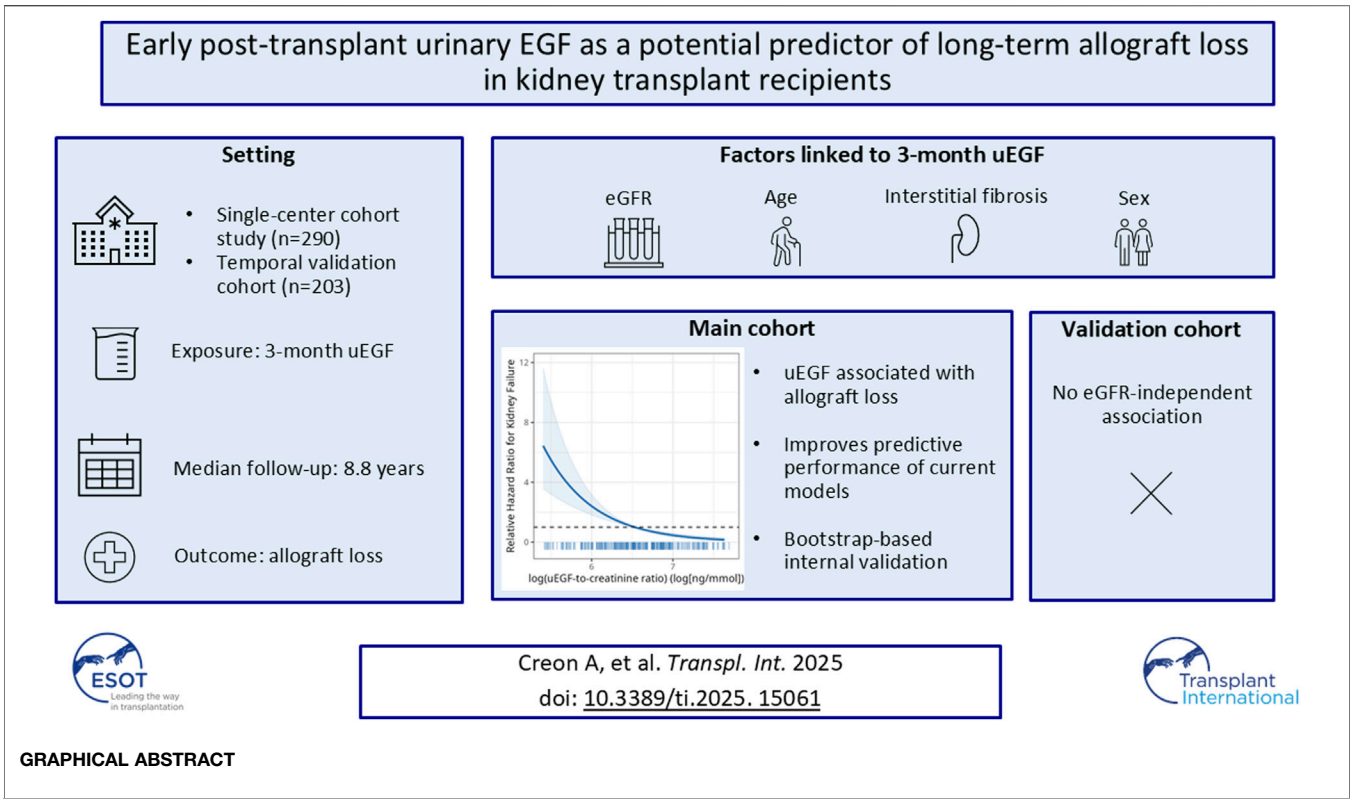
INTRODUCTION

Kidney transplantation is the standard-of-care for kidney failure. However, dialysis is still the predominant therapy in many countries [1]. One limiting factor to access kidney transplantation is an insufficient number of kidney donors to meet the needs [2]. As such, improving allografts long-term outcomes is paramount. Although marked advances in acute rejection prevention and treatment have been made over the past decades, they failed to translate into meaningful improvement in kidney allograft survival [3]. International societies acknowledged the need for better predictors of long-term outcomes, to guide patients' monitoring and tailor therapeutic strategies, but also to be implemented in clinical trials as surrogate endpoints for efficacy [4]. As



GRAPHICAL ABSTRACT

causes of late allograft loss are heterogenous, efforts have been made to include known predictors of poor outcome into prognostic scores, yielding much better accuracy than when taken individually [5]. A complementary approach involves developing innovative markers able that better capture the risk of long-term kidney injury, irrespective of its cause. The overall burden of chronic kidney damage has been strongly associated with allograft loss, regardless of the underlying etiology [6]. Therefore, detecting subclinical molecular mechanisms involved in fibrotic processes may offer a valuable strategy to improve the prediction of long-term allograft failure.

Several animal models have highlighted the key role of the Epidermal Growth Factor Receptor (EGF-R) pathway in mediating kidney fibrosis [7]. While its activation has been linked to CKD progression, it is paradoxically the reduction of its ligand, urinary EGF (uEGF), that has been associated with disease progression. uEGF has been shown to be decreased in renal biopsies of patients with chronic kidney disease (CKD) and was associated with early decline in glomerular filtration rate (eGFR) in patients with CKD, transplant recipients, and in the general population [8–11]. This observation suggests that uEGF may have a protective role in kidney physiology, or that its levels may serve as a surrogate marker of preserved nephron mass.

We hypothesized that uEGF may reflect a subclinical signaling process involved in accelerated allograft damage, that would eventually translate into reduced long-term allograft survival. In the current study, we prospectively evaluated the association between early post-transplant uEGF and long-term allograft survival in a cohort of kidney transplant recipients. We aimed to assess its association with known prognostic factors, and whether uEGF improves long-term allograft loss prediction. Finally, we evaluated the incremental value of uEGF through internal validation using bootstrap resampling, and examined whether its association with allograft loss could be replicated in a temporally distinct validation cohort from the same center.

MATERIALS AND METHODS

The study followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines for the development of prediction models [12].

Population

All consecutive adults who received a kidney transplant in our center from June 13th, 2009, to June, 6th, 2012 were considered for inclusion in this prospective, longitudinal, single-center cohort study. The retrospective validation cohort was a random sample of patients transplanted from June 10th 2012 to November 4th 2020, for whom stored urine samples were available. Selection was performed by a laboratory technician blinded to clinical characteristics. Patients with active HIV or Hepatitis C virus infection, allograft loss before 3 months post-transplant, death or lost to follow-up before 6 months post-transplant were excluded. The present study was approved by the Ethics Committee of Ile-de-France XI (#13016). All participants provided written informed consent.

Kidney Biopsies

Protocol biopsies were performed at months 3 and 12 post-transplant. Indication biopsies were performed for clinical indications. In addition to light microscopy evaluation, C4d immunohistochemical staining was systematically performed (rabbit anti-human monoclonal anti-C4d, Clinisciences, Nanterre, France, 1:200 dilution). Kidney allograft biopsies were classified using the Banff 2017 classification [13].

Immunosuppression

All but 11 patients received induction therapy with rabbit anti-thymocyte globulin (Thymoglobuline, Sanofi, Marcy l'Etoile, France [n = 152]) or basiliximab (Simulect, Novartis Pharma AG, Basel, Switzerland [n = 127]). Maintenance immunosuppression consisted of a three-drug regimen that included steroids (n = 290) and mycophenolate mofetil (n = 290) with a calcineurin inhibitor (n = 287, ciclosporine n = 59 and tacrolimus n = 228) or everolimus (n = 3). All patients with Donor Specific anti-HLA Antibodies (DSA) at time of transplantation (n = 128) received four courses of intravenous immunoglobulines in addition to the three-drug regimen. DSA-positive patients with mean fluorescence intensity (MFI) > 1,000 at day 0 (n = 55) received additional prophylactic rituximab therapy (Mabthera, Roche Pharmaceuticals, Basel, Switzerland), together with plasmapheresis.

Samples Collection and Analysis

Urine samples were collected at month 3 post-transplant, both in the derivation and validation cohort. Samples were centrifugated at 1,000 g for 10 min, within 4 h of collection. The supernatant was collected after centrifugation and stored with protease inhibitors (cOmplete™, EDTA-free Protease Inhibitor Cocktail, Roche, Basel, Switzerland) at −80 °C. uEGF was quantified by ELISA (human EGF Quantikine EG00 kit, R&S Systems, Minneapolis, USA) and standardized to urine creatinine.

Covariates and Outcomes

Covariates were prospectively collected from the medical records by research assistants. Baseline covariates were measured at 3 months post-transplant. Glomerular filtration rate was estimated using the 2009 CKD-EPI equation [14]. The outcomes were allograft loss, defined as definitive return to dialysis or pre-emptive kidney retransplantation, and death. Patients were followed from inclusion (at month 3 post-transplantation) to the date of allograft loss, death or administrative censoring (March 11th of 2024), whichever occurred first.

Statistical Analyses

Continuous variables were described using mean and standard error or median and interquartiles intervals if not normally distributed. Median follow-up was calculated using the inverse Kaplan-Meier method. For descriptive purposes, uEGF was also categorized into tertiles.

A random forest regression was performed to identify the baseline variables predicting uEGF at 3 months post-transplant. The model's parameters were optimized by 10-fold cross-validation. A grid of 100 parameter combinations was tested, with a number of predictors to be randomly sampled at each split (mtry) between 10 and 34, a number of trees in the ensemble between 500 and 1,500, and a minimum number of data points in a node that are required for the node to be split further (min_n) between 1 and 34. The optimal combination of parameters was selected based on root mean square error (RMSE), and the model was updated with these optimized parameters (mtry = 19, trees = 1,198, min_n = 20). Linear regression analysis was also performed to evaluate the association between uEGF at month 3 post-transplant and the patients' characteristics. For continuous variables, the slope corresponds to the variation in uEGF for one unit variation of the independent variable. For categorical variables, it corresponds to the difference in uEGF means between the category of interest and the reference one. Finally, we report the Spearman's rank correlation coefficient between uEGF and eGFR to avoid assumptions of normality and linearity in their relationship.

Cumulative incidence functions were estimated using the Aalen-Johansen estimator, accounting for the competing risk of death. Univariable cause-specific Cox regression analyses were performed to assess the association between allograft loss and all studied variables. For categorical variables, proportional hazards assumption was checked with a Schoenfeld residuals test. Log-linearity was assessed using the cubic splines method. Before integration in survival analyses, uEGF-to-creatinine and protein-to-creatinine ratios were log-transformed. We used cause-specific Cox models rather than Fine and Gray subdistribution hazard models to ensure consistency with the iBox scoring system, which is based on a Cox model.

To assess the robustness of the association between uEGF and allograft loss, several adjustment strategies were used. First, a stepwise forward selection procedure was applied: starting from a null model, covariates were sequentially added based on statistical significance, with the most strongly associated covariate added at each step. The selection stopped when a maximum of one covariate per 10 events was reached or when no additional covariate met the significance threshold ($p < 0.05$). Second, a model was built by selecting covariates most associated with uEGF using random forest variable importance rankings. Finally, a model was constructed by adding uEGF to the iBox model, which is the reference model for allograft loss prediction [5].

The models' discrimination ability was evaluated using the time-dependent area under the curve (AUC) at 7 years, as risks of allograft loss beyond 7 years could not be derived from the original iBox publication (see Supplementary Methods). Discrimination was assessed for both the iBox model and the extended model including uEGF, and their 7-year AUC was compared as in Blanche et al [15]. Confidence intervals for the AUC were obtained using the estimated standard error of the AUC and assuming approximate normality. The Akaike Information Criterion (AIC) was also used to compare model fit, with lower AIC values indicating a better balance between complexity and goodness of fit. Harrell's C-index was not used, as it may be less appropriate in this setting where risk predictions are

made at a specific time point [16]. To account for overfitting, internal validation was performed using 1,000 bootstrap resamples. Discrimination and calibration were optimism-corrected, with the latter assessed visually using a calibration plot comparing predicted and observed 7-year risks across quantiles of predicted risk. To reflect the original iBox publication, observed 7-year risks were estimated using the Kaplan-Meier method rather than the Aalen–Johansen estimator when assessing calibration [5]. Only complete cases were used in the analysis. Data management, statistical analyses and graphics were performed using R software 4.1.2.

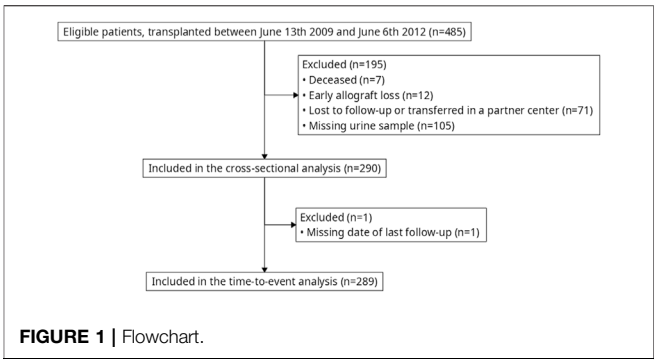


FIGURE 1 | Flowchart.

RESULTS

Characteristics of the Cohort

Between June 13th 2009 and June 6th 2012, 485 patients were transplanted in our center (Necker Hospital, Paris, France). Among them, 290 were included in the present study. A 3-month kidney biopsy that yielded adequate results was available for 274 patients. Donor specific anti-HLA antibodies (DSA) at months 3 were available for 277 patients (**Figure 1**).

The characteristics of the cohort are detailed in **Table 1**. Kidney transplant recipients had mean age of 50.8 years at the time of surgery, and 59% of them were males. The main causes of kidney failure were glomerulonephritis (26.6%), unknown nephropathy (20.7%), autosomal dominant polycystic kidney disease (14.8%) and diabetes (10.7%). Among donors, 24.5% were living donors, 39% expanded-criteria deceased donors (ECD) and 36.6% standard-criteria deceased donors. 44.1% had pre-transplant DSA and 14.1% had a previous kidney transplant. Induction therapy consisted of Basiliximab (43.8%) or anti-thymocyte globulin (52.4%). Maintenance therapy was always a triple therapy, including steroids and mycophenolate mofetil, associated with tacrolimus (78.6%), ciclosporine (20.3%) or everolimus (1%). At 3 months, the mean (SD) estimated glomerular filtration rate (eGFR) was 56.3 (23) mL/min/1.73 m^2 and the median (Q1-Q3) proteinuria was 0.02 (0.01–0.04) g/mmol. The uEGF:Cr ratio was normally distributed when log-transformed (**Supplementary Figure S1**).

UEGF Is Associated With Long-Term Allograft Loss in Univariable Survival Analysis

After a median follow-up of 8.8 years, 43 patients experienced allograft loss and 62 died. Among those with allograft loss, 29 were in the first uEGF tertile, 10 in the second, and 4 in the third, with a significant difference in allograft failure cumulative incidence (Gray test, p-value <0.001) (**Figure 2A**). Patient survival across uEGF tertiles was comparable (**Figure 2B**). A time-dependent Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the discriminatory ability of uEGF levels measured at 3 months in distinguishing between patients who experienced allograft loss and those who did not over time. The model demonstrated good discrimination from 1200 to 4000 days post-transplant, with an area under the curve (AUC) ranging from 0.727 to 0.778 (**Figure 2C**).

UEGF Is Associated With Markers of Allograft Chronic Damage

To identify the patient characteristics associated with uEGF concentrations, a random forest analysis was performed. The strongest association was observed with eGFR (**Figure 2A**), which also showed a high correlation with uEGF (correlation coefficient = 0.65, $p < 0.0001$; **Figure 2B**). To a lesser extent, uEGF was associated with recipient sex and markers of chronic allograft damage such as interstitial fibrosis, donor and recipient age (**Figure 3**). These findings were consistent with the univariable linear regression results (**Supplementary Table S1**).

UEGF Is Associated With Allograft Loss in Multivariable Analysis

To further investigate the association between uEGF at 3 months and allograft loss, several cause-specific Cox models were constructed using different adjustment strategies: (1) stepwise forward selection, (2) adjustment for variables most associated with uEGF in a random forest analysis, and (3) combination of uEGF and iBox model. Stepwise forward selection approach identified uEGF as the first covariate added to the model, as it showed the strongest univariable association with the outcome (**Supplementary Table S2**). Once adjusted for uEGF, eGFR was not significantly associated with allograft loss. The final model included uEGF (adjusted hazard ratio (HR) [95% CI] 0.19 [0.11–0.32]), sex and donor-specific antibodies (DSA) immunodominant mean fluorescence intensity (MFI). When adjusting on the 3 variables most strongly predicting uEGF levels by random forest, or on the iBox model, uEGF remained significantly associated with the risk of allograft loss (**Figure 4**; **Supplementary Table S3**).

UEGF Improves Allograft Loss Risk Prediction

Given that uEGF was independently associated with allograft loss, we assessed whether adding it to the iBox model improved predictive performance. The addition of uEGF to the iBox model improved discrimination (7-year AUC: 0.72 [0.61–0.82] vs. 0.63 [0.53–0.74],

TABLE 1 | characteristics at baseline.

Baseline Characteristics	Overall, N = 290[a]	uEGF tertiles			Missing
		113.34–546.49 ng/mmol, N = 97[a]	546.49–916.26 ng/mmol, N = 96[a]	916.26–3,790.27 ng/mmol, N = 97[a]	
Donor age	54 (18)	61 (14)	55 (17)	47 (21)	0 (0%)
Donor type					0 (0%)
Standard-Criteria	106 (37%)	28 (29%)	33 (34%)	45 (46%)	
Expanded-Criteria	113 (39%)	59 (61%)	31 (32%)	23 (24%)	
Living Donor	71 (24%)	10 (10%)	32 (33%)	29 (30%)	
Recipient age	51 (15)	52 (15)	50 (15)	51 (15)	0 (0%)
Recipient sex					0 (0%)
Male	171 (59%)	66 (68%)	59 (61%)	46 (47%)	
Female	119 (41%)	31 (32%)	37 (39%)	51 (53%)	
Recipient ethnicity					0 (0%)
Caucasian	183 (63%)	58 (60%)	60 (63%)	65 (67%)	
Black	52 (18%)	20 (21%)	19 (20%)	13 (13%)	
North-african	46 (16%)	18 (19%)	14 (15%)	14 (14%)	
Other	9 (3.1%)	1 (1.0%)	3 (3.1%)	5 (5.2%)	
Cause of kidney failure					0 (0%)
Diabetes	31 (11%)	10 (10%)	12 (13%)	9 (9.3%)	
Glomerulonephritis	77 (27%)	25 (26%)	28 (29%)	24 (25%)	
Hypertensive	19 (6.6%)	6 (6.2%)	5 (5.2%)	8 (8.2%)	
Tubulo-interstitial	24 (8.3%)	8 (8.2%)	9 (9.4%)	7 (7.2%)	
Autosomal dominant polycystic kidney disease	43 (15%)	14 (14%)	12 (13%)	17 (18%)	
Unknown	60 (21%)	19 (20%)	19 (20%)	22 (23%)	
Other	36 (12%)	15 (15%)	11 (11%)	10 (10%)	
Recipient body mass index	24.4 (4.7)	24.8 (5.0)	24.2 (4.1)	24.4 (4.9)	0 (0%)
Prior kidney transplant	41 (14%)	20 (21%)	7 (7.3%)	14 (14%)	0 (0%)
Cold ischaemia time (min)	960 (547–1,423)	1,100 (797–1,602)	887 (158–1,380)	900 (176–1,346)	3 (1.0%)
HLA A/B/DR mismatch	5.00 (4.00–5.00)	5.00 (4.00–6.00)	5.00 (4.00–5.00)	4.00 (4.00–5.00)	0 (0%)
ABO compatibility	260 (90%)	90 (93%)	86 (90%)	84 (87%)	0 (0%)
Pre-existing anti-HLA donor-specific antibody					0 (0%)
MFI <500	162 (56%)	56 (58%)	51 (53%)	55 (57%)	
MFI 500–1,000	73 (25%)	23 (24%)	23 (24%)	27 (28%)	
MFI 1000–3,000	38 (13%)	13 (13%)	16 (17%)	9 (9.3%)	
MFI >3,000	17 (5.9%)	5 (5.2%)	6 (6.3%)	6 (6.2%)	
DSA Immunodominant MFI at M3					13 (4.5%)
<500	124 (45%)	40 (43%)	40 (43%)	44 (48%)	
500–3,000	126 (45%)	42 (45%)	43 (47%)	41 (45%)	
3,000–6,000	12 (4.3%)	4 (4.3%)	5 (5.4%)	3 (3.3%)	
>6,000	15 (5.4%)	7 (7.5%)	4 (4.3%)	4 (4.3%)	
Induction immunosuppression					0 (0%)
Anti-thymocyte globulin	152 (52%)	56 (58%)	42 (44%)	54 (56%)	
Basiliximab	127 (44%)	38 (39%)	48 (50%)	41 (42%)	
No induction	11 (3.8%)	3 (3.1%)	6 (6.3%)	2 (2.1%)	
Maintenance immunosuppression					0 (0%)
Steroids, Mycophenolate Mofetil and Ciclosporine	59 (20%)	23 (24%)	18 (19%)	18 (19%)	
Steroids, Mycophenolate Mofetil and Tacrolimus	228 (79%)	72 (74%)	77 (80%)	79 (81%)	
Steroids, Mycophenolate Mofetil and Everolimus	3 (1.0%)	2 (2.1%)	1 (1.0%)	0 (0%)	
Delayed graft function	61 (21%)	32 (33%)	21 (22%)	8 (8.2%)	0 (0%)
Estimated glomerular filtration rate at 3 months (ml/min/1.73 m^2)	56 (23)	40 (14)	57 (18)	72 (22)	0 (0%)
Proteinuria at 3 months (g/mmol)	0.02 (0.01–0.04)	0.02 (0.02–0.04)	0.02 (0.01–0.03)	0.03 (0.02–0.04)	1 (0.3%)
Glomerulitis (g)					16 (5.5%)
0	215 (78%)	69 (77%)	68 (76%)	78 (83%)	
1	44 (16%)	13 (14%)	19 (21%)	12 (13%)	
2	11 (4.0%)	6 (6.7%)	1 (1.1%)	4 (4.3%)	
3	4 (1.5%)	2 (2.2%)	2 (2.2%)	0 (0%)	
Interstitial inflammation (i)					16 (5.5%)
0	261 (95%)	87 (97%)	85 (94%)	89 (95%)	
1	10 (3.6%)	2 (2.2%)	4 (4.4%)	4 (4.3%)	
2	3 (1.1%)	1 (1.1%)	1 (1.1%)	1 (1.1%)	
3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

(Continued on following page)

TABLE 1 | (*Continued*) characteristics at baseline.

Baseline Characteristics	Overall, N = 290[a]	uEGF tertiles			Missing
		113.34–546.49 ng/mmol, N = 97[a]	546.49–916.26 ng/mmol, N = 96[a]	916.26–3,790.27 ng/mmol, N = 97[a]	
Total interstitial inflammation (ti)					16 (5.5%)
0	252 (92%)	76 (84%)	86 (96%)	90 (96%)	
1	14 (5.1%)	8 (8.9%)	4 (4.4%)	2 (2.1%)	
2	6 (2.2%)	4 (4.4%)	0 (0%)	2 (2.1%)	
3	2 (0.7%)	2 (2.2%)	0 (0%)	0 (0%)	
Tubulitis (t)					16 (5.5%)
0	237 (86%)	77 (86%)	80 (89%)	80 (85%)	
1	14 (5.1%)	6 (6.7%)	3 (3.3%)	5 (5.3%)	
2	7 (2.6%)	2 (2.2%)	2 (2.2%)	3 (3.2%)	
3	16 (5.8%)	5 (5.6%)	5 (5.6%)	6 (6.4%)	
Intimal arteritis (v)					16 (5.5%)
0	271 (99%)	90 (100%)	89 (99%)	92 (98%)	
1	2 (0.7%)	0 (0%)	1 (1.1%)	1 (1.1%)	
2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
3	1 (0.4%)	0 (0%)	0 (0%)	1 (1.1%)	
Peritubular capillaritis (ptc)					16 (5.5%)
0	235 (86%)	75 (83%)	81 (90%)	79 (84%)	
1	24 (8.8%)	7 (7.8%)	7 (7.8%)	10 (11%)	
2	12 (4.4%)	6 (6.7%)	1 (1.1%)	5 (5.3%)	
3	3 (1.1%)	2 (2.2%)	1 (1.1%)	0 (0%)	
Interstitial fibrosis (ci)					16 (5.5%)
0	156 (57%)	32 (36%)	51 (57%)	73 (78%)	
1	59 (22%)	22 (24%)	27 (30%)	10 (11%)	
2	32 (12%)	20 (22%)	7 (7.8%)	5 (5.3%)	
3	27 (9.9%)	16 (18%)	5 (5.6%)	6 (6.4%)	
Tubular atrophy (ct)					16 (5.5%)
0	154 (56%)	32 (36%)	51 (57%)	71 (76%)	
1	63 (23%)	24 (27%)	26 (29%)	13 (14%)	
2	34 (12%)	21 (23%)	9 (10%)	4 (4.3%)	
3	23 (8.4%)	13 (14%)	4 (4.4%)	6 (6.4%)	
C4d graft deposition (c4d)					16 (5.5%)
0	226 (82%)	72 (80%)	67 (74%)	87 (93%)	
1	27 (9.9%)	11 (12%)	12 (13%)	4 (4.3%)	
2	15 (5.5%)	5 (5.6%)	7 (7.8%)	3 (3.2%)	
3	6 (2.2%)	2 (2.2%)	4 (4.4%)	0 (0%)	
Vascular Fibrous Intimal Thickening (cv)					16 (5.5%)
0	101 (37%)	23 (26%)	33 (37%)	45 (48%)	
1	62 (23%)	17 (19%)	24 (27%)	21 (22%)	
2	82 (30%)	37 (41%)	25 (28%)	20 (21%)	
3	29 (11%)	13 (14%)	8 (8.9%)	8 (8.5%)	
Glomerular basement membrane double contours (cg)					16 (5.5%)
0	269 (98%)	89 (99%)	88 (98%)	92 (98%)	
1	5 (1.8%)	1 (1.1%)	2 (2.2%)	2 (2.1%)	
2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Arteriolar hyalinosis (ah)					16 (5.5%)
0	108 (39%)	21 (23%)	39 (43%)	48 (51%)	
1	116 (42%)	40 (44%)	38 (42%)	38 (40%)	
2	35 (13%)	20 (22%)	12 (13%)	3 (3.2%)	
3	15 (5.5%)	9 (10%)	1 (1.1%)	5 (5.3%)	

[a]*Mean (SD); n (%); Median (25%–75%).*

p-val = 0.002) and reduced the AIC (394 vs. 383), indicating a better trade-off between model complexity and goodness of fit (**Table 2**). Similarly, removing uEGF from the stepwise selection model decreased the 7-year AUC (80.35 [76.06–84.64] vs. 65.02 [59.12–70.92], p = 0.004) and increased the AIC (406 vs. 443). In the random forest–based model, removing uEGF did not significantly decrease the 7-year AUC (76.18 [71.63–80.73] vs. 74.73 [69.85–79.61], p = 0.54) but increased the AIC (434 vs. 438) (**Supplementary Table S4**). The association between uEGF and allograft loss, adjusted on the iBox score, is visually depicted in **Figure 5**.

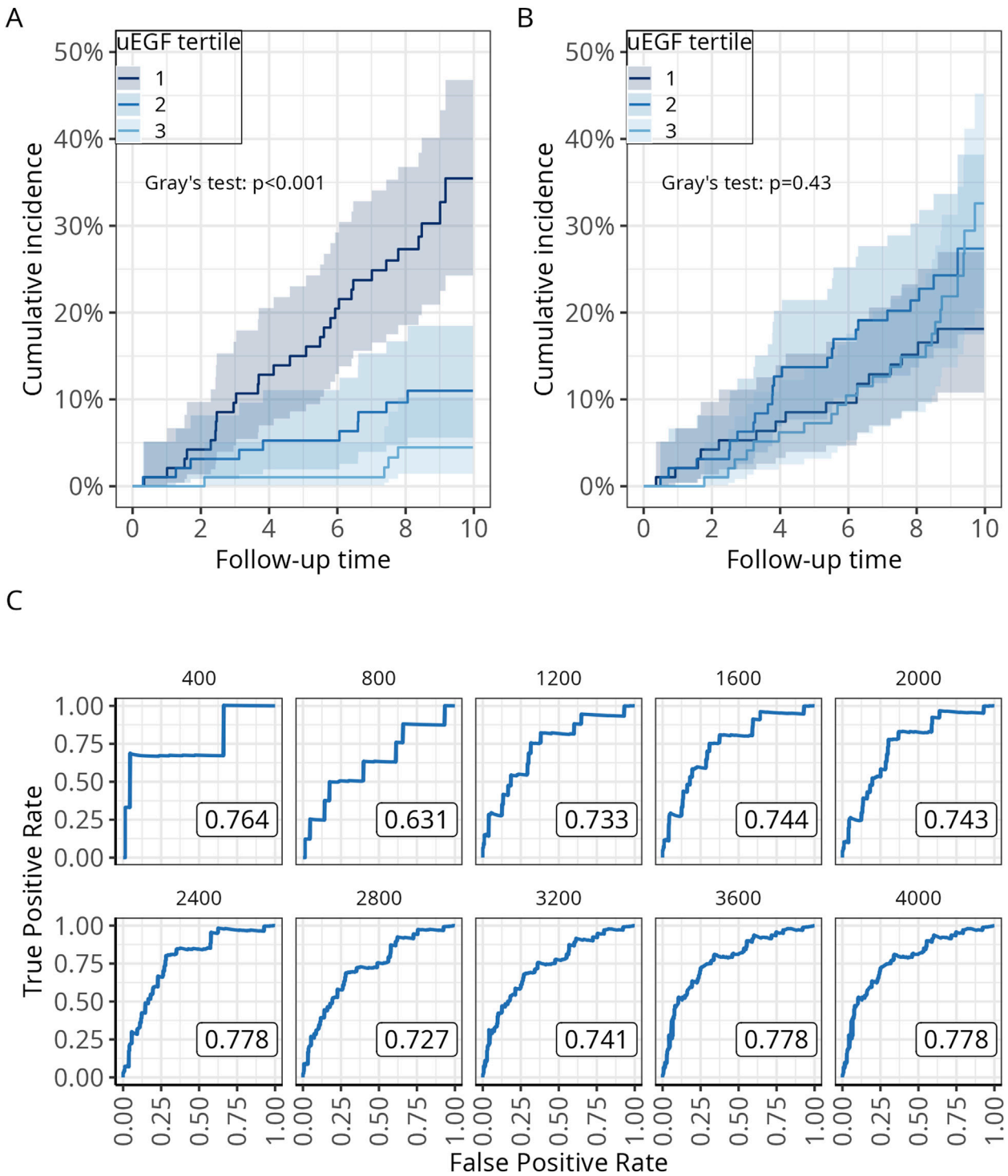


FIGURE 2 | Relationship between allograft loss, death, and uEGF at 3 months post-transplant in univariable survival analysis. **(A)** Cumulative incidence curves for allograft loss across tertiles of uEGF at 3 months; **(B)** Cumulative incidence curves for all-cause death across tertiles of uEGF at 3 months; **(C)** Time-dependent ROC curves for uEGF at 3 months in diagnosing allograft loss, evaluated every 400 days following transplantation. The statistical significance of differences in survival across uEGF tertiles is assessed using Gray's test. uEGF, urinary Epidermal Growth Factor. ROC, receiver operating curve.

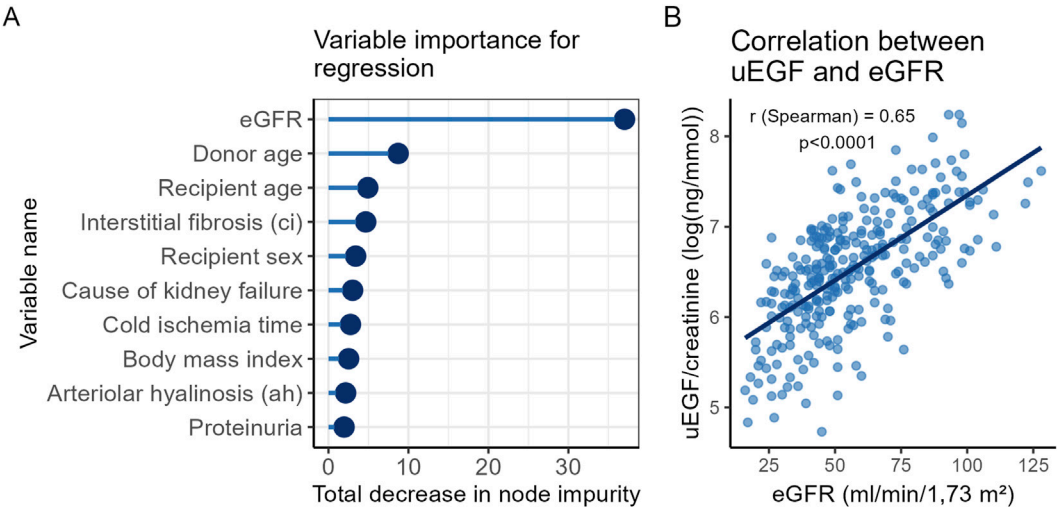


FIGURE 3 | Covariates associated with uEGF levels at 3 months post-transplant. **(A)** Variable importance in explaining uEGF levels at 3 months post-transplant, measured by the total reduction in residual sum of squares in random forest regression analysis. Hyperparameters optimized by 10-fold cross validation were trees = 1,198, mtry = 19 and min_n = 20. Only the top 10 variables contributing most significantly to the model's predictive performance are displayed. **(B)** Scatterplot of uEGF and eGFR distributions, with Sperman's correlation coefficient. uEGF: urinary Epidermal Growth Factor. eGFR: estimated Glomerular Filtration Rate.

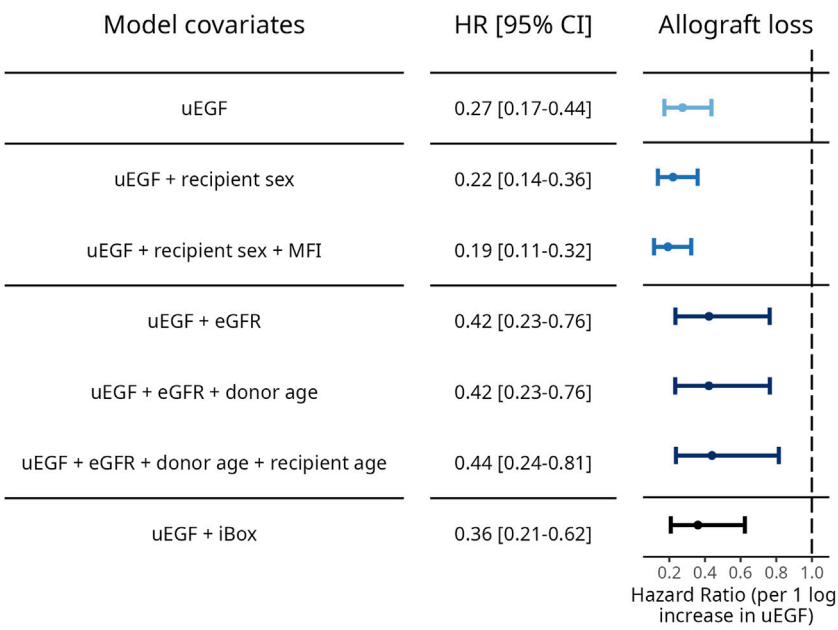


FIGURE 4 | Cause-specific hazard ratios for allograft loss associated with uEGF levels at 3 months post-transplant. Models 1: uEGF alone. Models 2 and 3: step-forward variable selection. Variables were added sequentially based on significance starting from the null model. Model 2: uEGF and recipient sex. Model 3: uEGF, recipient sex and DSA immunodominant MFI at 3 months post-transplant. Models 4 to 6: variable selection based on random forest importance ranking. Variables identified as most associated with uEGF in the random forest analysis were included. Model 4: uEGF and eGFR. Model 5: uEGF, eGFR and donor age. Model 6: uEGF, eGFR, donor age and recipient age. Model 7: uEGF and iBox (see supplementary methods). uEGF: urinary Epidermal Growth Factor. eGFR: estimated Glomerular Filtration Rate. MFI: anti-HLA donor-specific antibody immunodominant mean fluorescence intensity.

Internal Validation

1,000 random samples from the original cohort were generated using a bootstrapping procedure. The optimism-corrected 7-year AUC of the uEGF+iBox model was 0.71 [0.68–0.74]. The optimism-corrected calibration plot suggested that the model tended to overestimate risk in individuals at higher predicted risk and underestimate it in those at lower predicted risk (**Figure 6**).

TABLE 2 | Discrimination performance and model fit of the iBox model with and without uEGF.

Model	7-year AUC [95% CI]	P-value	AIC
iBox	0.63 [0.53–0.74]	-	394
iBox + uEGF	0.72 [0.61–0.82]	0.002	383

uEGF: urinary Epidermal Growth Factor. AIC: Aikake Information Criteria. 7-year AUCs, were compared as in Blanche et al. [15].

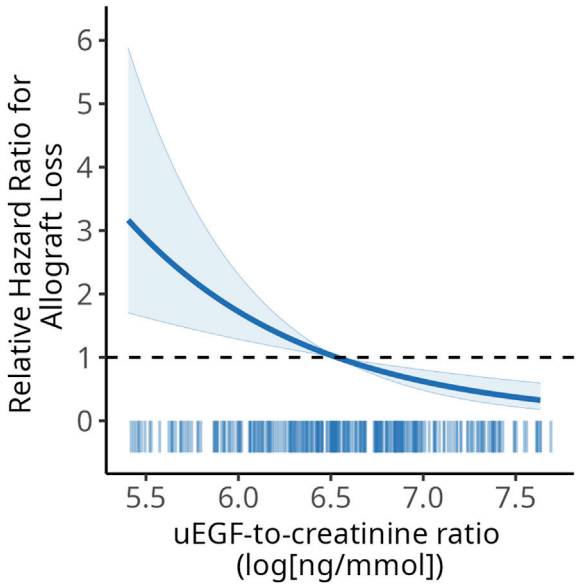


FIGURE 5 | Adjusted hazard ratios of allograft loss associated with uEGF levels. Adjusted on average iBox value. The shaded area corresponds to 95% confidence interval. uEGF: urinary Epidermal Growth Factor.

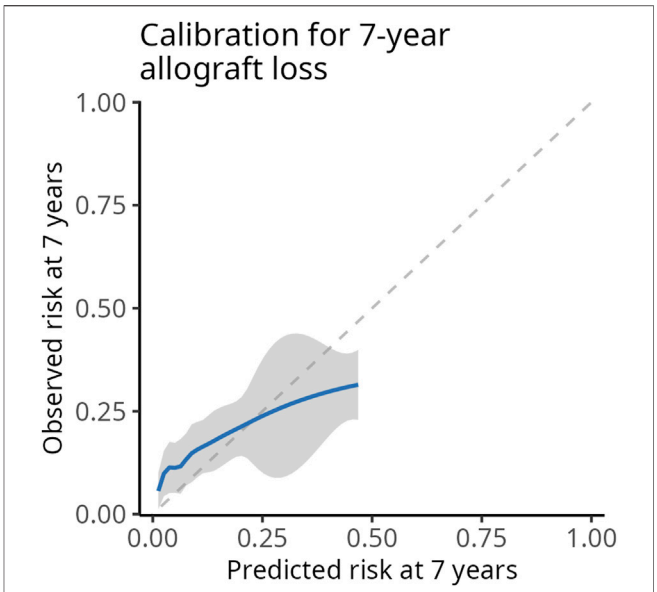


FIGURE 6 | Optimism-corrected calibration plot at 7 years of the iBox + uEGF model. Average predicted (x-axis) and observed (y-axis) 7-year risks across quantiles of predicted risk. To reflect the original iBox publication, observed 7-year risks were estimated using the Kaplan-Meier method rather than the Aalen–Johansen estimator.

Temporal Validation of the Association Between uEGF and Allograft Loss

Temporal validation was performed in a retrospective cohort of 203 patients recruited from our center from December 27th 2012 to November 4th 2020 (**Supplementary Table S5**), to examine whether the association between early post-transplant uEGF levels and long-term allograft loss could be replicated in a temporally distinct population. After a median follow-up of 5.5 years, 30 patients died and 18 experienced allograft loss. UEGF was significantly associated with allograft loss in univariable Cox analysis (HR 0.35 [0.15–0.80], p-value = 0.01), but not once adjusted for eGFR (HR 0.71 [0.26–1.94], p-value = 0.5). The low number of events did not allow for reliable multivariable analysis and performance assessment.

DISCUSSION

Headway has been made in the past several years to combine predictors of allograft loss like eGFR, proteinuria, allograft scarring or inflammation and anti-HLA DSA profiling into prognostic scores. The current study evaluated the hypothesis that early uEGF, a biomarker of kidney fibrosis, may serve as an independent predictor of long-term allograft loss. Indeed, uEGF measured at 3 months post-transplant was prospectively associated with allograft survival. As anticipated, uEGF levels correlated with markers of chronic kidney injury such as eGFR, donor age, and interstitial fibrosis. Nevertheless, uEGF remained independently associated with allograft loss after adjusting for these factors or for the current reference prediction model. Moreover, adding uEGF to this model improved its predictive performance. While results were robust to internal validation, temporal validation did not show an independent association of uEGF with allograft loss.

UEGF was measured at 3 months post-transplant, together with a screening biopsy. The rationale for early identification of patients at high risk of reduced long-term allograft survival is to target them with dedicated therapeutic strategies apt to modify their eGFR trajectory. Although several kidney donor characteristics are informative regarding transplantation outcomes, risk evaluation in the very first weeks post-surgery may be confounded by acute events: so far, urinary biomarkers measured at the time of donation provided limited insight in allograft function prediction [17]. Similarly, in the iBox derivation cohort, day 0 parameters were not associated with allograft survival after adjustment for post-transplant parameters, which were mostly evaluated within the first 18 months post-transplant [5].

As uEGF is strongly associated with markers of chronic kidney damage, we may wonder the extent to which uEGF is a marker of functional nephron mass or provides independent information *per se*. Yepes-Calderon et al. [10] suggested a link between uEGF and early allograft loss, but the interpretation of their results was limited by important heterogeneity in risk evaluation timing, the lack of

histological data to properly adjust allograft loss prediction and shorter follow-up interval. We were able to thoroughly evaluate the relationship between uEGF and the other markers of chronic kidney damage including histological ones, and assess their association with long-term allograft loss. At 3 months post-transplant, none of them were independently associated with allograft loss when adjusted on uEGF. Taken together, these results suggest molecular mechanisms related to kidney fibrosis may be detectable early and carry prognostic value for long-term allograft function. Lower uEGF may reflect ongoing fibrotic processes triggered by peri-transplant injury or an underlying susceptibility to future fibrosis progression. However, the lack of temporal replication—evidenced by the absence of an independent association between uEGF and allograft loss in the validation cohort—underscores the need to further investigate the consistency and robustness of uEGF as a prognostic biomarker.

This study has several strengths. We were able to assess uEGF prognostic value in a well-phenotyped, homogenous cohort of transplant recipients, with a median follow-up time of nearly 9 years. Extensive availability of allograft histology at the time of uEGF measurement allowed us to better understand the interrelations between uEGF and the other markers of chronic kidney damage, as well as to include them in our multivariable models. The association between uEGF and graft failure was internally validated and robust to adjustment for the iBox model.

This study has several limitations. First, uEGF measurements were not repeated, and data on how uEGF levels fluctuate over time are lacking. Additionally, some uncertainty remains regarding the added value of uEGF in predicting allograft loss. Although the addition of uEGF improved the predictive performance of the iBox model in our cohort, it is important to note that the baseline performance of the iBox was substantially lower than that reported in its original derivation and validation studies. Several factors may account for this discrepancy. Notably, our cohort consisted exclusively of patients assessed at 3 months post-transplant, an earlier time point than the one used in the development of the iBox score. At 3 months, important prognostic events and risk factors may not yet have fully manifested, potentially limiting the model's ability to stratify long-term risk. Furthermore, the relatively small cohort size limited the statistical power and increased the risk of overfitting. It restricted the number of covariates that could be reliably included, potentially overlooking important confounders. Additionally, it may have contributed to less precise effect estimates and limited the generalizability of our findings to broader transplant populations.

Altogether, our findings contribute to the ongoing discussion of whether uEGF offers prognostic information beyond established markers such as eGFR, or integrated prognostic models like the iBox. While uEGF shows promise as an independent predictor, further studies in larger, diverse cohorts are needed to clarify its added value and potential role in clinical risk stratification.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are available from the corresponding author on reasonable request. Requests will be reviewed to ensure compliance with ethical guidelines and data protection regulations, and a data-sharing agreement may be required.

ETHICS STATEMENT

The studies involving humans were approved by Ethics Committee of Ile-de-France XI (#13016). 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, AC and DA; Methodology, AC and DA; Formal Analysis, AC; Investigation, VG; Resources, DA; Data Curation, LM, VG, LA; Writing – Original Draft Preparation, AC; Writing – Review and Editing, MR, FT, DA; Supervision, DA; Funding Acquisition, DA. 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.

GENERATIVE AI STATEMENT

The author(s) declare that Generative AI was used in the creation of this manuscript. OpenAI's ChatGPT (GPT-4) was used to assist with grammar correction and phrasing improvements during the preparation of this manuscript. The authors reviewed and edited all AI-assisted text to ensure accuracy and adherence to scientific standards. No AI tools were used for data analysis, interpretation of results, or generation of original scientific content.

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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.2025.15061/full#supplementary-material

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ORIGINAL RESEARCH
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Long-Term Outcomes of Pediatric Kidney Transplants From DCD and DBD Donors: A Comparative OPTN Study

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We compared the long-term outcomes of pediatric kidney transplants from DCD and DBD donors over a 33-year period in the USA. Data were retrieved and analysed on kidney transplants from deceased donors in paediatric recipients in 1994–2020 from the OPTN. Data were compared between those receiving kidney transplants from DBD and DCD donors. There were 11,071 paediatric kidney transplants from deceased donors including 350 from DCD donors. DCD transplants were more likely to have delayed allograft function (20.1% vs. 11.9%, $p < 0.01$). However, there was no significant difference in allograft or patient survival between transplants from DBD and DCD donors at 10 years (56% vs. 55%, $p = 0.76$ and 90% vs. 91%, $p = 0.89$). We describe the largest cohort of pediatric DCD kidney transplant recipients in the literature. We showed that despite higher rates of delayed allograft function in DCD transplants, long-term outcomes were not significantly different. Kidney transplants from DCD donors are a viable option and should be offered to children comparable to DBD kidneys as their long-term outcomes do not differ. DCD transplantation is illegal in some countries, however, it offers an opportunity to increase the number of transplants for children; this data should be considered in ongoing policy discussions.

Keywords: registry, kidney transplant, DCD, pediatric, DBD donor

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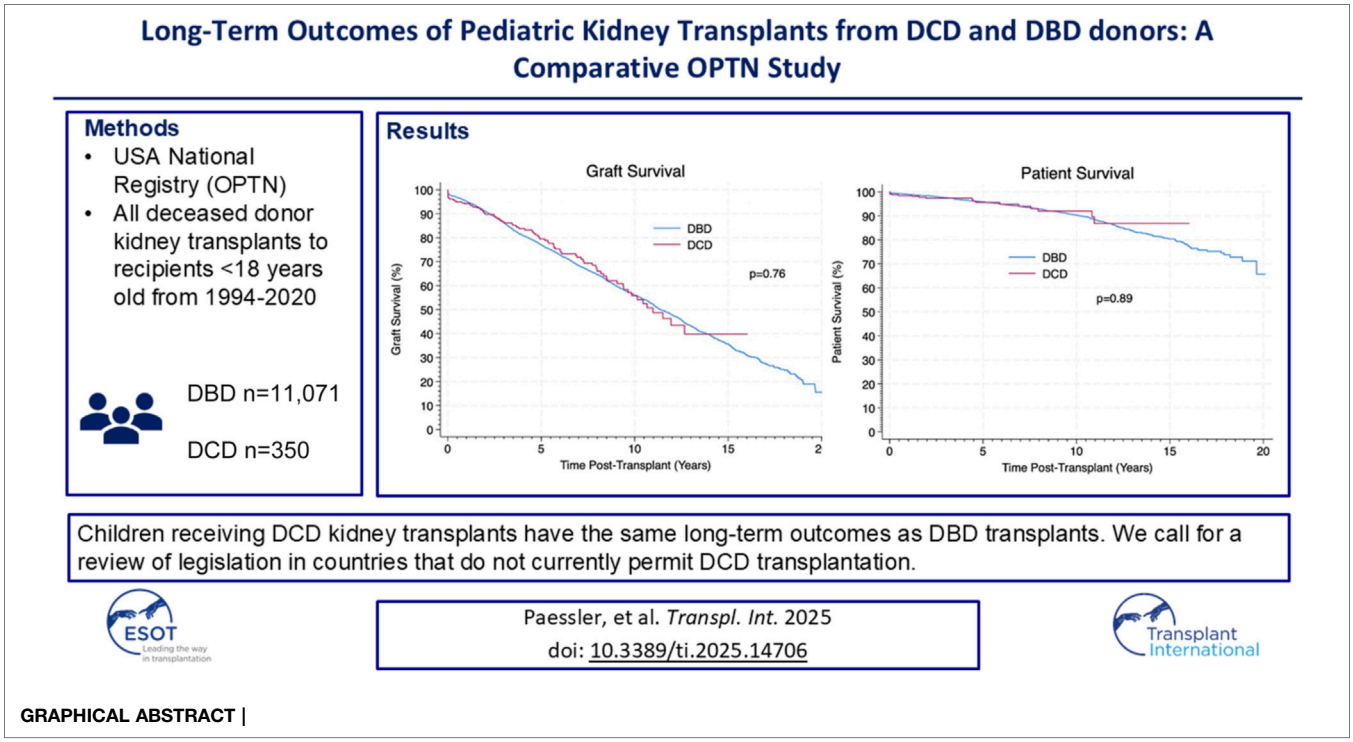
Abbreviations: ANOVA, Analysis of Variance; DGF, Delayed Graft Function; DBD, Donation after brainstem determination of death; DCD, Donation after circulatory determination of death; HLA, Human Leucocyte Antigen; OPTN, Organ Procurement and Transplantation Network; PNF, Primary Non-Function; PSM, Propensity Score Matched; SPSS, Statistical Package for Social Sciences; UNOS, United Network of Organ Sharing; WIT, Warm Ischaemia Time.



GRAPHICAL ABSTRACT |

INTRODUCTION

As modern medicine advances, there is an increasing number of children with complex conditions surviving outside infancy, who are now presenting to transplant professionals as potential transplant candidates. Over the last 20 years there has been a 54% increase in children being listed for a kidney transplant from a deceased donor in the USA [1]. Unfortunately, transplant rates have not increased to the same degree, leaving children waiting for organs longer than previously. In 2023, 29% of children on the waiting list had been waiting for longer than 2 years for their transplant [1]. Furthermore, 16 children were removed from the waiting list that year because they had died or were too sick for transplantation [1]. There is a clear need to increase the potential donor pool for paediatric kidney transplant recipients.

One of the things that has become increasingly common to increase the donor pool is using organs that have been donated after circulatory determination of death (DCD). The difference between DCD and DBD (donation after brainstem determination of death) is the criteria used to confirm the death of the donor–either circulatory or brainstem. DCD rates rapidly declined in the USA after brain death legislation was adopted in 1968, although the interest in DCD began to increase again in the 1990s as a way to meet the increasing demand for donor organs; largely led by the Maastricht team in the Netherlands [2, 3].

There is still a large variation in DCD practice across the world with some countries such as the USA, UK and the Netherlands, predominantly practicing controlled DCD - donation occurs after cardiac arrest in donors following withdrawal of life-sustaining therapy [4]. In other countries such as France and Spain uncontrolled DCD is also practiced–donation following unsuccessful resuscitation attempts in the donor [4]. However, there are also several other countries such as Germany [5], Greece [6], Hungary [7] and others, which do not allow any form of DCD [5, 8]. There is now significant global experience in the safe performance of DCD in children, with the key concept of the permanence of terminal cardiorespiratory arrest based on the concept of loss of function that can resume spontaneously, and a decision that there will be no resuscitation attempts. One of the issues with such different donation practices is that it has somewhat limited the amount of evidence produced on the long-term outcomes of DCD transplantation. DCD transplantation is widely accepted in adult practice in countries which permit it. As adults represent a much higher proportion of overall transplant activity than children, there are many studies with large datasets looking at the long-term outcomes of DCD in adults, these are unfortunately lacking in paediatrics so far. These large-scale studies have shown positive results with DCD transplants having equivocal allograft survival, despite initially higher rates of delayed allograft function (DGF) [9, 10]. However, partially due to a lack of the same positive evidence and the lack of large-scale studies in paediatrics, to this day there is some skepticism among some professionals on the long-term effects associated with DCD organs in paediatrics. There remains a concern amongst some clinicians about perceived increased risk of primary non-function, DGF and long-term allograft outcomes. The largest study to date on

paediatric DCD transplants included less than 300 patients and found increased rates of DGF, with another study finding increased rates of late allograft loss [11, 12]. DCD kidneys sustain a warm ischaemic injury around the time of donation, this occurs due to the period of hypoperfusion that happens between the withdrawal of life-sustaining treatment until asystole. This is then further compounded by the period of no perfusion during the mandated stand-off time between asystole and the retrieval. This warm ischaemic injury is thought to contribute significantly to the previously reported higher rates of delayed allograft function, although whether this impacts long-term outcomes remains, at least in paediatrics, unclear [9, 13, 14]. This scepticism is partially reflected by the slower increase in the use of DCD organs for paediatric recipients in comparison to adult recipients. For example, in the USA, over the last 20 years there has been a 19x increase in adults receiving kidney transplants from DCD donors, whereas in paediatric recipients there has only been a 2.4x increase [1]. This could partially be explained by a lower proportion of paediatric donors being DCD donors than in adult donors (30% vs. 44% in 2024) [1], however, the majority of children still receive organs from adult donors and so the use of DCD organs for paediatric recipients should see a similar increase as in adults.

This study aims to compare the long-term outcomes of kidney transplants from DCD donors and DBD donors to paediatric recipients in the USA over a 26-year period.

MATERIALS AND METHODS

The Organ Procurement and Transplantation Network (OPTN) database is an online registry developed by United Network of Organ Sharing (UNOS) that contains all data pertaining to patient waiting lists, living and deceased organ donation, organ matching and organ transplants that have taken place in the U.S. since 1st October 1987 [15]. Data is 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.

OPTN registry data for all kidney transplants performed for recipients under the age of 18 years from deceased donors in the U.S. from October 1994 (date of first DCD transplant) until September 2020 were requested. Data collected included donor and recipient demographics, primary renal disease, number of prior transplants, dialysis status at transplantation, number of Human Leucocyte Antigen (HLA) mismatches, primary allograft non-function, delayed allograft function, allograft survival and patient survival time. All patients' follow up data was based on their status on the registry in January 2021. Patients with no data recorded on the donor type were excluded. All variables collected and proportion of patients with missing data for each variable can be seen in **Supplementary File 1**.

All statistical analysis was carried out with IBM Statistical Package for Social Sciences (SPSS) Version 28 [16]. Propensity-Score-Matched (PSM) groups were created on a 1:2 basis based on recipient age, dialysis, prior-transplant status, year of transplantation, number of HLA mismatches and donor creatinine. Demographics were described for the whole cohort and the PSM cohort. Post-transplant outcomes including allograft and patient survival were compared between patients with transplants from DBD and DCD donors from the PSM group. Means and (95% confidence intervals) were reported to describe all numerical data, frequencies and percentages were used to describe categorical data. Independent T-test, chi-squared test and Analysis of Variance (ANOVA) was used for significance testing to compare groups of patients. Distribution analysis prior to group comparisons was carried out by visual assessment of histograms in order to identify the appropriate test to use. Patient and allograft survival at 1, 3, 5 and 10 years post-transplant by different eras of transplantation were estimated using Kaplan-Meier analysis and log-rank testing was used to assess comparisons. Multiple Multivariate Cox Regression Models for allograft and patient survival were also done from the PSM cohort in a sensitivity analysis. Bonferroni corrections were implemented to account for the number of comparisons made between the DBD and DCD group which left a threshold of significance of $p < 0.01$. Patients with missing data were excluded from proportional analysis for each analysis that required the variable in question.

The results from this data have been reviewed by all current members of the Paediatric Donation and Transplantation Working Group of the Ethical, Legal and Psychosocial Aspects of Organ Transplantation Section of the European Society of Organ Transplantation. The recommendations and suggestions that are included in this manuscript based on our results from this study were discussed, supported and agreed upon by all working group members prior to publication.

RESULTS

Patients and Transplant Characteristics

Overall, during the study period there were 11,071 paediatric kidney transplants from deceased donors, of which 350 were from DCD donors.

Patients receiving allografts from DCD donors were significantly older than from DBD donors at 12.90 (12.45–13.37) years old vs. 11.52 (11.42–11.61) years old ($p < 0.01$). There was no significant difference in the distribution across different ethnicities ($p = 0.36$). The first DCD transplant in this cohort of patients took place in 1994 and rates of DCD transplantation have progressively increased since then. The mean follow up time for patients was 6.69 (6.59–6.79) years for DBD and 5.10 (4.69–5.52) years for DCD. Further details including underlying sex, underlying renal disease, dialysis status and number of prior transplants for both the baseline cohort and the PSM cohort can be seen in **Table 1**.

Patients with transplants from DCD donors were more likely to have transplants with an unfavourable number of HLA mismatches (4, 5 or 6 mismatches) with 82.9% of transplants having an unfavourable HLA mismatch compared to 80.7% of DBD donors, although this was not statistically significant ($p = 0.34$). There was no significant difference in the mean cold ischaemia time between DCD and DBD donors – 15.27 h (14.61–15.94 h) vs. 14.59 h (14.44–14.74 h), $p = 0.06$. The

TABLE 1 | Number and proportions of DBD and DCD transplants for different baseline characteristics for the overall cohorts and for the propensity score matched (PSM) cohorts. Patients with "unknown" listed as their primary renal disease were excluded from the proportions that were compared between DBD and DCD. Patients with no data recorded for each variable were excluded from analysis for their respective category.

Participant characteristics		DBD (n = 10,721)	DCD (n = 350)	p-value	DBD-PSM (n = 662)	DCD-PSM (n = 349)	p-value
Mean age (95% CI)		11.52 (11.42–11.61)	12.90 (12.45–13.37)	<**0.01**	12.84 (12.52–13.15)	12.90 (12.44–13.36)	0.41
Male (%)		6,231 (58.1)	194 (55.4)	0.31	366 (55.3)	193 (55.3)	0.99
Ethnicity (%)	White	4,475 (41.7)	149 (42.6)	0.75	255 (38.5)	149 (42.7)	0.19
	Black	2,624 (24.5)	87 (24.9)	0.87	170 (25.7)	86 (24.6)	0.71
	Hispanic	2,897 (27.0)	80 (22.9)	0.73	195 (29.5)	80 (22.9)	0.02
	Asian	388 (3.6)	18 (5.1)	0.13	23 (3.5)	18 (5.2)	0.19
	Other/Mixed	337 (3.1)	16 (4.6)	0.13	19 (2.9)	16 (4.6)	0.15
Underlying Renal Disease (% of known causes)	Unknown	1,304 (12.2)	36 (10.3)	0.29	66 (10)	35 (10)	0.98
	Cystic	669 (7.1)	20 (6.4)	0.61	39 (6.5)	20 (6.4)	0.91
	Pyelonephritis/ Obstruction/Reflux	2,147 (22.8)	75 (23.9)	0.65	126 (21.1)	78 (23.9)	0.34
	Glomerulonephritis	3,135 (33.3)	112 (35.7)	0.37	234 (39.3)	112 (35.7)	0.3
	Hypertension/Vascular	444 (4.7)	17 (5.4)	0.56	29 (4.9)	17 (5.4)	0.71
	Hereditary/Metabolic	602 (6.4)	13 (4.1)	0.1	41 (6.9)	13 (4.1)	0.09
	Hypoplasia/Dysplasia	1,693 (18.0)	57 (18.2)	0.93	100 (16.8)	57 (18.2)	0.6
	Other	727 (7.7)	20 (6.4)	0.37	27 (4.5)	20 (6.4)	0.23
Era (%)	1990–1999	1933 (18.0)	11 (3.2)	<**0.01**	34 (5.1)	11 (3.2)	0.14
	2000–2009	4,030 (37.6)	106 (30.3)	<**0.01**	184 (27.8)	105 (30.1)	0.45
	2010–2020	4,758 (44.4)	233 (66.6)	<**0.01**	464 (67.1)	233 (66.8)	0.27
Number of Prior Transplants (%)	0	9,581 (89.4)	307 (87.7)	0.32	593 (89.6)	307 (88.0)	0.43
	1	1,040 (9.7)	41 (11.7)	0.21	65 (9.8)	40 (11.5)	0.41
	2	92 (0.9)	2 (0.6)	0.56	3 (0.5)	2 (0.6)	0.79
	3	8 (0.1)	0 (0)	-	1 (0.2)	0 (0)	-
Favourable Number of HLA Mismatches (%)		2050 (19.1)	60 (17.1)	0.34	122 (18.4)	60 (17.2)	0.62
Pre-emptive Transplant (%)		2,233 (20.8)	66 (18.9)	0.37	122 (18.4)	66 (18.9)	0.85
Mean Follow Up Time in Years (95% CI)		6.69 (6.59–6.79)	5.10 (4.69–5.52)	<**0.01**	5.02 (4.72–5.32)	5.12 (4.68–5.55)	0.37
Mean Cold Ischaemia Time in Hours (95% CI)		14.59 (14.44–14.74)	15.27 (14.61–15.94)	0.06	13.96 (13.36–14.56)	15.27 (14.61–15.94)	<**0.01**
Mean Warm Ischaemia Time in Minutes (95% CI)		-	12.01 (10.73–13.30)	-	-	16.36 (15.15–17.58)	-
Mean Donor Creatinine in mg/DL (95% CI)		0.96 (0.94–0.97)	0.81 (0.78–0.85)	<**0.01**	0.83 (0.80–0.85)	0.81 (0.78–0.85)	0.23

Bold values show statistical significance of p < 0.01.

mean warm ischaemia time (WIT) for all DCD transplants was 12.01 min (10.7–13.3).

Post-Transplant Outcomes

Patients with transplants from DCD donors were significantly more likely to have delayed graft function (DGF) than DBD donors (n = 71, 20.3% vs. n = 60, 9.1%, p < 0.01) however there was no significant difference in the rates of primary non-function (PNF) between the donor types (n = 4, 1.2% vs. n = 5, 0.8%, p = 0.52). There was also no significant difference in the incidence of renal vessel thrombus (n = 9, 2.6% vs. n = 11, 1.7%, p = 0.31).

The mean creatinine (mg/dL) at the point of hospital discharge post-transplant was significantly higher in patients with transplants from DCD donors – 2.21 mg/dL (1.99–2.43 mg/dL) than in patients with transplants from DBD donors - 1.36 mg/dL (1.24–1.48 mg/dL) (p < 0.01).

Kaplan-Meier allograft and patient survival was stratified into three categories representing three different eras of transplantation–Pre-2000, 2000–2009 and 2010-present. Within each time period there was no significant difference in allograft or patient survival between transplants from DBD and DCD donors. 1, 3, 5 and 10 years allograft and patient survival for these patients is summarized in **Tables 2**, **3** and survival curves can be seen in **Figures 1**, **2**.

TABLE 2 | Overall estimated Kaplan-Meier allograft survival for transplants from DBD and DCD donors in the propensity score matched (PSM) cohort at 1, 3, 5 and 10 years post-transplant. P-values were derived with the Log Rank Test.

Patient group	1 year	3 years	5 years	10 years	p-value
DBD 1990–2000	93.8%	62.5%	50.0%	31.0%	p = 0.71
Number at risk	*31*	*21*	*17*	*10*	
DCD 1990–2000	80.0%	50.0%			
Number at risk	*9*	*6*			
DBD 2000–1,010	92.9%	76.8%	70.0%	47.1%	p = 0.19
Number at risk	*169*	*130*	*112*	*57*	
DCD 2000–2010	94.1%	82.7%	70.2%	54.1%	
Number at risk	*95*	*77*	*62*	*38*	
DBD 2010–2020	97.5%	90.4%	82.2%	49.0%	p = 0.37
Number at risk	*357*	*209*	*120*	*2*	
DCD 2010–2020	94.7%	89.3%	85.8%	53.1%	
Number at risk	*182*	*124*	*76*	*1*	

Italic values represent number at risk at each time point.

After PSM, within the new cohort the following variables were equally matched: dialysis status at transplantation, year of

TABLE 3 | Overall estimated Kaplan-Meier patient survival for transplants from DBD and DCD donors from the propensity score matched (PSM) cohort at 1, 3, 5 and 10 years post-transplant. P-values were derived with the Log Rank Test.

Patient group	1 year	3 years	5 years	10 years	p value
DBD 1990–2000	97.0%	97.0%	97.0%	79.0%	p = 0.55
Number at risk	*33*	*31*	*26*	*15*	
DCD 1990–2000	90.0%	80.0%	66.7%	66.7%	
Number at risk	*10*	*7*	*6*	*5*	
DBD 2000–1,010	99.5%	98.2%	95.0%	86.1%	p = 0.17
Number at risk	*179*	*156*	*135*	*65*	
DCD 2000–2010	99.0%	98.0%	96.7%	93.8%	
Number at risk	*97*	*84*	*71*	*46*	
DBD 2010–2020	99.5%	98.5%	97.3%	96.3%	p = 0.17
Number at risk	*359*	*211*	*125*	*2*	
DCD 2010–2020	98.7%	97.5%	95.3%	90.0%	
Number at risk	*187*	*129*	*78*	*1*	

Italic values represent number at risk at each time point.

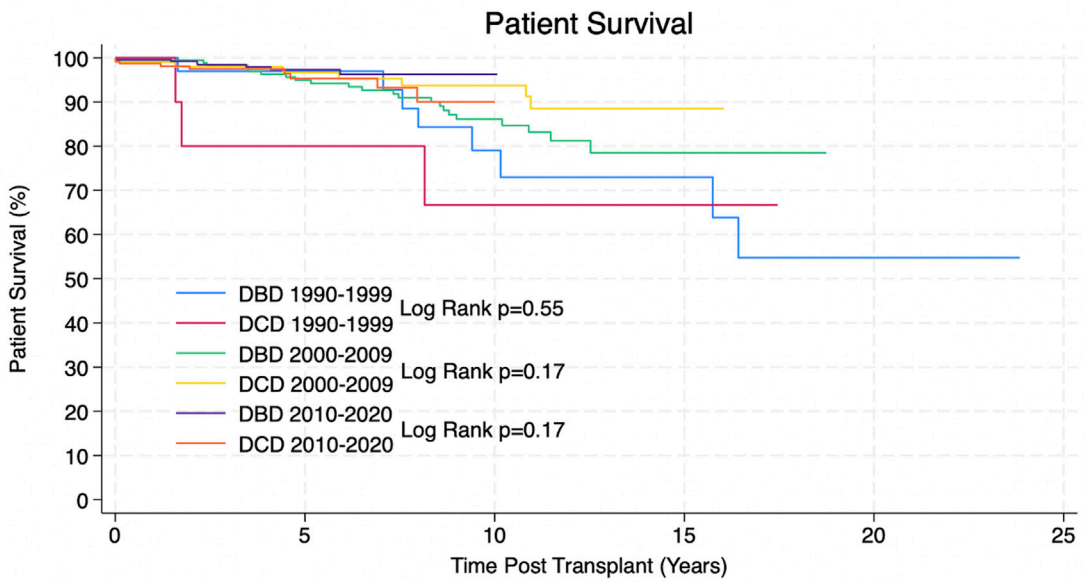
transplant, number of HLA mismatches, donor creatinine and recipient age. Multivariate Cox Regression analysis was undertaken with multiple different models accounting for other potential residual confounders including some that were stratified by era of transplantation, early graft failure, early death and follow up time for allograft and patient survival as a sensitivity analysis. This found that DBD vs. DCD transplantation consistently had no statistically significant impact on allograft and patient survival. Hazard ratios and significance for the different models can be seen for these in **Tables 4**, **5**.

DISCUSSION

This observational retrospective study describes the clinical outcomes of the largest cohort of paediatric kidney transplant recipients from DCD donors in the literature. Overall, we have shown that kidney transplants from DCD donors have equivocal outcomes to kidney transplants from DBD donors in paediatric recipients.

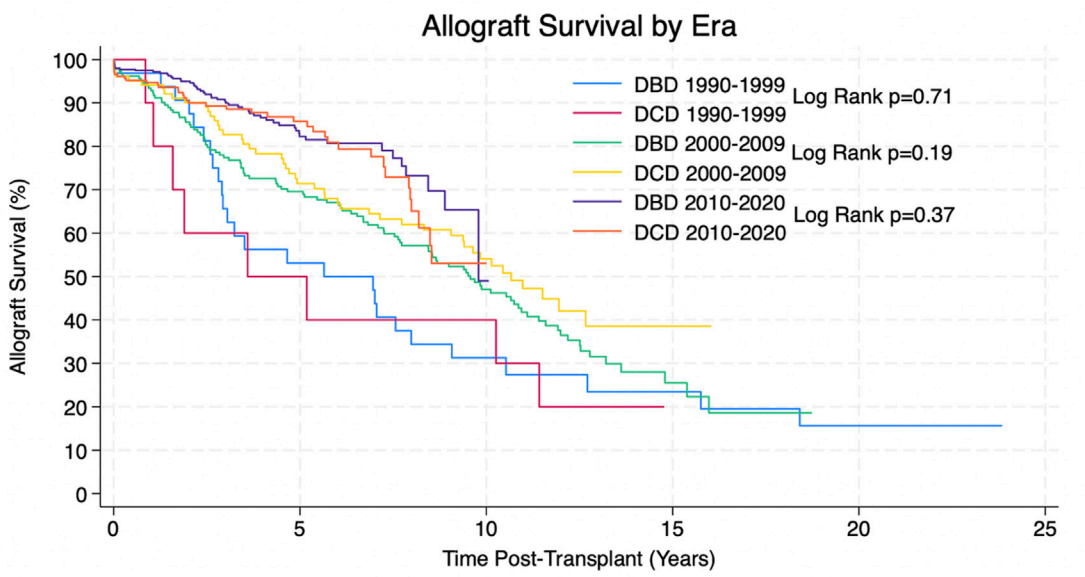
One of the positive trends identified in this data is that there does not seem to be any racial disparities within DCD transplantation which unfortunately does still exist in access to transplantation as a whole [17].

One of the main concerns with allografts from DCD donors is the impact of the WIT which is associated with these allografts and the higher rates of DGF. Our mean WIT was 12.01 min which is better than or equivocal to other studies [18, 19]. The higher risk of



Number at Risk	0 Years	5 Years	10 Years	15 Years	20 Years
DBD 1990-1999	34	26	15	9	3
DCD 1990-1999	11	6	5	1	0
DBD 2000-2009	184	135	65	12	0
DCD 2000-2009	105	71	46	4	0
DBD 2010-2020	444	125	2	0	0
DCD 2010-2020	233	78	1	0	0

FIGURE 1 | Estimated Kaplan-Meier allograft survival post-transplant for transplants from DBD and DCD donors from the propensity score matched (PSM) cohort. P-values were derived from the Log Rank Test.



Number at Risk	0 years	5 years	10 years	15 years	20 years
DBD 1990-1999	34	17	10	6	3
DCD 1990-1999	11	5	4	0	0
DBD 2000-2009	184	112	57	9	0
DCD 2000-2009	105	63	39	4	0
DBD 2010-2020	444	120	2	0	0
DCD 2010-2020	233	76	1	0	0

FIGURE 2 | Estimated Kaplan-Meier patient survival post-transplant for transplants from DBD and DCD donors from the propensity score matched (PSM) cohorts. P-values were derived from the Log Rank Test.

TABLE 4 | Sensitivity analysis with Multivariate cox regression models for allograft survival in the propensity score matched (PSM) cohorts.

Variables	Hazard ratio	p-value	95% CI
Model 1			
DCD	0.93	0.56	0.72–1.19
Model 2			
DCD	0.9	0.44	0.70–1.17
CIT	0.1	0.11	0.99–1.02
Ethnicity	0.93	0.06	0.86–1.00
Model 3			
DCD	0.93	0.57	0.73–1.19
Number of Previous Transplants	1	0.95	0.74–1.39
Model 4 - Stratified by Era of Transplantation			
DCD	0.95	0.69	0.74–1.22
Model 5 - Stratified by Early Graft Failure (<1 year post-transplant)			
DCD	1.57	0.15	0.85–2.87
Model 6 - Stratified by Late Graft Failure (>1 year post-transplant)			
DCD	0.85	0.25	0.65–1.12
Model 7 - Stratified by Short Follow Up Time (<1 year post-transplant)			
DCD	1.92	0.1	0.88–4.21
Model 8 - Stratified by Long Follow Up Time (>1 year post-transplant			
DCD	0.85	0.24	0.66–1.11
Model 9 - Stratified by Very Long Follow Up Time (>5 years post-transplant)			
DCD	0.88	0.47	0.62–1.25

TABLE 5 | Sensitivity analysis with Multivariate cox regression models for patient survival in the propensity score matched (PSM) cohorts.

Variables	Hazard ratio	p-value	95% CI
Model 1			
DCD	0.94	0.83	0.54–1.63
Model 2			
DCD	0.95	0.87	0.54–1.69
CIT	1.02	0.09	0.99–1.05
Ethnicity	0.96	0.60	0.81–1.13
Model 3			
DCD	0.96	0.88	0.55–1.67
Number of Previous Transplants	1.41	0.25	0.79–2.55
Model 4 - Stratified by Era of Transplantation			
DCD	0.99	0.98	0.57–1.73
Model 5 - Stratified by Early Death (<1 year post-transplant)			
DCD	0.94	0.83	0.54–1.64
Model 6 - Stratified by Late Death (>1 year post-transplant)			
DCD	2.2	0.3	0.50–9.91
Model 7 - Stratified by Short Follow Up Time (<1 year post-transplant)			
DCD	2.77	0.16	0.68–11.3
Model 8 - Stratified by Long Follow Up Time (>1 year post-transplant			
DCD	0.71	0.29	0.37–1.35
Model 9 - Stratified by Very Long Follow Up Time (>5 years post-transplant)			
DCD	0.75	0.63	0.23–2.42

DGF with DCD allografts has been widely reported in the literature and is also found in our data and is also reflected by the higher creatinine levels at discharge in these patients [10, 18–20]. Currently, we are unclear as to what potential downstream effects this higher creatinine level might have, while it does not appear to impact allograft survival, we do not have data to clarify if it affects other aspects such as CKD progression. However, our rate of DGF in DCD allografts was not quite as high as reported in adults [18]. DGF occurs due to a multitude of reasons including but not limited to increased cold ischaemia time, increased WIT, donor hypertension and obesity and pre-transplant dialysis [21–23]. The literature on adult patients suggests that DGF can be associated with poorer long-term outcomes including shorter death-censored allograft survival and higher rates of acute rejection and so it is important to try and avoid this [10, 18, 21, 23]. However, one adult study found that DCD allografts may be more resilient, and that DGF in a DCD allograft has less impact on long-term outcomes than DGF in DBD allografts [10]. Nevertheless, strategies to try and reduce the incidence of DGF remain important. Some adult studies have found that the use of both hypo- and normothermic machine perfusion of the allografts prior to transplantation can significantly reduce the incidence of DGF and positively impact long-term allograft survival when compared to static cold storage [24–28]. Higher rates of DGF in DCD allografts may prompt retrieval teams to consider the use of these perfusion techniques more often when retrieving DCD allografts to improve their outcomes. In addition to perfusion techniques, studies have found that reducing CIT can also help mitigate the increased risk of DGF in DCD kidneys [9].

Reassuringly, despite higher rates of DGF, the long-term outcomes of transplants from DCD donors appear equivocal to those from DBD donors with regards to allograft and patient survival. This is similar to some of the adult and paediatric evidence in the literature [11, 18–20], although some studies have not found this to be the case and have shown increased rates of late-allograft loss [12]. Some of the reasons our study may vary from that is our larger sample size and longer follow up time; that study referred to late-allograft loss as 4 years-post transplant, however they only had 4 years follow up data for 31 DCD patients, whereas we have 4 years follow up data for 183 DCD patients [12]. The warm ischaemia time in our cohort was also lower than some other studies; evidence shows that warm ischaemia time correlates with poorer outcomes and so this may also account for our positive [14]. Our results show DCD donors are a valuable resource that provide good outcomes, comparable to those of DBD donors, and have the potential to facilitate more kidney transplants for paediatric recipients. While some centres may be hesitant to use these kidneys for paediatric recipients, we have now shown that they can have good clinical outcomes, in line with DBD kidneys and so one should consider utilizing these as a viable transplant option. Furthermore, one adult study has shown that there is a significant survival benefit of accepting a DCD organ offer compared to remaining on the waiting list for an allograft from a DBD donor [29]. Utilizing DCD donors for paediatric transplant recipients can also lead to an increase in pre-emptive transplantation which is known to be associated with better clinical outcomes [30].

In countries that do not perform DCD in children any approach to consider it will need to address the specific national reasons. If elective withdrawal of life-sustaining therapies at end-of- life in ICU is not the national norm, then DCD can only follow a much more involved discussion about usual end-of-life practices in ICU which may need legal changes/clarification, as well as changes in medical norms. If DCD is already practiced in adults, though not in children, this is a far easier argument. The clear global evidence for safe paediatric DCD means that with appropriate training and infrastructure, maintaining the distinction is unethical, as it prevents children, and their parents, from donating organs when they die, leading to the deaths of other children based on indefensible age discrimination. Initial controlled DCD will, of course, be easier to introduce than donation following failed acute resuscitation, which many countries with normalized paediatric DCD processes do not practice.

The main strength of this study is its large sample size, to date, the largest reported in the paediatric population, which allows significant trends to be identified reliably. It also presents a long follow-up time further distinguishing it from previous studies. However, the study could be limited by the potential heterogeneity of the data. While we have tried to control for some confounders by using propensity score matching, Multivariate Cox Regression models and sensitivity analysis; variables such as the use of machine perfusion, immunosuppression agents, centre effect, rejection episodes, CKD progression, donor age and organ quality were not reported and not accounted for in analysis and could be significant confounders. Furthermore, this is a retrospective registry study, which means some data may not be that reliable, many variables are unable to be accounted for and patients risk being lost to follow up. Our data is also based on the American allocations system and transplant practice which could limit the generalizability to other countries, however our positive results should remain encouraging to clinicians worldwide. Additionally, the allocation system in the USA since 2014, which allocates kidneys with a higher expected allograft survival to patients with the highest potential life-expectancy, may also be a confounding factor. This is because kidneys from DCD donors are currently considered to have a risk of lower expected allograft survival than DBD kidneys and so are not allocated in the same way [31]. We have tried to control for this by propensity score matching our group so that baseline characteristics between recipients in the DBD and DCD group do not differ, however some confounding may remain. Our current data does not support the notion that DCD kidneys are inferior organs, however further and more in depth research is required to confirm this and therefore allocation policies and clinicians' views may need to adjust to reflect this as more evidence becomes available.

Further studies are needed to explore the outcomes of DCD transplants around the world, and to look into other outcome data such as rejection rates. It would also be helpful to further investigate any potential factors that can reduce the rate of DGF in paediatric DCD transplant recipients. Qualitative and sociological studies are also important to aid understanding of the public and political views on DCD practices in countries that

so far do not permit it to better understand the barriers facing DCD transplant programmes.

CONCLUSION

In conclusion, within the limits of a retrospective observational study, paediatric patients receiving a kidney transplant from a DCD donor have the same long-term outcomes as those receiving transplants from DBD donors, despite a higher rate of DGF. Innovation in perfusion techniques may help reduce the rate of DGF in DCD kidneys. However, there may still be some potential residual confounding in our data despite using propensity-score matched data and cox regression models to control for these. While keeping this in mind, we recommend that allografts from DCD donors should be utilized more, and considered a viable option for paediatric recipients, as they can have excellent outcomes and offer the potential opportunity of reducing waitlist times and facilitating more transplants potentially leading to improved quality of life in these children. Allocation systems may need to be updated to reflect these findings. On behalf of the ELPAT (Ethical, Legal and Psychosocial Aspects of Transplantation) section at the European Society for Organ Transplantation, given the excellent results presented in this manuscript we suggest that findings should inform clinical decision making and policy discussions, particularly in countries where DCD is not yet allowed but is being considered. As groups attempt to unify the neurological determination of death criteria globally [32], we consider that consistent global approaches to the circulatory determination of death and DCD are legally and ethically justified.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: All clinical data is available as requested from the OPTN database. Requests to access these datasets should be directed to https://optn.transplant.hrsa.gov/data/view-data-reports/request-data/.

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

AP, IL, NK, and JS participated in research design. AP, JB, MS, and JS participated in the writing of the paper. AP completed data analysis. 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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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14706/full#supplementary-material

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ORIGINAL RESEARCH
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Right Atrial Contraction Strain Is Associated With Clinically Significant Cellular Rejection in Patients After Heart Transplantation

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Strain echocardiography (SE) may be used for surveillance in patients after heart transplantation (HTx); however, data on atrial strain are lacking. We aimed to compare the significance of ventricular and atrial strain with respect to an associated acute cellular rejection (ACR). Patients who underwent an endomyocardial biopsy (EMB) within 1 year after HTx were eligible for this retrospective analysis. The relationship between SE and ACR was assessed. EMB results of 52 patients (median age, 53 years; 63% male) at a median of 181 days post-HTx were identified. Mild ACR was present in 19 patients and ≥ moderate ACR in 6 patients. ACR ≥ moderate was associated with right ventricular free wall strain (OR 1.20, 95%CI 1.02–1.46, P = 0.04) and right atrial contraction strain (RASct; OR 1.55, 95%CI 1.18–2.43, P = 0.01). The RASct cut-off value of –9.3% had a sensitivity of 100% and a specificity of 79% for ≥ moderate ACR. None of these associations were observed for left ventricular or left atrial strain. A validation analysis was performed on another group of 23 HTx patients, which yielded similar results with regard to the specified RASct cut-off value. Our comprehensive strain analysis confirmed the association between reduced right ventricular strain and ACR and further identified robust associations between RASct and ACR. Right atrial strain analysis may be a promising method for excluding subclinical ACR after HTx.

Keywords: heart transplantation, cellular rejection monitoring, endomyocardial biopsy, strain echocardiography, right atrial contraction strain

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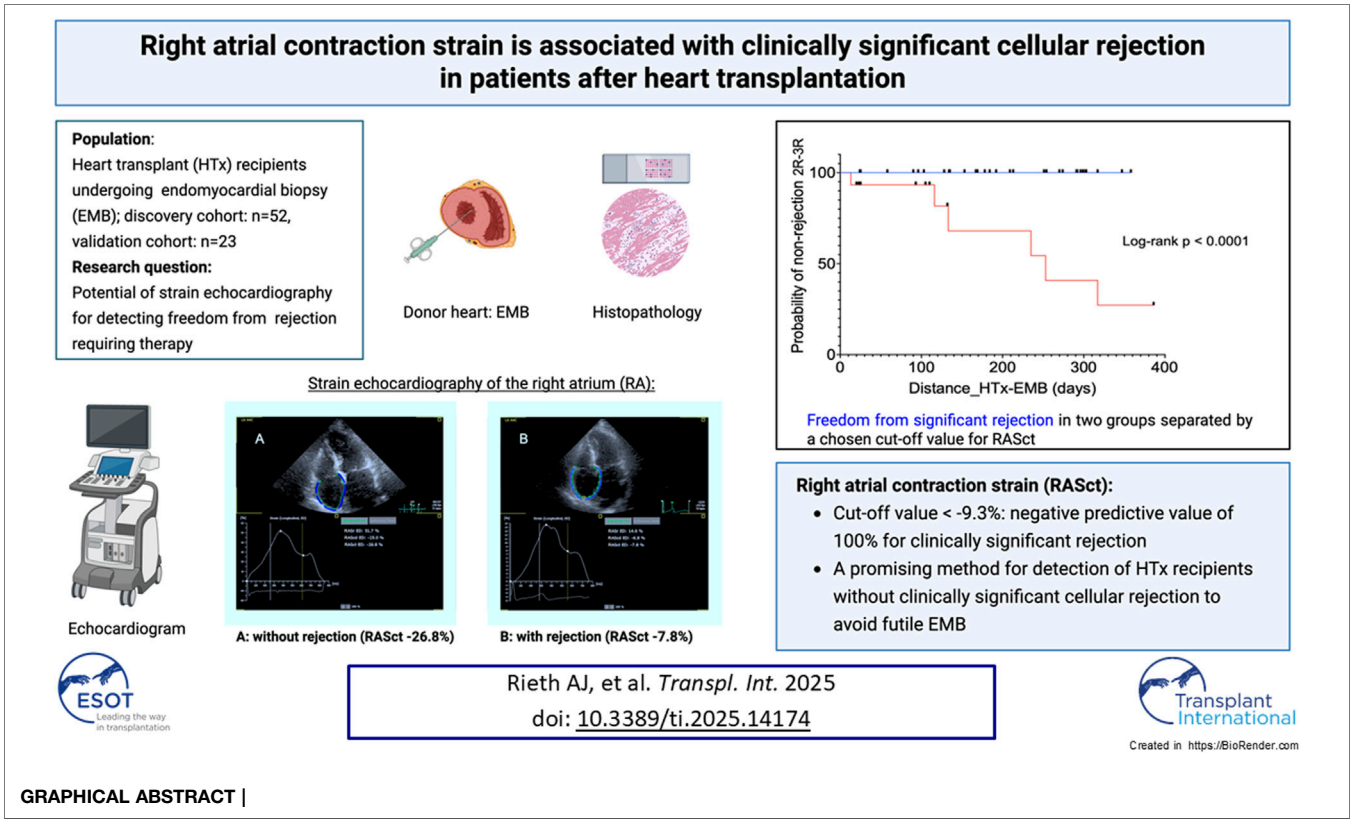
Abbreviations: ACR, acute cellular rejection Serial grading of ACR; 0R, no rejection; 1R, mild rejection; 2R, moderate rejection; 3R, severe rejection; EMB, endomyocardial biopsy; FA, fully automatic; HTx, heart transplantation; ISHLT, International Society for Heart and Lung Transplantation; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; RA, right atrial; RV, right ventricular; RV4CSL, right ventricular global 4-chamber contour strain longitudinal; RVFWSL, right ventricular free wall strain longitudinal; SA, semi-automatic; Sc, conduit strain; Sct, contraction strain; SE, speckle tracking-derived strain echocardiography; Sr, reservoir strain; TAPSE, tricuspid annular plane systolic excursion.



GRAPHICAL ABSTRACT |

INTRODUCTION

Rejection surveillance after heart transplantation (HTx) performed by routine endomyocardial biopsy (EMB) without clinical signs is currently a matter of debate, as the detection rates of moderate or higher-grade acute cellular rejection (ACR) requiring therapy seem low (1%–2%) in asymptomatic patients receiving standard immunosuppressive therapy [1–4]. However, rejection can occur in asymptomatic patients, particularly in the early post-transplant phase, with possible negative effects on the outcome; ACR was among the most important direct contributors to mortality within 1 year after HTx in a registry [4–6]. Therefore, there is an intensive search for non-invasive alternatives to EMB, which is performed periodically by many centers in the first 3–12 months post HTx in accordance with current guidelines [1, 4] but can have significant complications.

Among various approaches as alternatives to EMB, such as blood biomarkers, gene expression profiling, and donor-derived cell-free DNA, imaging modalities including cardiac magnetic resonance imaging (MRI) and echocardiography have been proposed [1, 7–10]. However, although several positive findings concerning strain echocardiography (SE) of the left and right ventricle and rejection monitoring after HTx exist [6, 11–16], there are no corresponding guideline recommendations for adults without significant restrictions [1]. To date, only one report on atrial SE and rejection has been published, which pertains to the left atrium [17].

The aim of the present study was to determine the usefulness of comprehensive SE analysis of both the atria and ventricles for rejection monitoring after HTx using a novel strain analysis software.

MATERIALS AND METHODS

Patient Population

We performed a monocentric, retrospective analysis of patients undergoing EMB between 2010 und 2024 at our Heart and Thorax Center for routine surveillance after HTx. All patients underwent bicaval anastomosis at the HTx and had sinus rhythm at the time of echocardiography. Key inclusion criteria were EMB within 12 months after HTx and echocardiographic examination of sufficient quality for strain analysis within a maximum of 3 weeks before or after EMB. Patient records were screened for EMB results and the corresponding echocardiograms (**Supplementary Figure S1**). The study conformed to the principles outlined in the Declaration of Helsinki. All the enrolled patients signed an informed consent form for this study. Data collection and analyses were approved by the responsible Ethics Committee (protocol no. 54/12; June 5th, 2012).

Echocardiography

All patients underwent transthoracic echocardiography in the left decubital position using a Philips, iE33 ultrasound system

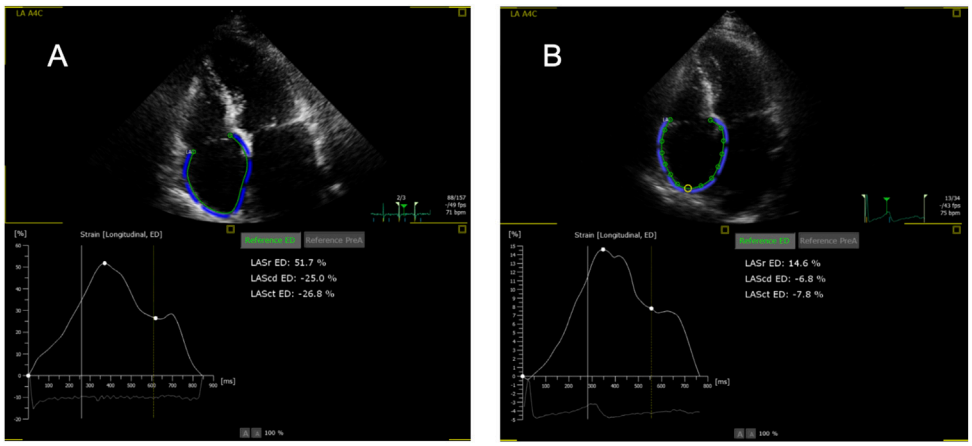


FIGURE 1 | Representative examples of right atrial strain imaging in one patient. **(A)** Without rejection (0R); **(B)** With rejection (2R). Note the wrong labeling as "LA" (left atrium), for the LA program is used for the right atrium. Sr, reservoir strain; Scd, conduit strain; Sct, contraction strain.

(Koninklijke Philips N.V., Amsterdam, Netherlands). In the majority of patients, echocardiography was performed on the day of EMB. Echocardiographic parameters were analyzed offline using dedicated software (AutoSTRAIN, TOMTEC-ARENA TTA2 2022, TOMTEC® imaging systems GmbH, Unterschleissheim, Germany; distributed by PHILIPS Ultrasound Workspace) according to international standards [18] and the manufacturer's specifications (Ultrasound Workspace (TTA2.50) AutoStrain Quick Guide December 2021).

A minimum of two recorded cardiac cycles of each view were required; however, the analyses were ultimately carried out on the cycle with the best quality. The following parameters were analyzed in accordance with current recommendations [19–21]: left ventricular (LV) systolic and diastolic volumes and volume-derived ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), LV global longitudinal strain (endocardial, averaged from: apical four-chamber, apical two-chamber, and apical three-chamber view), endocardial right ventricular longitudinal strain of the free wall (RVFWSL) and of the "global 4-chamber contour" i.e., including the septum (RV4CSL), endocardial left (LA) and right atrial (RA) reservoir strain (Sr), conduit strain (Scd), and contraction strain (Sct).

Initially, the adequacy of the automatic tracking of cardiac cycles was reviewed and corrected, if necessary. The endocardial borders of the ventricles and atria were outlined at end-diastole and end-systole in two alternative ways. The first was fully automatic (FA), without any correction by the examiner. If the FA measurement was roughly outside the anatomical boundaries, it was classified as insufficient and not used for analysis. Second, in a semi-automatic (SA) mode, with manual setting of two markers at the left and right base of the respective cardiac chamber and then automatic outlining of endocardial borders without any correction. RA measurements were conducted only via the SA mode, because the FA mode is only available for the LA; the use of LA strain software in the SA mode for measurements of RA strain is formally off-label but available by the manufacturer and used by other groups [22]. The R wave was used as a reference, and thus zero strain was set at the R wave as recommended [18]. Examples of RA measurements are shown in **Figure 1**.

Three different quality levels were defined as follows: insufficient (level 0), moderate (level 1) and good (level 2) quality echocardiographic recordings. The SA measurements were repeated at least three times to achieve three results with a deviation of <10%, and the median value of these three was used for analysis. Quality level 2 was assigned when a maximum of four measurements were sufficient to achieve this goal. If more than four measurements were necessary, Level 1 was chosen. Level 0 and thus exclusion from analysis, was issued if deviation <10% was not achieved by a maximum of nine measurements or in the FA mode, as outlined above. Because of the complexity of this procedure to achieve reproducible results as far as possible, analyses to determine interobserver variability were not carried out.

Outcomes

The revised criteria for ACR as defined by the International Society for Heart and Lung Transplantation (ISHLT) in 2004 were used as the primary outcome [23]. We analyzed the relationship between echocardiography (conventional parameters as described above and SE) and a) serial ACR grading (0R = no rejection, 1R = mild rejection, 2R = moderate rejection, 3R = severe rejection) as well as b) classification of patients as rejection requiring therapy (2R or 3R) versus patients with no need for therapy (0R or 1R) [1]. Histological examination of EMB specimens was carried out by an expert pathologist blinded to echocardiographic findings.

Statistical Analysis

Data are expressed as mean ± standard deviation or median [interquartile range] for normally or non-normally distributed parameters, respectively. Adherence to a Gaussian distribution was determined using the Shapiro-Wilk test. Statistical

significance was set at $P < 0.05$. For independent samples, comparisons were made using the Mann-Whitney U test for non-normally distributed parameters, the Student's t-test for normally distributed parameters, and the Pearson Chi-squared test or Fisher's exact test for categorical parameters.

Two separate analyses were performed. Analysis 1 included associations between echocardiographic parameters and a single EMB result within 12 months after HTx (any rejection grade and 0R/1R versus 2R/3R) that were assessed using simple logistic regression and calculation of odds ratios (OR). Receiver operating characteristics (ROC) analysis with the calculated area under the curve (AUC) was used to describe the association of a variable with endpoints. Group-wise comparisons of all rejection grades and RV4CSL were performed using ANOVA. Additionally, the probability of rejection 2R/3R in was assessed in two groups of patients divided according to an RA contraction strain (RASct) cut-off value with the highest sensitivity for 2R/3R using the Kaplan-Meier method.

Subordinate Analysis 2 pursued a different concept that focused on intraindividual SE variations depending on the rejection status. Patients for this substudy were selected if serial pairs of EMB and corresponding echocardiograms were available at different time points, preferably patients with intraindividual different EMB results (one EMB without rejection (0R) and one with rejection (1R, 2R, or 3R)). Here, the time interval between the HTx and EMB was not considered. Patients without any rejections and those without at least one 0R EMB were excluded from Analysis 2. For these analyses, the paired t-test or Wilcoxon test was used. Additionally, six individuals were analyzed, in whom one 2R or 3R EMB was available, as well as one 0R or 1R EMB. In a further modification ("extended cohort" with one additional patient previously not analyzed because no EMB within 12 months after HTx was available), we searched for every EMB with the result 2R or 3R in the patients of our study cohort, including several different EMB of the same patient, if present. The echocardiograms corresponding to those EMB were then compared with all echocardiograms corresponding to the 0R or 1R EMB in Analysis 2. For these analyses, we used an unpaired t-test or the Mann–Whitney U test.

Finally, RASct was assessed in a further cohort of patients (validation cohort) using a chosen cutoff value with regard to absence of rejection requiring therapy (Analysis 3). Statistical analyses were performed using GraphPad Prism version 10.0.2 (171) 2023.

RESULTS

Analysis 1

Clinical Characteristics and Echocardiographic Findings

Of 62 patients initially screened, 52 were included in the final analysis (**Figure 1**): 63% were male, with a median age of 53 [47–62] years (**Table 1**). All the patients were asymptomatic and underwent routine EMB without a clinical trigger. All patients were in sinus rhythm. The median period between HTx and EMB was 181 [104–298] days; 27 (52%) were completely free from any rejection, 19 (36.5%) had rejection 1R, and rejection 2R or 3R was present in six individuals (11.5%) (**Figure 2**), all of whom were male. Standard immunosuppression with tacrolimus and mycophenolate was used in 92% of the patients, and 81% were on steroids. Echocardiography was performed mostly on the same day as EMB (81%), the quality of scans was good [2] in 87% of the recordings. Mean LVEF was 60% (±6.0), and mean TAPSE was 15.0 mm (±3.2). Significant differences between patients with rejection 0R or 1R versus 2R or 3R were found for three of the four RV strain parameters and for RASct (**Table 2**).

Association of Echocardiographic Parameters With Outcomes

We analyzed the OR of all echocardiographic parameters for the prevalence of any degree of rejection (serial grading, see *Materials and Methods* under *Outcomes a)*) using logistic regression analysis (**Table 3**). Only FA RV4CSL was significantly associated with any degree of rejection (OR 1.18, 95% CI 1.02–1.41, P = 0.03; AUC 0.69, P = 0.02) (**Supplementary Figure S2**). In a group-wise comparison, RV4CSL values demonstrated a stepwise impairment from patients without rejection (0R) to those with 1R, 2R, and 3R (**Supplementary Figure S3**), although these differences were not statistically significant. All other parameters did not significantly differ, which remained unchanged if only recordings with good quality (level 2) were used for the analyses.

Using only clinically relevant rejection as the outcome (2R or 3R, Material and *Methods* under *Outcomes b)*), SA-RVFWSL (OR 1.20, 95% CI 1.02–1.46, P = 0.04; AUC 0.79, P = 0.02), SA-RV4CSL (OR 1.27, 95% CI 1.03–1.65, P = 0.04; AUC 0.76, P = 0.04), and RASct (OR 1.55, 95% CI 1.18–2.43, P = 0.01; AUC 0.92, P < 0.001) showed significant associations. All other parameters tested were not significantly different based on the AUC P-value (**Table 4**; **Figure 3**).

We further assessed the prognostic significance of RASct, which emerged as the parameter with the most robust association with rejection. A cut-off value of <−9.3% was chosen because of its sensitivity of 100% and a negative predictive value of 100% for rejection 2R or 3R (specificity 79%, positive predictive value 40%). Kaplan-Meier analysis showed a very pronounced difference in the probability of freedom of significant rejection (2R or 3R) within 1 year after HTX between patients with an RASct <−9.3% (indicating better RA contractility) vs. those patients with an RASct ≥−9.3% (log-rank HR 0.000, P < 0.0001) (**Figure 4**).

Analysis 2

Association of Intraindividual Echocardiographic Changes and Rejection

Twenty-seven patients met our inclusion criteria of having paired results of one EMB without rejection (0R) and one following EMB with rejection (1R-3R). Overall, the analysis of this population did not reveal echocardiographic differences between these two EMB statuses. Therefore, we further restricted our analysis to those six individuals with clinically significant rejection (2R-3R) and

TABLE 1 | Baseline characteristics of all patients.

Variable	All (n = 52)	No significant rejection (R0-1[a]) (n = 46)	Rejection (R2-3[a]) (n = 6)	P value[b]
Time period HTx to biopsy, days	181 [104,298]	181 [101–300]	184 [90–269]	0.7[c]
Male/female, n/n (%)	33/19 (63/37)	27/19 (59/41)	6/0 (100/0)	0.07[d]
Age, years	53 [47–62]	53 [48–62]	52 [32–59]	0.6[c]
Height, m	1.7 ± 0.11	1.7 ± 0.11	1.8 ± 0.07	0.4[e]
Weight, kg	71.0 ± 13	70.0 ± 13	79.0 ± 15	0.1[e]
BMI, kg/m^2	23.0 ± 3.8	23.0 ± 3.8	25.0 ± 4.5	0.2[e]
HTx diagnosis				0.08[d]
DCM, n (%)	33 (63)	31 (67)	2 (33)	
ICM, n (%)	16 (31)	12 (26)	4 (67)	
Others, n (%)	3 (6)	3 (7)	0 (0)	
Clinical characteristics				
Hypertension, n (%)	33 (63)	28 (61)	5 (83)	0.4[d]
Diabetes mellitus, n (%)	10 (19)	8 (17)	2 (33)	0.3[d]
COPD, n (%)	2 (3.8)	2 (4)	0 (0)	1.0[d]
CAV >12 months after HTx, n (%)	6 (11.5)	4 (9)	2 (33)	0.1[d]
Pacemaker, n (%)	5 (9.6)	3 (7)	2 (33)	0.1[d]
Immunosuppressive treatment[f]				
TAC/MMF, n (%)	48 (92)	43 (93)	5 (83)	0.4[d]
Prednisone, n (%)	42 (81)	36 (78)	6 (100)	0.6[d]
Prednisone dose, mg	5.0 [5.0–5.6]	5.0 [5.0–17.0]	5.0 [5.0–5.0]	0.3[c]
Outcomes				
Any rejection, n (%)	25 (48)			
Rejection grade 2–3R, n (%)	6 (11.5)			
Death, n (%)	8 (15)	7 (15)	1 (17)	1.0[d]
Follow-up time, years	7.5 ± 2.4	7.4 ± 2.3	8.5 ± 3.1	0.3[e]

Values represent n (%), mean ± standard deviation, or median [interquartile range].
[a]Refers to the 2004 ISHLT revised classification.
[b]Rejection (R2-3) vs. no significant rejection (R0-1).
[d]Fisher´s exact test.
[c]Mann-Whitney test.
[e]Unpaired t-test.
[f]At the time of biopsy.
Abbreviations: BMI, body mass index; HTx, heart transplantation; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; COPD, chronic obstructive pulmonary disease; CAV, cardiac allograft vasculopathy; AF, atrial fibrillation; TAC/MMF, tacrolimus and mycophenolate mofetil or mycophenolic acid.

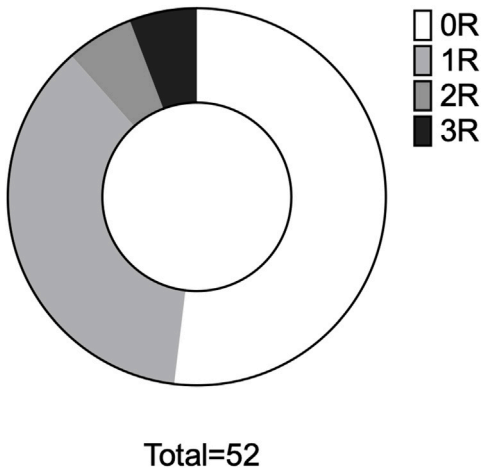


FIGURE 2 | Analysis 1 - rejection proportions. Proportional distribution of rejection in the entire cohort. 0R, rejection ISHLT 0R, etc.

compared their findings to when they were without significant rejection (0R-1R) (**Figure 5**). A significant change in RASct was observed between the situation of rejection and that of no rejection in these individuals (P = 0.008). In a further modified analysis ("extended samples"), instead of pairs of EMB, we analyzed pooled SE results of 2R-3R vs. 0R-1R in our HTx population (**Figure 6**). Accordingly, we chose each EMB with 2R-3R from the patients of the original Analysis 2 (the maximum was six relevant rejections in one single patient) and one additional patient with 3R, all in all 14 EMB with 2R-3R. These were compared with all EMB 0R-1R from the original Analysis 2 (27 0R + 21 1R). Groupwise comparisons showed significant differences in RASr (P = 0.007), RASct (P < 0.0001), and SA-RVFWS (P = 0.03).

Analysis 3

The validation cohort comprised 23 patients (out of 25 screened, 2 did not have echocardiograms of sufficient quality available). Three of 23 had rejection requiring therapy, and their corresponding RASct values were all ≥−9.3% (median −5.1%). EMB of those 3 patients at another point in time without the need for therapy (0R-1R) were corresponding to RASct values <−9.3% (median −13.4%). Of the other 20 patients with EMB 0R-1R, 19 had RASct values <−9.3% and one patient had −8.0% (median of the whole group −13.75%). In summary, 95.7% of all 23 EMB 0R-1R in this cohort corresponded to RASct values <−9.3%.

TABLE 2 | Hemodynamic and echocardiographic analyses.

Variable	n	All	No significant rejection (0R-1R[a]) (n = 46)	Rejection (2R-3R[a]) (n = 6[b])	P value[c]
Time difference biopsy-echo, days	52	0.0 [0.0–0.0]	0.0 [0.0–0.0]	3.0 [0.0–7.5]	0.007[d]
Maximum difference, days		15.0	14.0	15.0	
Heart rate,/min	52	82 ± 11	81 ± 10	85 ± 19	0.4
CO, L/min	28	4.82 [4.1–5.79]	4.80 [4.13–5.78]	5.27 [3.70–7.87]	0.8
SPAP, mmHg	28	30 ± 8	30 ± 7	27 ± 11	0.5
PAWP, mmHg	28	11 ± 6	11 ± 6	10 ± 8	0.7
RAP, mmHg	28	6 [2–9]	5	6	0.5
PVR, WU	28	1.84 ± 0.97	1.88 ± 1.02	1.53 ± 0.18	0.6
LV Analyses					
LVEF biplane, %	50	60.0 ± 6.0	61.0 ± 5.7	56.0 ± 6.9	0.07[e]
LVEDV biplane, ml	50	103.0 [87.0–118.0]	102.0 [86.0–117.0]	111.0 [88.0–127.0]	0.6[d]
LVESV biplane, ml	50	39.0 [34.0–53.0]	38.0 [34.0–48.0]	48.0 [36.0–62.0]	0.2[d]
LVSV biplane, ml	50	63.0 [51.0–73.0]	63.0 [51.0–73.0]	58.0 [52.0–67.0]	0.6[d]
LV Strain (GLS)					
SA-peak avg	50	−17.0 ± 3.7	−17.0 ± 3.5	−15.0 ± 4.6	0.3[e]
FA-peak avg	50	−14.0 [−17.0 to −11.0]	−14.0 [−17.0 to −11.0]	−12.0 [−15.0 to −9.0]	0.2[d]
RV Analyses					
TAPSE, mm	52	15.0 ± 3.2	15.0 ± 3.0	17.0 ± 4.4	0.3[e]
RV Strain					
SA-RVFWSL	52	−20.0 ± 5.2	−21.0 ± 5.0	−16.0 ± 4.7	0.03[e]
SA-RV4CSL	52	−17.0 ± 4.1	−18.0 ± 3.8	−14.0 ± 4.5	0.03[e]
FA-RVFWSL	51	−16.0 ± 5.8	−16.0 ± 5.6	−12.0 ± 6.7	0.08[e]
FA-RV4CSL	51	−14.0 ± 4.1	−14.0 ± 3.9	−10.0 ± 4.9	0.03[e]
LA Analyses					
SA-LASr	50	25.0 [18.0–35.0]	25.0 [18.0–36.0]	18.0 [14.0–31.0]	0.3[d]
SA-LAScd	50	−14.0 [−20.0 to −10.0]	−14.0 [−20.0 to −10.0]	−14.0 [−19.0 to −11.0]	0.97[d]
SA-LASct	50	−9.4 [−14.0 to −5.2]	−9.5 [−14.0 to −5.5]	−4.4 [−12.0 to −3.1]	0.1[d]
FA-LASr	49	22.0 ± 9.7	23.0 ± 10.0	20.0 ± 8.3	0.5[e]
FA-LAScd	49	−14.0 ± 6.7	−14.0 ± 6.9	−14.0 ± 5.6	0.99[e]
FA-LASct	49	−7.0 [−13.0 to −4.9]	−7.6 [−13.0 to −5.0]	−6.3 [−10.0 to −2.6]	0.3[d]
RA Analyses					
RA area, cm^2	49	16.3 ± 4.5	16.2 ± 4.7	17.8 ± 2.1	0.4
SA-RASr	49	31.0 ± 11.0	32.0 ± 10.0	23.0 ± 14.0	0.06[e]
SA-RAScd	49	−16.0 ± 8.4	−16.0 ± 7.9	−17.0 ± 12.0	0.8[e]
SA-RASct	49	−15.0 ± 7.6	−16.0 ± 7.2	−5.7 ± 2.4	0.002[e]

Values represent mean ± standard deviation or median [interquartile range].
Except TAPSE, all analyses were performed using TOMTEC-ARENA®.
[a]*Refers to the 2004 ISHLT revised classification.*
[b]*All measurements were available for these 6 patients.*
[c]*Rejection (2R-3R) vs. no significant rejection (0R-1R).*
[d]*Mann-Whitney test.*
[e]*Unpaired t-test.*
Abbreviations: CO, cardiac output; SPAP, systolic pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; PVR, pulmonary vascular resistance; WU, wood units; CAV, cardiac allograft vasculopathy; LV, left ventricle; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; GLS, global longitudinal strain; SA, semi-automatic; avg, averaged; FA, fully automatic; RV, right ventricle; TAPSE, tricuspid annular peak systolic excursion; RVFWSL, RV free wall strain; RV4CSL, RV global longitudinal strain; LA, left atrium; LASr, LA reservoir strain; LAScd, LA conduit strain; LASct, LA contraction strain; RA, right atrium; RASr, RA reservoir strain; RAScd, RA conduit strain; RASct, RA contraction strain.

DISCUSSION

We present a comprehensive analysis of the standard and strain echocardiographic parameters of all cardiac chambers to evaluate subclinical ACR after HTx. The relevant findings of our study are as follows: (i) conventional parameters such as LVEF, LV stroke volume, and TAPSE did not show any association with ACR in our cohort; (ii) the association between impaired RV strain and ACR was confirmed; (iii) we identified a robust association between RASct and clinically relevant ACR (2R-3R) that was not present in the LA strain; (iv) the use of a recently developed dedicated SE software may partly overcome previous limitations due to the variability of measurements caused by the necessity for manual corrections of endocardial tracking.

Echocardiography has been used for routine surveillance after HTx for decades, and the use of Doppler tissue imaging for this purpose has been discussed since the late 1990s [24, 25]. Positive results for SE of the LV and RV for ACR evaluation have been reported [11–16], but there are also ambivalent results [26–29]. Furthermore, the impact of inter-vendor variability and the lack of standardization of the parameters to be measured and dedicated software packages for obtaining such measurements are important issues [17, 18, 30]. In summary, the diagnostic value of echocardiographic myocardial deformation imaging for

TABLE 3 | Univariate logistic regression analysis of echocardiographic parameters and any rejection after heart transplantation.

Outcome: Rejection 1R-3R					
Variable	**OR**	**95% CI**	**P value**	**AUC**	**P value**
LVEF biplane	0.97	0.87–1.06	0.5	0.58	0.3
LVEDV biplane	1.01	0.99–1.04	0.3	0.64	0.08
LVESV biplane	1.04	0.99–1.10	0.1	0.61	0.2
LVSV biplane	1.01	0.98–1.04	0.6	0.62	0.2
LV Strain (GLS)					
SA-peak avg	1.03	0.88–1.20	0.8	0.52	0.8
FA-peak avg	1.00	0.90–1.11	0.96	0.59	0.3
RV Strain					
SA-RVFWSL	1.07	0.96–1.20	0.3	0.63	0.1
SA-RV4CSL	1.06	0.93–1.23	0.4	0.60	0.2
FA-RVFWSL	1.11	1.01–1.25	0.05	0.71	0.01
FA-RV4CSL	1.18	1.02–1.41	0.03	0.69	0.02
TAPSE	1.08	0.91–1.30	0.4	0.57	0.4
LA Analyses					
SA-LASr	0.99	0.95–1.04	0.8	0.52	0.8
SA-LAScd	0.99	0.93–1.05	0.7	0.54	0.6
SA-LASct	1.03	0.96–1.12	0.4	0.57	0.4
FA-LASr	1.02	0.96–1.09	0.5	0.55	0.5
FA-LAScd	0.96	0.88–1.05	0.4	0.58	0.3
FA-LASct	1.00	0.89–1.13	0.95	0.52	0.8
RA Analyses					
SA-RASr	0.98	0.92–1.03	0.4	0.61	0.2
SA-RAScd	0.98	0.91–1.05	0.6	0.55	0.5
SA-RASct	1.08	1.00–1.19	0.07	0.70	0.01

LV, left ventricle; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; GLS, global longitudinal strain; SA, semi-automatic; avg, average; FA, fully automatic; RV, right ventricle; TAPSE, tricuspid annular peak systolic excursion; RVFWSL, RV free wall strain; RV4CSL, RV global longitudinal strain; LA, left atrium; LASr, LA reservoir strain; LAScd, LA conduit strain; LASct, LA contraction strain; RA, right atrium; RASr, RA reservoir strain; RAScd, RA conduit strain; RASct, RA contraction strain.

TABLE 4 | Univariate logistic regression analysis of echocardiographic parameters and rejection 2R-3R after heart transplantation.

Outcome: Rejection 2R-3R					
Variable	**OR**	**95% CI**	**P value**	**AUC**	**P value**
LVEF biplane	0.88	0.76–1.01	0.08	0.72	0.08
LVEDV biplane	1.00	0.97–1.03	0.8	0.56	0.6
LVESV biplane (mL)	1.06	0.98–1.14	0.2	0.67	0.2
LVSV biplane (mL)	0.98	0.92–1.03	0.5	0.57	0.6
LV Strain (GLS)					
SA-peak avg	1.14	0.90–1.48	0.3	0.61	0.4
FA-peak avg	1.05	0.90–1.19	0.5	0.68	0.2
RV Strain					
SA-RVFWSL	1.20	1.02–1.46	0.04	0.79	0.02
SA-RV4CSL	1.27	1.03–1.65	0.04	0.76	0.04
FA-RVFWSL	1.13	0.98–1.32	0.09	0.69	0.1
FA-RV4CSL	1.24	1.01–1.56	0.04	0.72	0.09
TAPSE	1.17	0.89–1.58	0.3	0.62	0.4
LA Analyses					
SA-LASr	0.95	0.86–1.03	0.3	0.65	0.2
SA-LAScd	1.01	0.92–1.14	0.8	0.51	0.96
SA-LASct	1.16	0.98–1.46	0.2	0.70	0.1
FA-LASr	0.97	0.87–1.06	0.5	0.57	0.6
FA-LAScd	1.00	0.88–1.15	0.99	0.52	0.9
FA-LASct	1.13	0.93–1.46	0.3	0.64	0.3
RA Analyses					
SA-RASr	0.92	0.82–1.00	0.07	0.74	0.06
SA-RAScd	0.98	0.89–1.10	0.8	0.50	1.0
SA-RASct	1.55	1.18–2.43	0.01	0.92	<0.001

LV, left ventricle; LVEF, left ventricular ejection fraction; LVEDV, left ventricular enddiastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; GLS, global longitudinal strain; SA, semi-automatic; avg, average; FA, fully automatic; RV, right ventricle; TAPSE, tricuspid annular peak systolic excursion; RVFWSL, RV free wall strain; RV4CSL, RV global longitudinal strain; LA, left atrium; LASr, LA reservoir strain; LAScd, LA conduit strain; LASct, LA contraction strain; RA, right atrium; RASr, RA reservoir strain; RAScd, RA conduit strain; RASct, RA contraction strain.

detection of ACR after HTx is quite variable so far [31], and our negative results for SE of the LV are most likely to be seen against this background.

In comparison with reference ranges for strain in a healthy population, HTx patients show significantly lower ventricular and left atrial strain values early after transplantation in the absence of relevant rejection [17, 22, 32–36]. Reference ranges for RA strain in HTx patients have not been published; in our study, SE measurements of all four chambers were lower than those published in healthy controls. There was a high rate of concordance between serial measurements using up-to-date SE analysis software in our cohort (quality level 2 in 87% of measurements), which makes the current software version significantly different from the previous version in our experience. FA measurements in general showed markedly worse ventricular strain results than measurements made in the SA mode; for the LA, this was true only for reservoir and contraction strain, whereas conduit strain was identical. The RA strain was only available in the SA mode. Overall, there was a certain, albeit low, rate of dropouts due to insufficient FA endocardial demarcation, and SA measurements seemed more realistic to us. Furthermore, the SA mode produced more

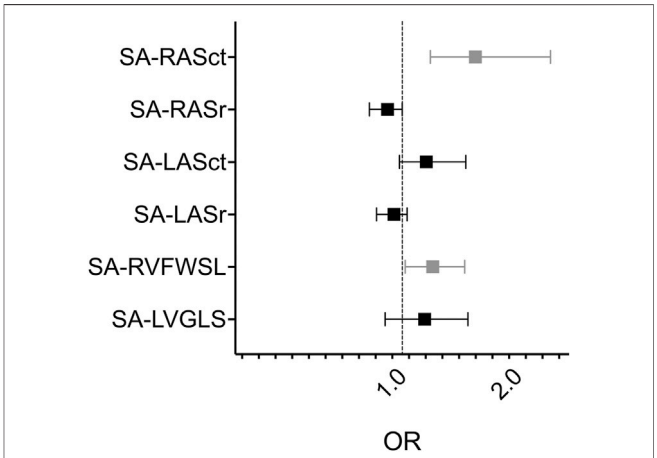


FIGURE 3 | Forest plot of univariate logistic regression analysis of selected semiautomatic strain parameters and rejection 2R - 3R SA, semi-automatic; RAS, right atrial strain; ct, contraction; r, reservoir; LAS, left atrial strain; RVFWSL, right ventricular free wall longitudinal strain; LVGLS, left ventricular global longitudinal strain, OR, odds ratio. Grey datapoints represent significant parameters (SA-RASct: OR 1.55, 95%CI 1.18–2.43, P = 0.01; SA-RVFWSL: OR 1.20, 95%CI 1.02–1.46, P = 0.04).

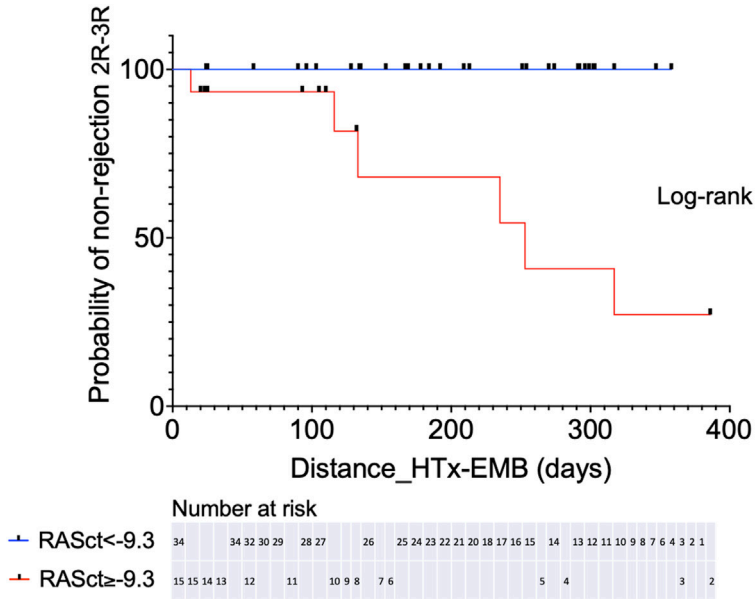


FIGURE 4 | Kaplan-Meier analysis for probability of non-rejection 2R-3R in two groups separated by a chosen cut-off value for RASct (right atrial contraction strain). HTx, heart transplantation; EMB, endomyocardial biopsy.

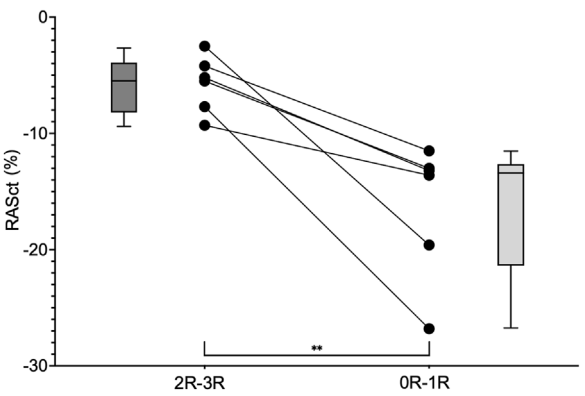


FIGURE 5 | Groupwise comparison of RASct values (minimum, maximum and median) at the time of rejection (2R-3R) and without relevant rejection (0R-1R) in six individuals. RASct, right atrial contraction strain. ** = P = 0.008.

significant results in our study. Accordingly, we prefer the SA mode for the analysis of strain measurements.

A recent study investigated the role of LA longitudinal strain (LALS) in the non-invasive diagnosis of ACR episodes in HTx recipients. LALS variables principally discriminated between studies without rejection and those with any grade of ACR, but reproducibility between comparable LALS parameters was poor, and inter-vendor variability was significant [17]. To the best of our knowledge, our study is the first investigation of SE of the RA for ACR screening. In contrast, there is a growing body of literature concerning RA SE in heart failure and pulmonary hypertension [37, 38]. We found an impaired RASct to be strongly associated with clinically relevant ACR, and based on the main target to avoid futile EMB, we chose a cut-off value enabling the identification of patients not in need of EMB. Patients with RASct values below this value had a 100% probability of freedom from relevant ACR. This was achieved at the cost of specificity, so that the positive predictive value for ACR was low, which is very similar to the findings of several studies evaluating ventricular SE and ACR [16]. In uncertain cases, EMB will be undoubtedly still essential. However, patients with preserved RASct and no clinical suspicion of ACR could be spared from unnecessary EMB.

However, why should RA contractility, in particular, be useful for ACR evaluation? This thin-walled structure can be seen as "the weakest link in the chain," as it is exposed to only low pressures in the healthy circulation and may have heightened vulnerability for different hazards. The LA is also normally exposed to low pressures, but diastolic LV dysfunction occurs early after HTx [39] and may increase the LA load and thus its muscularization. However, in our study, there is one obvious obstacle that may lead to a situation in which LA strain is prone to be incorrect. While all our patients received a bicaval anastomosis at HTx with complete resection of the recipient RA, the donor LA was anastomosed using the usual technique to a remnant of the recipient LA. Accordingly, there was an enlargement of the long-axis dimension of the LA with a ridge at the site of anastomosis, leading to difficult or even impossible measurement of correct SE parameters [27, 40]. In one study, LA function was generally worse in HTx patients than in controls [41]. As a consequence, measurement of LA strain may not be of particular use in HTx recipients.

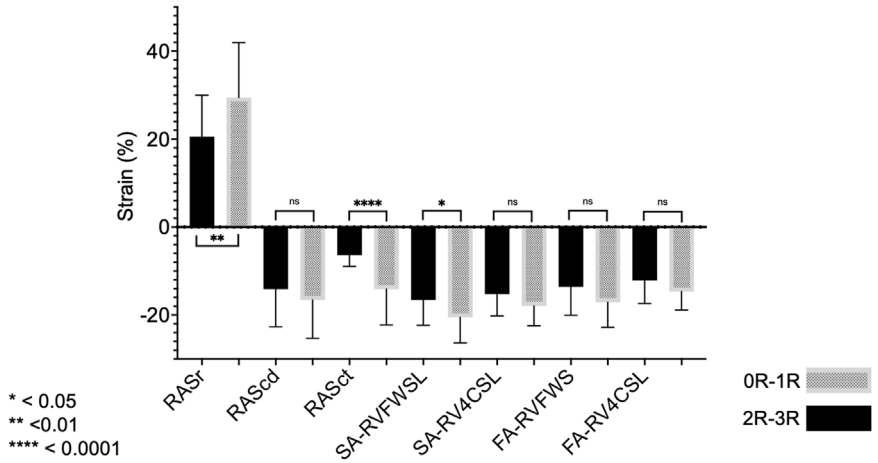


FIGURE 6 | Analysis 2 (extended samples): groupwise comparisons of different strain parameters corresponding to EMB samples with 0R-1R (n = 48) vs. 2R-3R (n = 14). Note that reservoir strain has a positive value, and a higher value indicates better reservoir function. The opposite is true for the other strain parameters. For abbreviations, please refer to the above figures.

Limitations

Given the retrospective, non-randomized study design and the limited sample size, our findings should be interpreted with caution. In the confirmatory Analysis 2, we attempted to expand the findings of Analysis 1 to an extended number of EMB so that our results could be reproduced and adapted to the intraindividual course. Image quality of echocardiograms was judged to be insufficient in 16% of patients initially screened, which is a relatively high rate and limits applicability in clinical practice. Furthermore, an elaborate procedure was necessary to achieve reproducible results. Even though the semi-automatic approach enables to get timely results of single measurements, the whole process is more time consuming than routine measurements. However, this effort could be worthwhile to avoid unnecessary EMB. The SE of the RA with the software used is formally off-label; however, it is based on the same principles as LA strain, its application is straightforward with high reproducibility, and other groups have taken a similar approach.

Published reference ranges for RA contractile strain have shown wide confidence intervals including values similar to those we found in patients with significant rejection [22, 42]. However, within the overall range, these values were at the extreme edge of the spectrum. Therefore, an approach using better RA contractile strain as a clue for absence of significant rejection would be compatible with this.

Antibody-mediated rejection was not the subject of this study but was not present in any of our patients. Our findings should be regarded as hypothesis generating and applied to a greater number of HTx patients in future studies.

CONCLUSION

In the times of gene expression profiling and DNA analysis for rejection monitoring, the utility of echocardiography may be underestimated, and SE may have been underused for reasons of practicability and lack of reliability. RA strain analysis using recent technical developments may be a promising tool for reducing the likelihood of subclinical ACR after HTx and for avoiding futile EMB. In accordance with the ISHLTguideline statement "an echo-supported minimization of biopsy surveillance appears the optimal approach" [1], analysis of RA contraction strain could be a step towards further EMB minimization. However, this should be investigated in future, prospective studies.

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 Ethics Committee of the Faculty of Medicine at the University of Giessen. 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

AR and UF-R: conception and design, acquisition of data, statistical analysis and interpretation of data, drafting of the manuscript, and final approval of the submitted manuscript. TK: conception, design, and final approval of

the manuscript. IF: data acquisition and final approval of the submitted manuscript. KC, Y-HC, SK, SS, and CH: critical revision of the manuscript for intellectual content and final approval of the submitted manuscript. 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.2025.14174/full#supplementary-material

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Machine Learning for Predicting Pulmonary Graft Dysfunction After Double-Lung Transplantation: A Single-Center Study Using Donor, Recipient, and Intraoperative Variables

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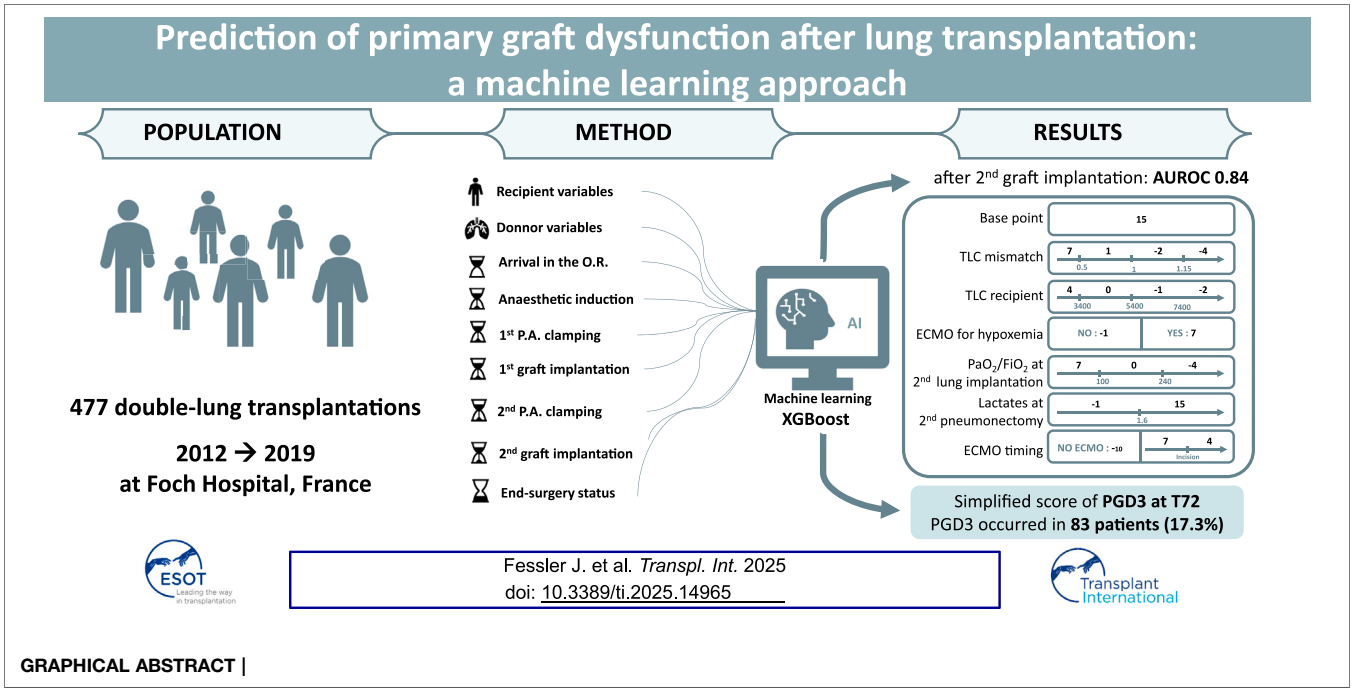
Grade 3 primary graft dysfunction at 72 h (PGD3-T72) is a severe complication following lung transplantation. We aimed to develop an intraoperative machine-learning tool to predict PGD3-T72. We retrospectively analyzed perioperative data from 477 patients who underwent double-lung transplantation at a single center between 2012 and 2019. Data were structured into nine chronological steps, and supervised machine-learning models (XGBoost and logistic regression) were trained to predict PGD3-T72, with hyperparameters optimized via grid search and cross-validation. PGD3-T72 occurred in 83 patients (17.3%). XGBoost outperformed logistic regression, achieving peak performance at second graft implantation with an AUROC of 0.84 IQR: 0.065, $p < 0.001$, with a sensitivity of 0.81 and a specificity of 0.68. The top predictors included extracorporeal membrane oxygenation (ECMO) use, blood lactate levels, PaO2/FiO2 ratio, and total lung capacity mismatch. Subgroup analyses confirmed robustness across ECMO and non-ECMO cohorts. PGD3-T72 can be reliably predicted intraoperatively, offering potential for early intervention.

Keywords: lung transplantation, ECMO, primary graft dysfunction, machine-learning, gradient-boosting



GRAPHICAL ABSTRACT |

INTRODUCTION

Following double-lung transplantations, grade 3 primary graft dysfunction at 72 h (PGD3-T72) is associated with increased risks of graft failure, bronchiolitis obliterans syndrome, and higher one-year mortality [1, 2]. Its incidence varies widely across centers, ranging from 3% to 25%, underscoring the need to reevaluate its risk factors while considering the evolving clinical practices. For instance, *ex vivo* lung perfusion has expanded the lung donor pool, extending the grafts' ischemic times, with favorable outcomes [3, 4]. Likewise, tremendous strides have been made with the wider use of intraoperative extracorporeal membrane oxygenation (ECMO) [5] and its extension into the postoperative period [6]. Such dynamic changes in clinical practice, while beneficial for patients, can pose challenges in identifying risk factors for PGD3-T72 development using mathematical models. In fact, the complex interrelationships among these factors often complicate their integration into traditional linear regression models.

Emerging machine learning techniques are promising tools, offering the capacity to detect complex, non-linear relationships among numerous variables associated with PGD3-T72. These approaches have been successfully employed to predict outcomes in kidney [7], liver [8], and pediatric heart transplantation [9]. Yet, their application to lung transplantation remains limited [10–13], particularly in the perioperative setting. Recently, Michelson et al. compared four algorithms to predict PGD3-T72, using features selected via LASSO regression to guide graft selection [14]. Such tools hold potential for informing bedside decisions, though further development is needed to adapt intraoperative strategies dynamically as the surgical procedure progresses.

Building on this foundation, our study leverages a large, prospectively collected dataset with detailed, step-by-step intraoperative data from patients undergoing double-lung transplantation (DLT). We aimed to identify risk factors for PGD3-T72 and develop a simplified, clinically practical, risk scoring system.

MATERIALS AND METHODS

Study Design

This retrospective analysis utilized a prospectively collected, single-center database, approved by the Ethics Committee of the French Society of Anesthesia and Critical Care (IRB No. 00010254–2019–019). All patients provided informed consent, and the data were anonymized in accordance with the International Society for Heart and Lung Transplantation (ISHLT) ethical guidelines. We included all DLT recipients at our center from January 2012 to December 2019, excluding those undergoing multiorgan transplantation, cardiopulmonary bypass, or retransplantation (if the index surgery was already collected and analyzed). Surgery involved two anterolateral thoracotomies with standardized anesthetic management, as previously described [15].

Study Data and Variables

Anonymized data were prospectively collected in real-time during each surgery from patients' electronic health records and stored using the FileMaker Pro database (FileMaker Company, Santa Clara, CA, USA). The transplantation process was divided into a nine-step analysis. Variables

TABLE 1 | Variables included in the model at each of the nine time points and their values.

Variables	PGD3 n = 83	No PGD3 n = 394	P
Step 1			
Age, years	41 [29–55]	40 [28–54]	0.98
Male gender	41 (49.4%)	198 (50.25%)	0.88
Weight, kg	59 [48–74]	54 [47–64]	0.03
Height, cm	165 [158–172]	166 [160–173]	0.75
Body mass index, $kg.m^{-2}$	21 [18–25]	20 [18–22]	0.001
Total lung capacity, L	4.9 [3.2–6.3]	6 [4.9–7.5]	<0.001
Primary lung disease			
Cystic Fibrosis	34 (41%)	218 (55.3%)	0.017
COPD/Emphysema	9 (10.8%)	107 (27.2%)	0.001
Pulmonary Fibrosis	28 (33.7%)	39 (9.9%)	<0.001
Other	12 (14.5%)	30 (7.6%)	0.001
Retransplantation	2.4%	1.8%	0.70
Preoperative pulmonary hypertension*	32 (38.5%)	156 (39.6%)	0.86
Diabetes	20 (24.1%)	122 (31%)	0.21
Patent foramen ovale	7 (8.4%)	37 (9.3%)	0.65
Previous thoracic surgical procedure	19 (22.9%)	83 (21.1%)	0.71
Preoperative status			
Time on waiting list, days	15 [5–40]	18 [7–43]	0.22
Lung Allocation Score	38.6 [36.0–47.2]	36.7 [34.2–40.5]	<0.001
High emergency lung transplantation	13 (15.7%)	32 (8.1%)	0.03
Preoperative ICU	16 (19.3%)	43 (10.9%)	0.035
Preoperative mechanical ventilation	9 (10.8%)	9 (2.3%)	<0.001
Preoperative vasopressors	4 (4.8%)	10 (2.5%)	0.26
Prognostic Nutritional Index	45 [35–53]	45 [39–51]	0.86
Blood chemistry			
Hemoglobin, g/dL	11.9 [10.0–13.4]	11.9 [10.8–13.2]	0.48
Total bilirubin, µmol/L	1.8 [1.4–2.2]	1.6 [1.3–2]	0.08
Albumin, g/L	37 [28–41]	37 [31–42]	0.16
Creatinine, µmol/L	62 [46–82]	60 [49–73]	0.35
Creatinine GFR (MDRD ml/min)	119.7 [91.5–151.2]	118.7 [95.5–152.3]	0.48
Lymphocytes, G/L	1.7 [1.2–2.4]	1.5 [1.0–2.1]	0.07
Main treatment			
Preoperative antihypertensive drug	26 (31.3%)	125 (31.7%)	0.94
Preoperative antiplatelet therapy	10 (12%)	62 (15.7%)	0.39
Step 2			
Age, years	50 [42–59]	49 [37–61]	0.62
Male gender	51 (61.5%)	223 (56.6%)	0.42
Body mass index, $kg.m^{-2}$	24.2 [21.1–26.2]	24.7 [22.1–27.7]	0.03
Estimated total lung capacity, L	6.5 [5.1–7.1]	6.4 [5.10–7.0]	0.41
Smoking history, pack-years	0 [0–19]	0 [0–12]	0.09
Bronchial aspirations			
Minimal, clear	39 (49.4%)	195 (52.1%)	<0.001
Moderate	8 (10.1%)	37 (9.9%)	0.006
Major, thick	31 (39.2%)	137 (36.6)	<0.001
Not Applicable	1 (1.2%)	5 (1.3%)	1
Chest X ray			
Normal	28 (33.7%)	132 (33.5%)	<0.001
Minimal	25 (30.1%)	91 (23.1%)	<0.001
Consolidation ≤1 lobe	16 (19.3%)	69 (17.5%)	<0.001
Consolidation >1 lobe	9 (10.8%)	85 (21.6%)	0.003
Not Applicable	5 (6%)	17 (4.3%)	0.03
PaO2/FiO2 ratio	357 [307–418]	362 [314–436]	0.18
Oto score	8 [6.5–11]	8 [6–10]	0.30
Length under mechanical ventilation, days	2 [1–3.5]	2 [1–3]	0.30
Maastricht III	0 [0–0]	0 [0–0]	0.30
Age mismatch	0.8 [0.6–1.1]	0.8 [0.6–1.2]	0.52
Gender mismatch	51 (61.5%)	247 (62.7%)	0.70
Total lung capacity mismatch	0.8 [0.5–1]	1 [0.8–1.2]	<0.001
Step 3			
Year of transplant	2016 [2015–2018]	2016 [2013–2018]	0.051
Ex Vivo lung perfusion	15 (18.1%)	87 (22.1%)	0.42
Preoperative plasmapheresis	36 (43.3%)	151 (38.3%)	0.39
Thoracic epidural analgesia	67 (80.7%)	349 (88.6%)	0.05

(Continued on following page)

TABLE 1 | (*Continued*) Variables included in the model at each of the nine time points and their values.

Variables	PGD3 n = 83	No PGD3 n = 394	P
Step 4			
Hemoglobin concentration, g/dL	11.9 [10–13.4]	11.9 [10.8–13.2]	0.48
Blood lactate level, mmol/L	0.9 [0.7–1.35]	0.8 [0.6–1]	<0.001
Step 5			
Blood lactate level, mmol/L	1.2 [0.8–1.9]	1 [0.7–1.4]	0.003
Step 6			
Blood lactate level, mmol/L	2 [1.4–2.8]	1.5 [1.1–2.1]	<0.001
First lung ischemic time, min	282 [232–364]	284 [236–370]	0.96
Step 7			
Blood lactate level, mmol/L	2.3 [1.7–3.6]	1.5 [1.1–2.3]	<0.001
Step 8			
Blood lactate level, mmol/L	3 [2.2–4.8]	2.2 [1.7–3.2]	<0.001
Second lung ischemic time, min	432 [358–517]	412 [351–512]	0.36
PaO2/FiO2 ratio	156 [86–243]	242 [153–338]	<0.001
Step 9			
Graft lung reduction			0.005
None	56 (67.5%)	318 (80.7%)	<0.001
Wedge	6 (7.2%)	23 (5.8%)	0.02
Lobectomy	14 (16.8%)	39 (9.9%)	<0.001
Bilateral or >1 lobectomy	7 (8.4%)	14 (3.5%)	0.011
PaO2/FiO2 ratio	157 [94–236.5]	256 [172–360]	<0.001
Epinephrine use during surgery	15 (18.1%)	41 (10.4%)	0.05
Postoperative epinephrine requirement	16 (19.3%)	22 (5.6%)	<0.001
Norepinephrine infusion dose, μg/kg/min	0 [0–0.29]	0 [0–0]	0.025
Blood lactate level, mmol/L	3.3 [2.4–4.9]	2 [1.5–3.1]	<0.001
Estimated Blood Loss, L	1.4 [0.84–2.5]	1.0 [0.6–1.5]	<0.001
Packed Red Blood Cells, units	6 [4–10]	4 [3–6]	<0.001
Fresh-Frozen Plasma, units	6 [4–9]	4 [3–6]	<0.001
Platelet, Units	0 [0–1]	0 [0–0]	<0.001
Intraoperative fluid support, L	3 [2.5–4]	2.75 [2–3.5]	0.017
Inhaled nitric oxide dependence	14 (16.9%)	48 (12.2%)	0.25
Major intraoperative hemodynamic event	20 (24.1%)	13 (3.3%)	<0.001
Extubation in the operating room	3 (3.6%)	165 (41.9%)	<0.001

Results are expressed as n (%), or median [interquartile range].
Step 1: recipient variables, step 2: donor variables, step 3: arrival in the operating room, step 4: after anesthetic induction, step 5: first pulmonary artery clamping, step 6: first graft implantation, step 7: second pulmonary artery clamping, step 8: second graft implantation, and step 9: end-surgery status before transfer to the intensive care unit.
Age mismatch = recipient/donor.
TLC = total lung capacity is normalized on the height and gender [men = (height in cm x 7.992)-7.081; women =(height in cm x 6.602)-5.791].
Total lung capacity mismatch = recipient/donor (expressed as a continuous variable).
ECMO, extracorporeal membrane oxygenation.
COPD, chronic obstructive pulmonary disease.
iNO, inhaled nitric oxide;
Preoperative pulmonary hypertension: number of patients with a mean pulmonary artery pressure >25 mmHg.*
GFR: glomerular filtration rate.
*Data regarding ECMO (time of insertion) are presented in **Figure 2**.*

encompassing recipient and donor characteristics were entered into steps 1 and 2, respectively. Additionally, seven sequential surgical phases were entered into the analysis, step 3: arrival in the OR, step 4: post-anesthetic induction, step 5: first pulmonary artery clamping, step 6: first graft implantation, step 7: second pulmonary artery clamping, step 8: second graft implantation, and step 9: end-of-surgery status before ICU transfer (**Table 1**).

Main Outcome

The incidence of PGD3-T72 was assessed per the 2016 ISHLT definition [16]. PGD3-T72 was graded by consensus by a board-certified panel including an intensivist, a pulmonologist, and an anesthesiologist. Patients on postoperative ECMO for hypoxemia were classified as grade 3. Predictive models were built for all nine steps, searching for the earliest high-discrimination step selected for clinical utility. We also compared the postoperative complications between patients who had PGD3-T72 and those who did not.

Statistical Analyses

Authors followed the STROBE guidelines for observational studies.

All analyses were carried out in R (version 4.2.3). Normality of continuous variables was assessed using the Shapiro–Wilk test. Variables that conformed to a Gaussian distribution were described using mean and standard deviation and compared using the Student's t-test. For non-normally distributed variables, we used median and interquartile range and

performed comparisons using the Mann–Whitney U test. Categorical data are described as the number (percentage) and were compared using the Chi-squared test or Fisher's exact test.

Supervised Machine Learning Models

We employed supervised machine learning algorithms to predict PGD3-T72 in patients following double-lung transplantation (DLT). Supervised machine learning, a subset of artificial intelligence, involves training computer systems on labeled data to model the mathematical relationships between input features and outcomes [17–19]. In this study, we utilized the eXtreme Gradient Boosting (XGBoost) algorithm, which integrates multiple decision trees [19]. The weighted ensemble of these trees generates the final prediction [17–19]. For comparison, we benchmarked XGBoost against a baseline logistic regression (LR) model. To capture variation in clinical decision-making, particularly related to extracorporeal support, ECMO initiation timing was encoded as a categorical variable spanning six defined intraoperative periods (steps 4–9). While this does not directly model operator intent, it serves as a proxy for practice variation related to cannulation and intraoperative strategy.

Data Preparation, Missing Data

No data transformation process was performed on the numerical variables. Categorical variables were one-hot encoded without any further preprocessing. Missing data was not imputed since XGBoost treats missing data as a specific modality. ECMO timing was encoded as a categorical variable using the following keys: 1: at second lung implantation; 2: at second pneumonectomy; 3: at first lung implantation; 4: at first pneumonectomy; 5: at induction of general anesthesia; and 6: preoperative ECMO.

XGBoost Model Hyperparameter Tuning

We conducted hyperparameter tuning with the grid search approach and 5-fold cross-validation in 3 successive steps. First, we identified the optimal number of trees using a relatively high range of learning rates and standard values for the other hyperparameters (number of trees, maximum depth of each tree, regularization factor gamma, fraction of features by tree, minimum sum of instance weight needed in child tree, and subsampling rate). Then, we selected this number of trees, left the learning rate high, and conducted the grid search for all other parameters. Finally, in the third round, we fixed all hyperparameters and lowered the range of learning rates from 10E-5 to 10E-2.

The final chosen hyperparameters for the XGBoost model were: 50 trees, no early stopping, a maximum depth of 4 for each tree, a minimum sum of instance weight needed in child tree of one, a gamma of 0.75, and a learning rate of 10E-5. In addition to those conservative parameters chosen to prevent overfitting, only 40% of available columns were selected for tree construction in each round, and 95% of subjects were selected for tree construction (subsampling rate).

Feature Selection and Final Model Training

Feature selection was performed using a recursive additive strategy within each of 500 randomly generated train/test splits. For each split, an XGBoost model was first trained on the full feature set to derive variable importance rankings (based on Gain), and then new models were retrained using incrementally larger subsets of top-ranked features (from 2 to 66) to evaluate area under the receiver operating characteristic curve (AUROC) on the corresponding test set.

While this approach involves out-of-sample testing on data not used for model training, feature selection was not nested within a formal cross-validation loop. A more rigorous nested cross-validation was deemed infeasible due to sample size constraints. As such, performance estimates may be modestly optimistic due to the potential for information leakage. However, to mitigate this risk, we repeated the full process 500 times, reporting median AUROC and interquartile ranges across iterations, and also included LR benchmarks using the same feature subsets.

Model Performance Evaluation and Explanation Generation

We evaluated the performance of the XGBoost and LR models with their respective optimal number of features using standard metrics such as the AUROC, accuracy, sensitivity, specificity, positive predictive value, negative predictive value, precision, recall, and F1 score.

We used the SHapley Additive exPlanations (SHAP) methodology to generate post-hoc explanations for the model output. SHAP is based on game theory concepts and can be used to explain any machine learning model's predictions by calculating each feature's contribution to the prediction [20]. Specifically, we report the SHAP dependence plots, which represent the individual contribution of each selected feature to the outcome prediction.

All model performance metrics (e.g., AUROC, accuracy, sensitivity) were derived from the test set of each of the 500 random train/test splits. The final reported values are the median and interquartile ranges across these 500 out-of-sample estimates.

Subgroup Analyses

Because ECMO has been previously highlighted as a major predictive factor of PGD3-T72 in our cohort [21], and to assess the robustness of our results in specific patient populations, we conducted subgroup and sensitivity analyses in patients who received ECMO at any time point (pre-operatively and/or perioperatively) patients who never received ECMO. We also performed a subgroup analysis on the cystic fibrosis population as they accounted for half of the cohort. Each subgroup analysis used the same hyperparameters as the full cohort and included 500 different models, each trained on different random train/test data splits.

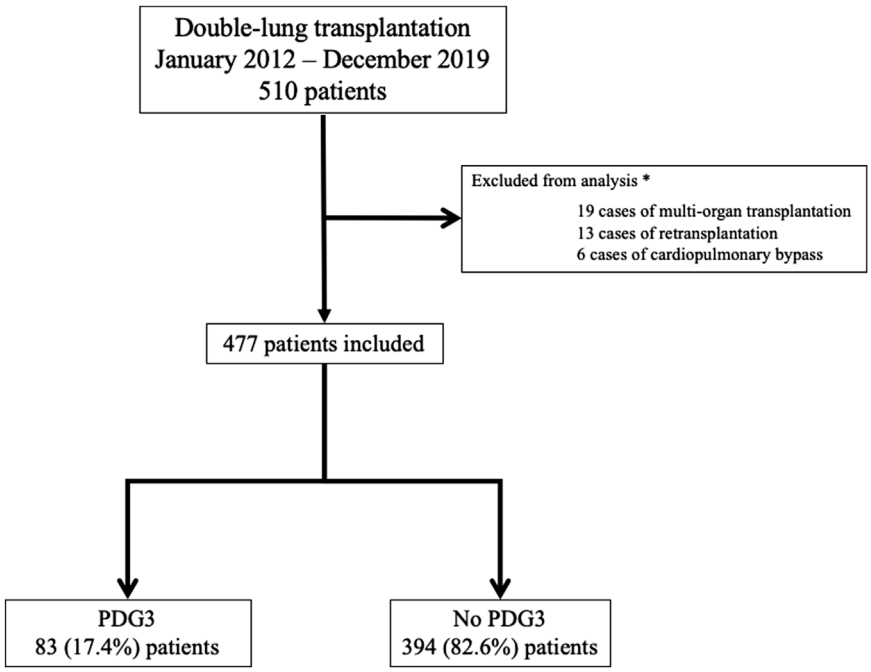


FIGURE 1 | Flow chart. PGD3: Grade 3 pulmonary graft dysfunction at postoperative day 3. *: Some patients may have several reasons for exclusion.

PGD3-T72 Simplified Risk Score

Using the top six features identified (from XGB) at surgical step 8, we trained an LR model to generate a clinically interpretable PGD3-T72 risk score. The model was developed as follows:

An LR model was fit using the training data subset of the full cohort (80% random split). We used the scorecard R package to convert the model's regression coefficients into a simplified point-based risk score. Feature-specific cutoff values were determined using thresholds derived from SHAP dependence plots, which identify inflection points where changes in feature values significantly alter predicted risk. To validate the score, we performed 10-fold cross-validation using the full dataset to evaluate the discriminatory performance of the risk score. For clinical interpretability, the resulting score was grouped into six ascending risk bins, each corresponding to progressively higher observed rates of PGD3-T72. This binning strategy enhances bedside applicability and stratified decision-making.

RESULTS

The patient inclusion flowchart is depicted in **Figure 1**. Of the 510 patients who underwent double-lung transplantation (DLT) at our institution during the study period, 477 met the inclusion criteria and were analyzed (83 in the PGD3 group and 394 in the No PGD3 group).

Of these, in 455 cases the organs were sourced from brain-dead donors, while 22 cases involved donation after circulatory death.

Table 1 summarizes the data collected at each step. Our cohort reflected a large portion of cystic fibrosis patients (252, 52.7%) and no patients with primary pulmonary hypertension. Notably, 83 patients (17.3%) who developed a PGD3-T72 had a higher body mass index 21 [18–25] vs. 20 [18–22], $p = 0.001$, more elevated lactate at all time points ($p < 0.001$, expect $p = 0.003$ at step 5), but lower total lung capacity (TLC) 4.9 [3.2–6.3] vs. 6 [4.9–7.5], $p = <0.001$. Additionally, patients who met the criteria for the French High Emergency Lung Transplantation (HELT) program were overrepresented in the PGD3-T72 group (13 (15.7%) vs. 32 (8.1%) $p = 0.03$).

ECMO was not used in 251 patients, 7 (8.4%) in the PGD3+ group and 244 (61.2%) in the No PGD3 group ($p < 0.001$). On the other hand, 27 patients had ECMO in place upon arrival to the operating room: 11 (13.3%) in the PGD3+ group and 18 (4.6%) in the No PGD3 group ($p = 0.003$). The timing of ECMO cannulation, shown in **Figure 2**, differed significantly between groups ($p = 0.005$). Postoperatively, ECMO was continued in 62 (74.7%) patients in the PGD3+ group and 47 (11.9%) in the No PGD3 group ($p < 0.001$). Primary and secondary postoperative complications are detailed in **Table 2**.

Performance of the Predictive Models at all Analytical Steps

Incorporating an increasing number of features across the nine-step analysis enhanced the XGBoost model's predictive performance (**Figure 3**). The AUROC was calculated in each fold, and the average cross-validated AUROC was 0.86 ± 0.01, indicating strong predictive accuracy and stability. The AUROC

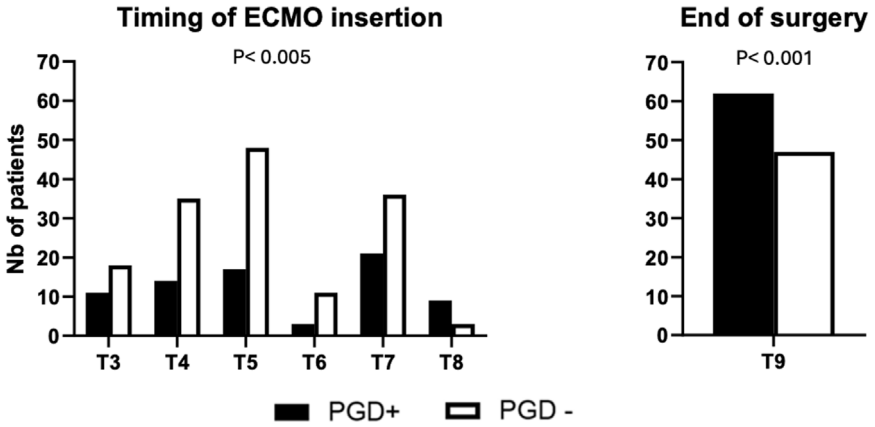


FIGURE 2 | Time of ECMO cannulation T3 (arrival in the OR), T4 (after anesthetic induction), T5 (first pulmonary artery clamping), T6 (first graft implantation), T7 (second pulmonary artery clamping), T8 (second graft implantation), and T9 (end-surgery status before transfer to the intensive care unit). PGD+: Patients having a grade 3 primary graft dysfunction on postoperative day 3. PGD-: Patients not having a grade 3 primary graft dysfunction on postoperative day 3.

TABLE 2 | Primary and secondary postoperative complications.

Postoperative complications	PGD3 n = 83	Non PGD3 n = 394	*p*-value
Pulmonary complications			
Secondary intubation	10 (12.05%)	44 (11.17%)	0.818
Tracheotomy	39 (46.99%)	51 (12.94%)	<0.001
Total time under mechanical ventilation, days	10 (5–26.5)	0.5 (0–4)	<0.001
Secondary ECMO	18 (21.69%)	5 (1.27%)	<0.001
PGD3			
at T24	77 (92.77%)	90 (22.84%)	<0.001
at T48	80 (96.39%)	83 (21.07%)	<0.001
at T72	83 (100%)	0 (0%)	<0.001
Reoperation for bleeding	48 (57.83%	45 (11.42%)	<0.001
Postoperative transfusion			
Red blood cell packs, units	6 (2–15)	0 (0–1)	<0.001
Fresh frozen plasma, units	2 (0–7.5)	0 (0–0)	<0.001
Platelet, units	1 (0–2.5)	0 (0–0)	<0.001
Other complications			
Cerebrovascular accident	6 (7.22%)	6 (1.52%)	0.002
Renal replacement therapy	26 (31.33%)	8 (2.03%)	<0.001
Atrial fibrillation	26 (31.33%)	85 (21.57%)	0.056
Thromboembolic complication	37 (44.58%)	63 (15.99%)	<0.001
Lower limb ischemia	11 (13.25%)	5 (1.27%)	<0.001
Septic shock	40 (48.19%)	51 (12.94%)	<0.001
Length of stay and in-hospital mortality			
In the intensive care unit, days	16 (10–32)	5 (4–8.75)	<0.001
In the hospital, days	38 (24–73)	29 (24–39)	0.001
In-hospital mortality	24 (28.92%)	8 (2.03%)	<0.001

Values are n (%), or median (25th and 75th percentile). PGD3, grade 3 pulmonary graft dysfunction.
PGD3, primary graft dysfunction.

improved from step 1 to step 2, remained stable from step 2 to step 6, and then increased at step 7, peaking at step 8 (AUROC: 0.84, IQR: 0.065, $p < 0.001$, IQR: 0.065, $p < 0.001$). No further improvement was observed at step 9 ($p = 0.19$). Step 8 was selected as the earliest step with the highest AUROC. Confidence intervals were derived via bootstrapping, based on 500 iterations with different random train/test splits. Model performance using the top 6 features (XGBoost) and top 7 features (LR) is detailed in **Supplementary Table 1**.

Performance of the Predictive Models at Surgical Step 8, Selection of Top Model Features

Figure 4 compares the AUROC for increasing features at step 8 using XGBoost and LR. XGBoost achieved the highest AUROC (0.84 ± 0.04) with 6 features, outperforming LR, which peaked at 7 features (AUROC 0.81 ± 0.05, sensitivity of 0.81, and specificity of 0.68). **Figure 5** displays the top 20 features for XGBoost,

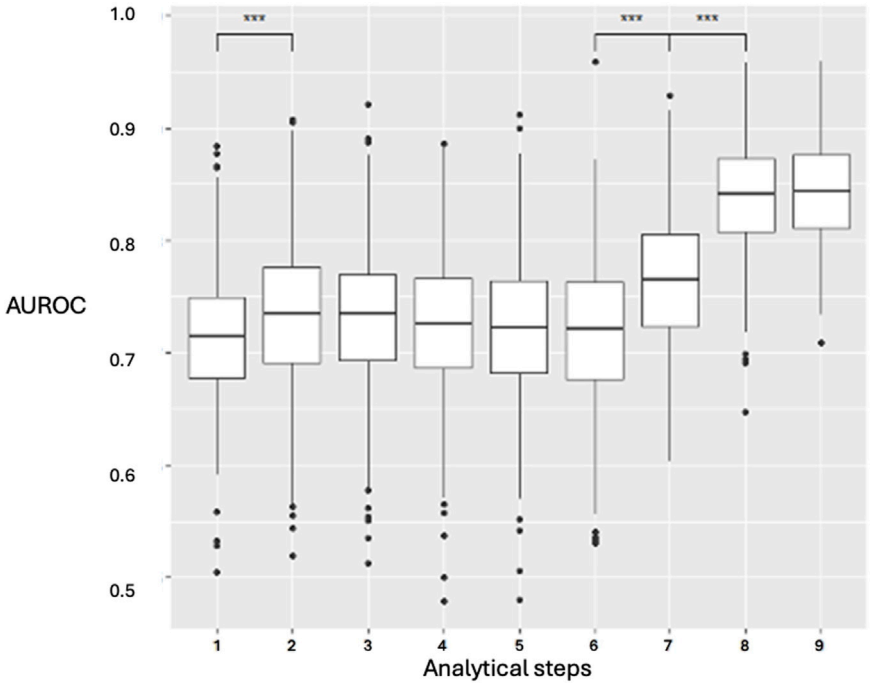


FIGURE 3 | XGBoost prediction model for the nine clinical stages and analyzed steps. Data are presented as boxplots, where the limits of the boxes are defined by the first and third quartiles, and the whiskers extend to 1.5 times the interquartile range in each direction. AUROC: area under the receiver operating characteristic curve. Analytical steps are the following are the following: 1, recipient variables; 2, donor variables; 3, arrival in the OR; 4, anesthetic induction; 5, first pulmonary artery clamping; 6, first graft implantation; 7, second pulmonary artery clamping; 8, second graft implantation; 9, end-surgery status.

ranked by decreasing importance. The relative importance (mean ± SD) of these top 20 features for the XGBoost model, based on the full cohort (N = 477) at surgical step 8, is reported. Comprehensive model performance metrics are provided in **Supplementary Table 2**.

Model Interpretation: SHAP Dependence Plots for the Top 6 Features

Figure 6 presents individual SHAP dependence plots for the top 6 features of the selected XGBoost model, illustrating the non-linear relationships between feature values and the outcome, such as TLC mismatch. As SHAP values reflect the marginal contribution of each feature within the model, we confirmed that ECMO use (at any time point) was independently linked to an elevated risk of PGD3-T72. Additional factors associated with increased PGD3-T72 risk included ECMO initiation for hypoxic indications, lactate levels exceeding 1.6 mmol/L after second pulmonary artery clamping, a PaO_2/FiO_2 ratio below 125 mmHg at first graft implantation, and a reduced recipient TLC.

Subgroup Analyses

In the subgroup analysis, 251 patients underwent lung transplantation without ECMO. XGBoost achieved a median AUROC of 0.82 ± 0.09 at step 8 (**Supplementary Figure 1**; **Supplementary Table 3**). In a second subgroup analysis of 226 patients who underwent lung transplantation with ECMO at any time (preoperative and/or perioperative), the XGBoost analysis yielded an AUROC of 0.64 ± 0.04 (**Supplementary Figure 2**; **Supplementary Table 4**). Finally, the third subgroup analysis focused on the most represented end-stage lung disease, patients transplanted for cystic fibrosis (252 patients). The XGBoost analysis yielded an AUROC of 0.82 ± 0.04 (**Supplementary Figure 3**; **Supplementary Table 5**).

Risk Score for PGD3

The simplified risk score for PGD3 at T72 is presented in **Table 3**. The final score, calculated as the sum of the base points and each component, ranges from −7 to 62. **Figure 7** illustrates the observed PGD3 rates across six distinct score bins. The estimated risk of PGD3 at T72 ranges from 0% (IQR: 0) for a score of 0 or below, to 72% (IQR: 68%–87%) for a score exceeding 33 points. The 10-fold cross-validated AUROC for the risk score is 0.86 ± 0.01.

DISCUSSION

Machine learning algorithms such as XGBoost offer a contemporary approach to clinical challenges [22]. Through automated variable selection, this method uncovered nonlinear relationships [23], adjusted for confounding factors, and delivered accurate, well-calibrated risk estimates. This study utilized such strengths of the XGBoost machine learning

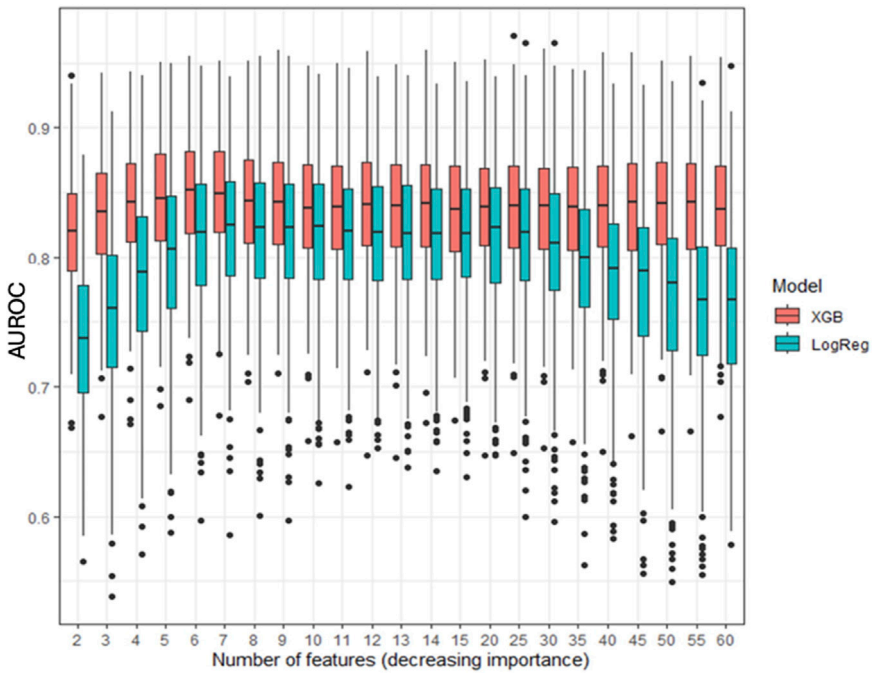


FIGURE 4 | Evolution of the area under the curve for XGBoost (XGB) and logistic regression (LogReg) at surgical step 8, for an increasing number of features. Data are presented as boxplots, where the limits of the boxes are defined by the first and third quartiles, and the whiskers extend to 1.5 times the interquartile range in each direction.

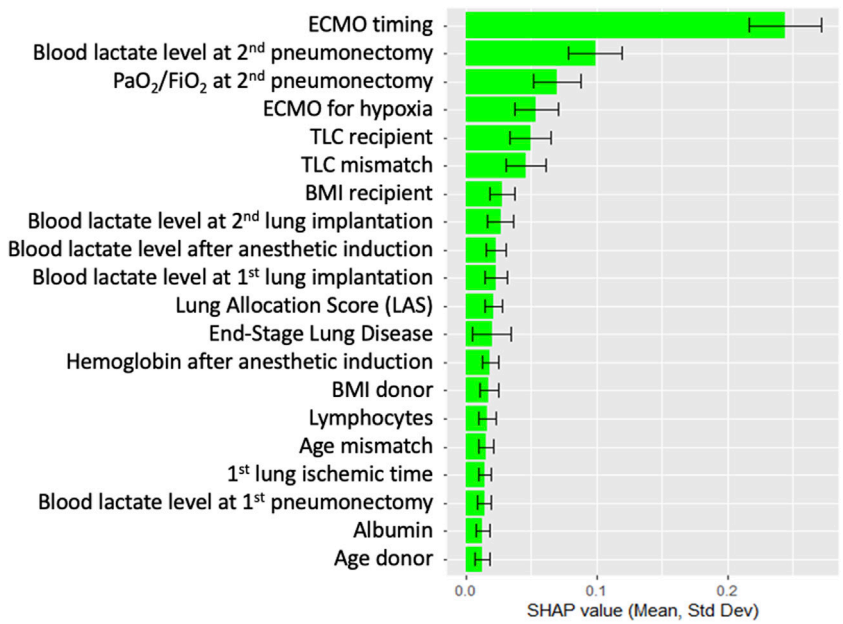


FIGURE 5 | Top 20 features for XGBoost at surgical time step 8, ranked by order of decreasing importance. Data are presented as boxplots, where the limits of the boxes are defined by the first and third quartiles, and the whiskers extend to 1.5 times the interquartile range in each direction.

algorithm to predict primary graft dysfunction (PGD3) at 72 h (PGD3-T72) following lung transplantation. A distinctive feature of this research was the sequential development of predictive models at distinct stages of surgery, spanning from the assessment of recipient and donor characteristics to the transfer to the ICU. By progressively integrating intraoperative

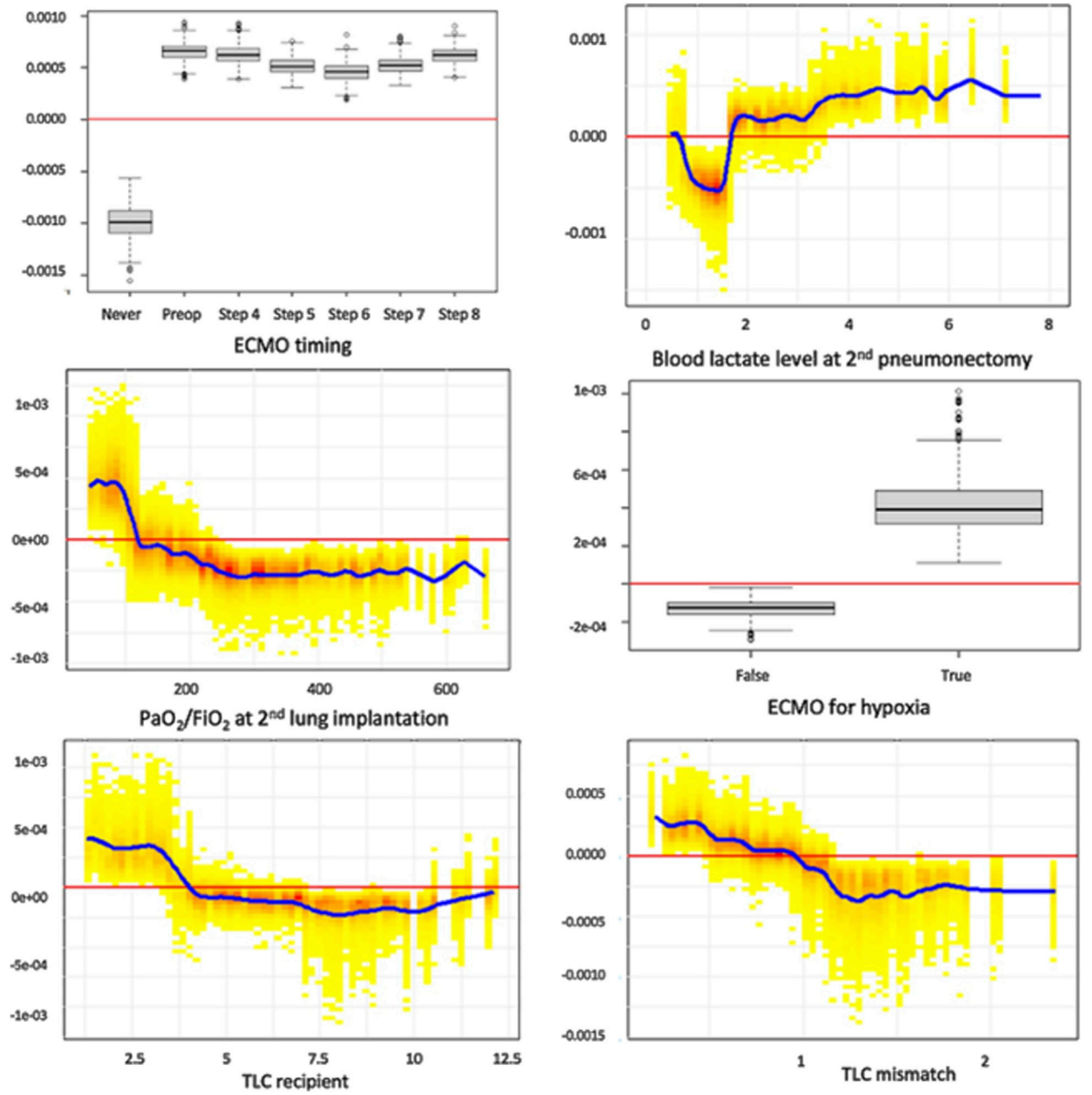


FIGURE 6 | Individual SHAP dependence plots for the top 6 features of the XGBoost model. This analysis captures the non-linear relationship between feature value and the risk of PDG3, while accounting for all covariates in the model. Positive SHAP values reflect a positive association between the value of a feature (for example, high values of lactates at second pneumonectomy) and the risk of PGD3-T72, and *vice versa*. Blood lactate level is expressed in mmol/L. TLC recipients are expressed in liters. TLC: total lung capacity.

data, we determined that the highest predictive AUROC for PGD3-T72 was achieved after the second graft was implanted. We identified six key predictive features: recipient TLC and its mismatch with donor TLC, blood lactate levels (reflecting microcirculation), use of ECMO at any point (particularly for hypoxemia), and the PaO2/FiO2 ratio. These factors highlight the complex interplay of recipient characteristics, donor attributes, and intraoperative variables. Additionally, we developed a practical risk score based on these top six features to aid clinicians in assessing PGD3-T72 risk.

Importantly, the top predictors identified by our XGBoost model, including ECMO use, elevated lactate levels, impaired PaO_2/FiO_2 ratio, and donor-recipient total lung capacity mismatch, are consistent with previously published risk factors for primary graft dysfunction [5, 6, 24–26]. Our contribution lies in confirming these variables in a large, granular intraoperative

TABLE 3 | Simplified score of PGD3-T72.

Variable	Bin	Points
Base points		15
TLC mismatch	<0.5	7
TLC mismatch	[0.5, 1)	1
TLC mismatch	[1, 1.15)	–2
TLC mismatch	>1.15	–4
Recipient TLC	<3400	4
Recipient TLC	[3400, 5400)	0
Recipient TLC	[5400, 7400)	–1
Recipient TLC	>7400	–2
ECMO for hypoxic indication	No	–1
ECMO for hypoxic indication	Yes	7
PaO2/FiO2 ratio at step 8	<100	7
PaO2/FiO2 ratio at step 8	[100, 240)	0
PaO2/FiO2 ratio at step 8	>240	–4
Lactate concentration at step 7	<1.6	–1
Lactate concentration at step 7	>1.6	15
ECMO timing	No ECMO	–10
ECMO timing	Before surgery or at anesthetic induction	7
ECMO timing	Later than at anesthetic induction	4

The final score is the sum of the base points and of each component, and ranges from –7 to 62.
TLC, total lung capacity.
TLC mismatch, mismatch in total lung capacity between recipient and donor.
ECMO, extracorporeal membrane oxygenation.

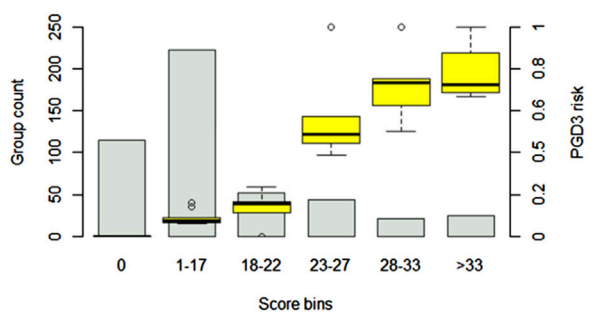


FIGURE 7 | PGD3-T73 risk prediction score. The score is based on a logistic regression model using the top 6 features identified in the primary analysis. Patient scores are divided into six bins of increasing risk. The estimated risk of PGD3-T72 ranges from 0 (IQR: 0) (for a score of 0 or less) to 72% (IQR: 68%–87%) (for a score above 33 points). Confidence intervals are generated by testing the score on 500 random patient samples of varying sizes from the cohort, with resampling. The estimated risk of PGD3-T72 is represented as boxplots for each score bins.

dataset and integrating them into a unified, interpretable risk score with strong predictive performance. Since this scoring system can be implemented mid-surgery immediately after the second graft implantation, it can serve as an early prediction tool that provides clinicians with critical prognostic information, potentially allowing for timely adjustments in intraoperative or immediate postoperative management.

While our findings align with prior studies on PGD3-T72 risk factors, it also revealed novel associations, likely due to variations in institutional practices, evolving definitions of PGD3-T72, graft selection criteria, and intraoperative management [27–29]. In our study cohort, early predictors of PGD included elevated blood lactate at step 7, the PaO2/FiO2 ratio at step 8, and the use of ECMO for hypoxemia. These findings suggest that the pathophysiological mechanism driving the development of PGD likely begins at the stage of initial graft-host interaction, consistent with studies linking biomarker emergence to second graft implantation [24, 25, 30]. Additionally, it is worth noting that blood lactate was particularly predictive in patients who did not require ECMO, possibly underscoring the importance of maintaining adequate microcirculation during surgery.

Consistent with findings from a previous large retrospective cohort study [5], ECMO use was associated with increased incidence of PGD3-T72, regardless of timing. To further investigate the role of ECMO and its impact on model performance, we conducted subgroup analyses stratified by ECMO exposure. In the subgroup of patients who did not receive ECMO, the model achieved strong discriminatory performance (AUROC 0.82), with early intraoperative features, such as elevated lactate and low PaO_2/FiO_2 ratios after anesthetic induction, emerging as key predictors. These findings support the notion that early physiologic deterioration may represent a critical window for intervention, possibly advocating for a lower threshold for ECMO initiation to maintain cellular oxygen delivery in at-risk patients.

In contrast, in patients who received ECMO at any time (preoperative or intraoperative), the model's performance was substantially reduced (AUROC ~0.64). This diminished accuracy likely reflects the greater clinical heterogeneity in this subgroup, including variation in ECMO indications, timing of ECMO initiation, and preexisting severity of illness. In this context, the model may be confounded by complex decision-making patterns. Importantly, ECMO initiated specifically for hypoxemia (PaO_2/FiO_2 < 100 mmHg) remained a strong risk

factor for PGD3, often occurring after second graft reperfusion, suggesting it may serve as an early clinical surrogate for emerging graft dysfunction.

Taken together, these findings indicate that the current risk score is best suited for use in non-ECMO patients or prior to ECMO initiation. In ECMO-supported patients, its interpretability and predictive power are more limited, and dedicated models tailored to this subgroup may be needed in future work [31, 32].

Another notable discovery is that recipient TLC emerged as a significant risk factor, independent of the type of end-stage lung disease. This may be attributed to the challenging surgical manipulation of severely retracted lungs in pulmonary fibrosis patients or the compromised nutritional status of cystic fibrosis patients [33]. However, TLC was not normalized to patient height in this analysis. Further research is needed to explore these specific patient groups, particularly to identify restrictive subpopulations with elevated chest wall elastance and to develop strategies for accelerating postoperative recovery of chest wall compliance [34].

In line with Tague et al., we found an optimal donor-recipient TLC ratio of 1.2–1.6, which prompted a practice shift following their publication, post-dating this cohort [26]. Such nonlinear relationships, obscured in traditional LR, underscore the value of machine learning.

Michelson et al. introduced a tool to support preoperative graft selection [14]. Our simplified score demonstrates superior discriminatory power, likely due to the inclusion of intraoperative factors affecting outcomes. Consequently, it serves as an effective instrument at the end of surgery for refining early postoperative approaches. Future studies could build on this foundation, developing tools with even greater AUROC values at later time points to optimize ICU postoperative care.

A key strength of this study lies in the detailed granularity of intraoperative data within our database, notably the comprehensive dataset organized around nine surgical steps, with systematic patient assessments at these specific time points. This structure enabled standardized data collection and its alignment with critical clinical moments. Another advantage is the use of a gradient boosting method, which, unlike LR, accommodates missing data without imputation, captures non-linear relationships, and delivers superior discrimination and calibration performance. Additionally, the application of state-of-the-art SHAP analysis provided an in-depth evaluation of how model features influence the risk of PGD3-T72, including the identification of clinically meaningful thresholds. Finally, we developed a simplified risk prediction score that avoids reliance on institution-specific variables, providing a practical tool for any transplantation center to assess PGD3-T72 risk effectively.

Our cohort predominantly featured cystic fibrosis patients, with primary pulmonary hypertension underrepresented due to recruitment patterns. While comprehensive, our dataset lacks variables such as immunologic compatibility and frailty. Unlike other studies, we prioritized early predictive factors to enable rapid clinical responses as primary graft dysfunction mechanisms emerge. Transfusion and fluid balance, introduced at step 9, did not enhance model performance [35, 36]. The repeated inclusion of ECMO-related variables, though unconventional in linear models, improved AUROC and was validated by supplementary analysis. A potential limitation of our study is the inability to explicitly account for variability in intraoperative decision-making, including differences in surgical technique, ECMO cannulation strategy, or operator-specific thresholds for intervention. Although our single-center setting with standardized surgical protocols helps mitigate this variability, some residual confounding is likely. Our model partially addresses this by encoding ECMO timing as a categorical feature, which may act as a surrogate for certain intraoperative choices. Nonetheless, future multi-center studies with access to surgeon- or institution-level metadata could benefit from hierarchical modeling frameworks to isolate operator-driven variability and better understand its impact on model generalizability. Another limitation is that, aside from LR, we did not evaluate a broader range of machine learning algorithms. While many supervised methods (e.g., random forests, support vector machines, deep neural networks) could potentially be applied, we selected XGBoost due to its strong empirical performance on structured data, built-in handling of missing values, and compatibility with SHAP-based interpretability. These characteristics make it well suited for real-time intraoperative applications. Future studies could compare alternative modeling strategies, including ensemble or hybrid architectures, to optimize performance and generalizability.

A key limitation of this study is the moderate sample size (n = 477), which may increase the risk of overfitting. To address this, we employed conservative hyperparameter settings and repeated random split validation, but future studies with larger multicenter cohorts are essential for external validation and generalizability.

Finally, an important limitation of this study is the absence of external validation. Despite outreach to several international centers through the ISHLT network, no collaborating institution was able to provide a dataset with comparable intraoperative granularity, particularly for stepwise modeling around second graft implantation. As a result, the model's performance has only been demonstrated within a single center, and its generalizability to other clinical environments remains untested. Given known variability in transplant practices (including graft selection, ECMO initiation strategies, anesthetic techniques, and changing indications such as the increasing prevalence of pulmonary fibrosis), model performance may differ across settings. Thus, this model should be viewed as hypothesis-generating. We strongly advocate for prospective, multicenter cohort studies to validate perioperative machine learning models in diverse clinical contexts. To support reproducibility and facilitate such efforts, our full codebase has been made publicly available.

After validation of such models by a multicentric prospective study, the score could be implemented in a simple application or to the electronic record to alert clinicians on the possible risk of PGD3-T72. Therefore, it would suggest discussing within a preventive strategy. Furthermore, it could help to build future studies on prophylactic strategies to reduce PGD3-T72.

In conclusion, gradient boosting effectively predicted PGD3-T72 with an AUROC of 84% immediately after second graft implantation using routine intraoperative data. Further studies are needed to solidify machine learning's role in primary graft dysfunction prediction and clinical practice. This tool could identify high-risk patients, enabling aggressive preventive measures to improve outcomes [37].

DATA AVAILABILITY STATEMENT

Data are not publicly available due to privacy concerns. Requests to access the datasets should be directed to juf4007@med.cornell.edu.

ETHICS STATEMENT

The studies involving humans were approved by Ethics Committee of the French Society of Anaesthesia and Critical Care (Société Française d'Anesthésie et de Réanimation - Institutional Review Board N°00010254 - 2019 - 019). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

All authors 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.

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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.2025.14965/full#supplementary-material

SUPPLEMENTARY IMAGES 1-2 | Subgroup analysis of the 251 patients who underwent lung transplantation without requiring ECMO at any time. Panel **A**: AUROC for an increasing number of features at surgical step 8 with XGBoost. Panel B: top 20 features for XGBoost, ranked by order of decreasing SHAP importance. In panel **A**, data are presented as boxplots. In panel **B**, the data are presented as mean and standard deviation. Confidence intervals are generated by bootstrapping with N = 500 models, each with a different random train/test split, with resampling. In panel **C**: SHAP dependence plots for the top features. AUROC, area under the receiver operating characteristic curve; LogReg, logistic regression; XGB, eXtreme Gradient Boosting.

SUPPLEMENTARY IMAGES 3-4 | Subgroup analysis of the 226 patients who underwent lung transplantation with ECMO at any time (preoperative and/or perioperative). Panel **A**: AUROC for an increasing number of features at surgical step 8 with XGBoost. Panel **B**: top 20 features for XGBoost, ranked by order of decreasing SHAP importance. In panel A, data are presented as boxplots. In panel **B**, the data are presented as mean and standard deviation. Confidence intervals are generated by bootstrapping with N = 500 models, each with a different random train/test split, with resampling. In panel **C**: SHAP dependence plots for the top features. AUROC, area under the receiver operating characteristic curve; LogReg, logistic regression; XGB, eXtreme Gradient Boosting.

SUPPLEMENTARY IMAGES 5-6 | Subgroup analysis of the 252 patients who underwent lung transplantation for cystic fibrosis. Panel **A**: AUROC for an increasing number of features at surgical step 8 with XGBoost. Panel **B**: top 20 features for XGBoost, ranked by order of decreasing SHAP importance. In panel A, data are presented as boxplots. In panel **C**: SHAP dependence plots for the top features. In panel **B**, the data are presented as mean and standard deviation. Confidence intervals are generated by bootstrapping with N = 500 models, each with a different random train/test split, with resampling. AUROC, area under the receiver operating characteristic curve; LogReg, logistic regression; XGB, eXtreme Gradient Boosting.

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LETTER TO THE EDITOR
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Efficacy and Safety of Low-Dose ATG Plus Basiliximab Induction in Deceased Donor Kidney Transplantation

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Keywords: kidney transplant, immunosuppresion, new approaches, patient and graft survival, induction therapy

Dear Editors,

Kidney transplantation offers the best strategy for patients with End-Stage Kidney Disease (ESRD) [1]. The choice of induction therapy has always been a challenge for transplant clinicians. Strategies have been implemented to modulate the immune system, reduce rejection risk, and limit side effects such as infections and *de novo* tumors. Currently, most transplant centers use either a thymoglobulin (ATG)-based regimen (a depleting drug), which is the most immunosuppressive but has greater side effects, or a regimen based on anti-CD25 antibodies like Basiliximab which has fewer side effects but is less potent [2–4].

Over the years, our transplant center has sought an alternative solution. For this reason, we decided to implement a regimen involving the administration of both drugs but at reduced dosages. This strategy was hypothesized by Ruggenenti et al. [5] and has already been utilized and described by Hod et al. (though only in living-donor patients) [6] and by a US registry study [7]. The rationale was to exploit the benefits of both drugs, reducing tumors and infections without increasing acute rejection.

In this study, we evaluated the efficacy and safety of this approach compared to standard dose ATG alone and Basiliximab alone and the impact on biopsy proven 1-year rejections, occurrence of post-transplant neoplasia and infections, delayed graft function (DGF), graft and patient survival only in deceased donor patients.

We selected retrospectively 759 consecutive patients who received a single kidney transplant from a deceased donor at the Policlinico A. Gemelli Kidney Transplant Center, Rome, Italy, from 01/01/2001 to 31/12/2022. Patients were divided into three groups: 147 patients in the standard ATG group (7 mg/kg cumulative till day 7 post-transplantation (1 mg/kg/day)), 278 in the Basiliximab group (20 mg before surgery and another 20 mg 4 days post-surgery), and 334 in the low-dose ATG-Basiliximab group (ATG 1.5 mg/kg just before transplantation, 20 mg of Basiliximab mg pre-surgery and day 4). The choice of induction therapy was mainly based on the best clinical practices of the time. Specifically, ATG only was predominantly used from 2004 to 2010, Bas only from 2011 to 2016, and subsequently low-dose ATG and Bas. Baseline demographic, maintenance therapy and immunologic characteristics were comparable across the groups, although the ATG-Basiliximab group had a slightly lower HLA mean mismatch score (3.0 vs. 3.6 in ATG and 3.7 standard-Basiliximab). Drug levels and renal function were monitored according to institutional protocols [8].

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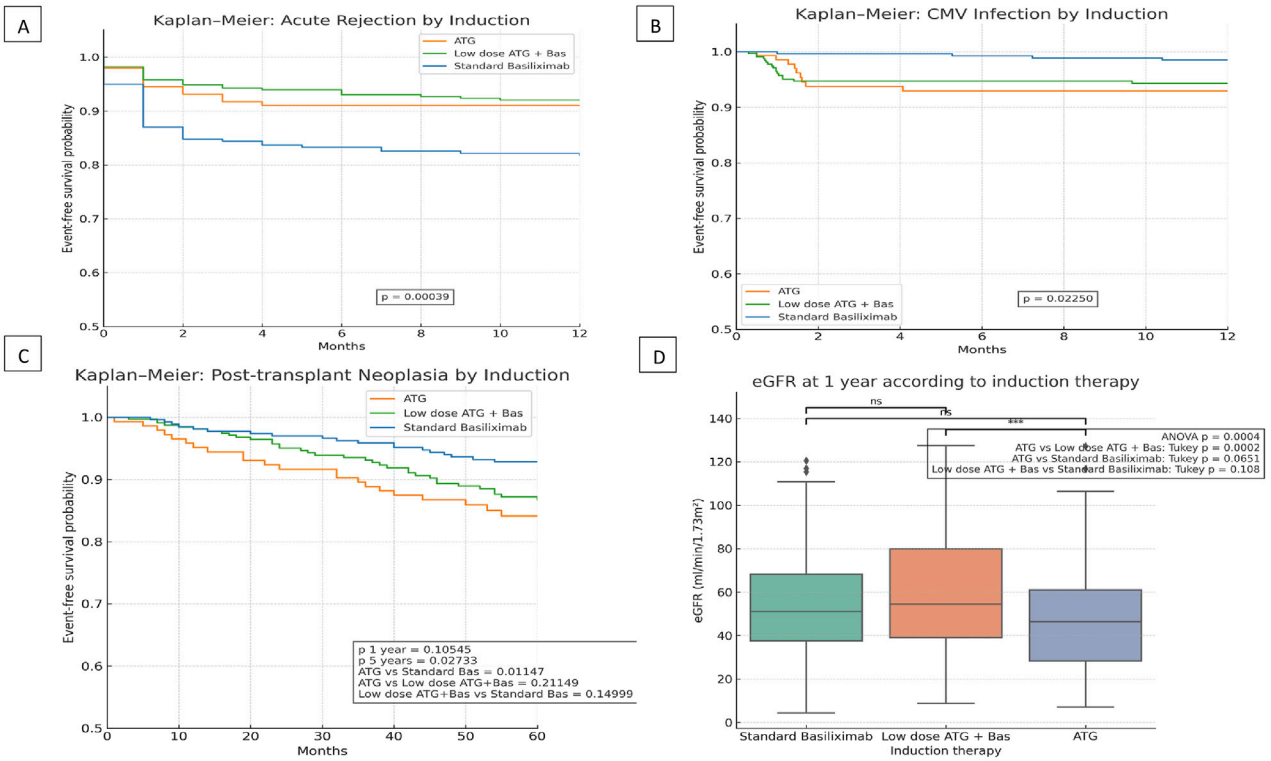

FIGURE 1 | Clinical outcomes according to induction therapy in kidney transplant recipients: **(A)** Kaplan–Meier curve for biopsy-proven acute rejection within 12 months stratified by induction protocol. **(B)** Kaplan–Meier curve for CMV infection-free survival within 12 months by induction protocol. **(C)** Kaplan-Meier curve for post-transplant neoplasia-free survival by induction therapy. **(D)** Serum eGFR levels at 12 months post-transplantation across induction protocols.

Our findings yield various interesting results. First, biopsy-proven acute rejection (AR) occurred significantly more frequently in the Basiliximab group if compared to both ATG-containing groups. In fact, the low-dose ATG+Basiliximab group showed a significant protection (HR = 0.5031; 95%CI: 0.3276–0.7724; p = 0.0017). The ATG group showed a non-significant trend towards lower AR (HR = 0.5542; 95%CI: 0.3029–1.0140; p = 0.0555) (**Figure 1A**). This data supports previous data suggesting that a combination approach offers a synergistic immunosuppression [5]. On the other hand, this may be partially explained by the potential for excessive immunosuppression with high-dose ATG, which can lead to early dose reduction due to adverse effects. Such interruptions could blunt the protective effect of induction on early alloimmune activation. In contrast, the combined low-dose protocol may provide a more favorable balance between tolerability and immunologic efficacy [9].

Regarding the incidence of DGF alone, we noted that although the use of ATG and low-dose ATG was associated with a lower probability of developing DGF, this finding was not statistically significant.

In terms of graft function, patients in the low-dose ATG+Basiliximab group exhibited significantly better renal function at 1 year, as consistently indicated by higher eGFR levels (p = 0.0004) (**Figure 1D**). This superior graft function observed in the combined regimen group is highly likely linked to the lower incidence of acute rejection that characterizes this induction strategy. In a predefined sub-analysis stratifying recipients by age (<65 vs. ≥65 years), we observed that older patients consistently exhibited lower eGFR at 1 year irrespective of the induction regimen.

As anticipated and consistent with the known risks associated with T-cell-depleting agents, CMV infection was significantly more prevalent in both ATG-based regimens. Conversely, the Basiliximab-alone protocol was independently associated with a reduced CMV infection risk compared to the standard ATG protocol (HR 0.2256; 95% CI 0.0693–0.7348; p = 0.0135) (**Figure 1B**). This finding underscores the critical importance of implementing robust CMV prophylaxis and diligent monitoring strategies, especially when T-cell-depleting agents are employed in the immunosuppressive regimen [3, 9, 10].

From a safety perspective, we found no statistically significant differences in overall graft or patient survival among the three induction groups, although older recipient age emerged as a significant predictor of increased cancer risk and patient survival. As for the incidence of post-transplant malignancy only at 5 years, patients who received ATG only had a higher incidence of malignancies (**Figure 1C**).

The novelty and strength of this study is that it considers only patients with deceased donors, who are considered at higher risk of rejection and complications. In addition to this, we have well-matched the three groups, unlike the US registry study where this

strategy was associated with worse outcomes, but it was often administered to patients with crucial differences in selection criteria and the specific dosing strategies employed was not indicated.

While acknowledging the inherent limitations of our study, including its retrospective, single-center design and the extended two-decade observational period, potentially introducing variability due to evolving standards of care, its strengths are considerable. These include the large cohort of only deceased donor recipients, and the detailed analysis of clinically relevant outcomes.

In conclusion, our extensive experience suggests that the use of a combined low-dose ATG and Basiliximab induction regimen offers a favorable balance between efficacy and safety in kidney transplant recipients from deceased donors. This specific protocol was consistently associated with improved one-year renal function and a tendency towards fewer acute rejections while maintaining manageable infectious risks compared with Basiliximab- or ATG-only strategies. Further prospective studies and well-designed randomized controlled trials are certainly warranted to validate these compelling findings and to further refine induction strategies based on individualized immunologic profiles, ultimately aiming to optimize clinical practices and enhance long-term patient outcomes in kidney transplantation.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by Fondazione Policlinico Universitario Agostino Gemelli IRCCS (CET) Lazio Area 3. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

AD: Writing, Conceptualization, Analysis; GB: Investigation; ES: Investigation; MA: Investigation; MS: Investigation; PS: Investigation; JR: Conceptualization, Reviewer; FP: Conceptualization, Analysis, Reviewer; GG: Conceptualization, Reviewer, Supervision. All authors contributed to the article and approved the submitted version.

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Roxadustat for the Treatment of Early Post-Transplantation Anemia

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Keywords: kidney, transplantation, anemia, roxadustat, erythropoietin (EPO)

Dear Editors,

Early post-transplantation anemia (ePTA) is common in kidney transplant recipients (KTRs) and contributes to cardiovascular events, reduced quality of life, and overall mortality [1, 2]. Early PTA is driven by pre-transplant hemoglobin (Hb), preexisting deficiency (iron, folate, vitamin B12), intraoperative bleeding, inflammation, and delayed graft function [1]. Aside from blood transfusions, which should be avoided regarding the risk of developing HLA antibodies, the standard treatment for ePTA includes iron and vitamin supplementation, along with the use of recombinant erythropoietin (rEPO) [3, 4]. However, the efficacy of rEPO in ePTA remains uncertain, frequently observed in case of absolute or functional iron deficiency [1, 4, 5].

Roxadustat is an oral drug recently approved for treating anemia in chronic kidney disease (CKD). However, KTRs were excluded from clinical development studies [6, 7]. Roxadustat belongs to the class of hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHi). By modulating HIF, it exerts pleiotropic effects on the expression of genes involved in EPO synthesis, iron mobilization and inflammation, making it interesting for ePTA [8, 9]. We therefore implemented roxadustat as a routine treatment for ePTA instead of rEPO and report in this letter its efficacy and safety compared with rEPO used in the first month post transplantation.

We enrolled all consecutive patients receiving roxadustat for ePTA (defined as Hb <10g/dL during the first month after transplantation) and estimated glomerular filtration rate <60 mL/min/1.73 m^2. Control group included all patients transplanted who received rEPO for ePTA during previous year. Data were retrieved from the ASTRE database, which prospectively collects data from KTRs (DR-2015-518). Additional data were adjudicated using medical records: Hb level, glomerular filtration rate, parathyroid hormone, blood transfusions, cardiovascular and thrombotic events, ferritin and transferrin saturation, C-reactive protein, date of treatment initiation, treatment dose and subsequent adjustments, and date of treatment discontinuation. Our protocol prioritizes correction of vitamin and iron deficiencies when indicated. Blood transfusions are performed in patients with Hb <7.5g/dL, or <9g/dL in the presence of symptoms or a history of vascular or cardiac stroke.

Roxadustat and rEPO were prescribed in accordance with the Summaries of Product Characteristics used for CKD. Roxadustat was started at 70 mg three times per week. Darbepoetin alfa was the single rEPO used, initiated at a dose of 0.45 μg/kg/week. In both groups, the dosage was increased in case of inefficacy at 1 month, the dosage was reduced or discontinued if Hb exceeded 12 g/dL or increased by more than 2 g/dL within 14 days. Efficacy was assessed by the proportion of patients achieving the target Hb level (>10 g/dL) and the need for blood

Abbreviations: CKD, chronic kidney disease; ePTA, early post transplantation anemia; GFR, glomerular filtration rate; Hb, hemoglobin; HIF, hypoxia inducible factor; rEPO, recombinant erythropoietin; KDIGO, Kidney Disease Improval Global Outcomes; KTR, kidney transplant recipient; PHI, prolylhydroxylase inhibitor; rEPO: recombinant erythropoietin.

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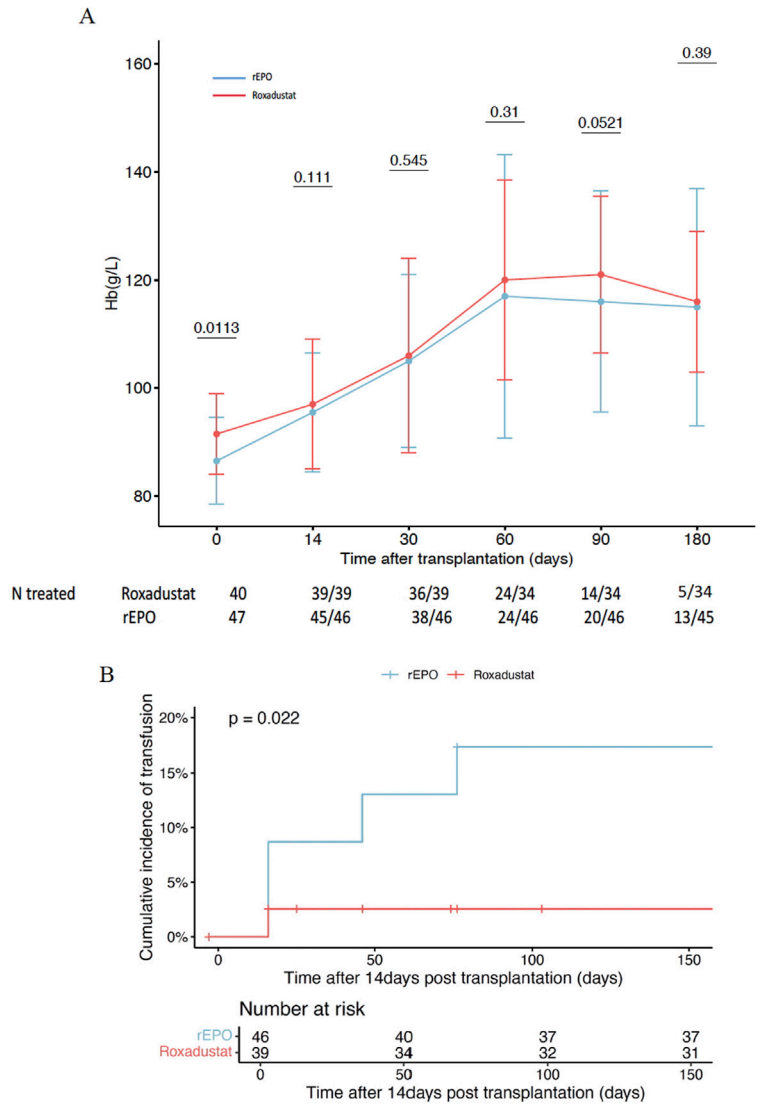

FIGURE 1 | Efficacy of Roxadustat to treat early post transplant anemia in comparison to recombinant erythropoetin. **(A)** Hemoglobin level between roxadustat group and recombinant erythropoetin group. **(B)** Cumulative incidence of blood transfusion between roxadustat group and recombinant erythropoetin group. rEPO: recombinant erythropoetin, Hb: hemoglobin.

transfusions beyond 2 weeks post-transplantation, to exclude the impact of perioperative bleeding. Safety was evaluated over the first 6 months, focusing on the incidence of severe adverse events, including vascular thrombosis, graft loss and major adverse cardiac events (4P-MACE).

Among 163 KTRs between May 2023 and July 2024, 46 received roxadustat for ePTA. Six patients were excluded (5 for early discontinuation of roxadustat unrelated treatment, 1 for concomitant use of rEPO). The prior year, 54 patients received rEPO for ePTA: 7 patients were excluded (5 for receiving fewer than 7 days of treatment, 1 for being under 18 years, 1 for bone marrow disease).

We observe that a greater proportion of patients in the roxadustat group achieved the target Hb of >10 g/dL at 3 months compared to the rEPO group (97% vs. 80% p = 0.04), which coincided with slightly higher Hb levels at that time point (**Figure 1A**). Moreover, a significantly higher number of patients treated with rEPO received transfusions beyond the first 2 weeks post-transplant (19.6% vs 2.6%, p = 0.02) (**Figure 1B**). At 6 months, 5 patients (15%) remained treated with roxadustat (28% in the rEPO group, p = 0.16), with a dose between 70 and 150 mg 3 times a week.

Globally, no difference was observed between both groups regarding safety outcomes. In the roxadustat group, 4 patients experienced thrombotic events (1 native kidney vein thrombosis, 2 lower limb deep vein thrombosis, and 1 arteriovenous fistula thrombosis); 2 patients experienced major cardiovascular events and 1 patient lost the graft due to severe artery stenosis leading to arterial thrombosis 6 months post-transplantation. In the rEPO group, 2 patients experienced thrombotic events (one lower limb

deep vein thrombosis and one iliac vein thrombosis), no cardiovascular event nor graft loss was observed, 1 patient died from septic shock.

To our knowledge, we report the first European cohort study evaluating the efficacy and safety of roxadustat for the treatment of ePTA in KTRs. In contrast to randomized controlled trials conducted in patients with CKD which demonstrated non-inferiority of roxadustat compared to rEPO, our findings suggest that roxadustat may be more effective during the early post-transplantation period. At 3 months, 97% of patients in roxadustat group achieved the targeted Hb level, maintained at 6 months, with less need for transfusions compared to patients treated with rEPO. While the treatment was generally well tolerated, we call for particular caution regarding thrombotic risk, especially during the first 3 months following initiation. Although no statistically significant difference was observed, we suspect high level or a rapid increase of Hb to be a favoring factor of thrombosis. These adverse events are aligned with the European Medicines Agency's recommendations for cautious use of roxadustat due to potential cardiovascular and thrombotic risks. These findings underscore the importance of closely monitoring Hb levels, especially at initiation and after each dose adjustment. Of note, 6/36 patients, who presented with persistently impaired graft function, were still receiving roxadustat at 6 months. This observation illustrates that some individuals may have a long-term indication for anemia treatment. It raises the question of long-term safety of roxadustat, particularly concerning its potential pro-angiogenic effects -through VEGF upregulation-in a population with an increased cancer risk. Nevertheless, randomized trials have not demonstrated an increased incidence of cancers, in line with findings from preclinical models [10]. This may be due to an incomplete activation of the HIF pathway, insufficient to trigger the VEGF gene expression and to the inhibition of tumor growth by modifying the microtumoral environment, as suggested by *in vitro* studies. In our opinion, this theorical risk should warrant vigilant monitoring rather than leading to the exclusion of KTRs.

In conclusion, our study suggests that the use of roxadustat may be more effective than rEPO in the management of ePTA in KTRs. However, its benefit-risk profile warrants further investigations in a randomized controlled trial.

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 (DR-2015-518) ASTRE Database ethics comitee. 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

LG, PG, and JG conducted the experiments, LG, PG, and JG wrote the manuscript and HL, LL, MB, J-MH, LM, AF, and CF participated to patients selection and inclusions and revised the manuscript. 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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LETTER TO THE EDITOR
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Use of Cross-Sectional Imaging Body Composition Assessment to Predict Pancreas Transplant Outcomes

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Keywords: body mass index, hazard ratio, pancreas transplant alone, post-transplant diabetes mellitus, skeletal muscle index

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Dear Editors,

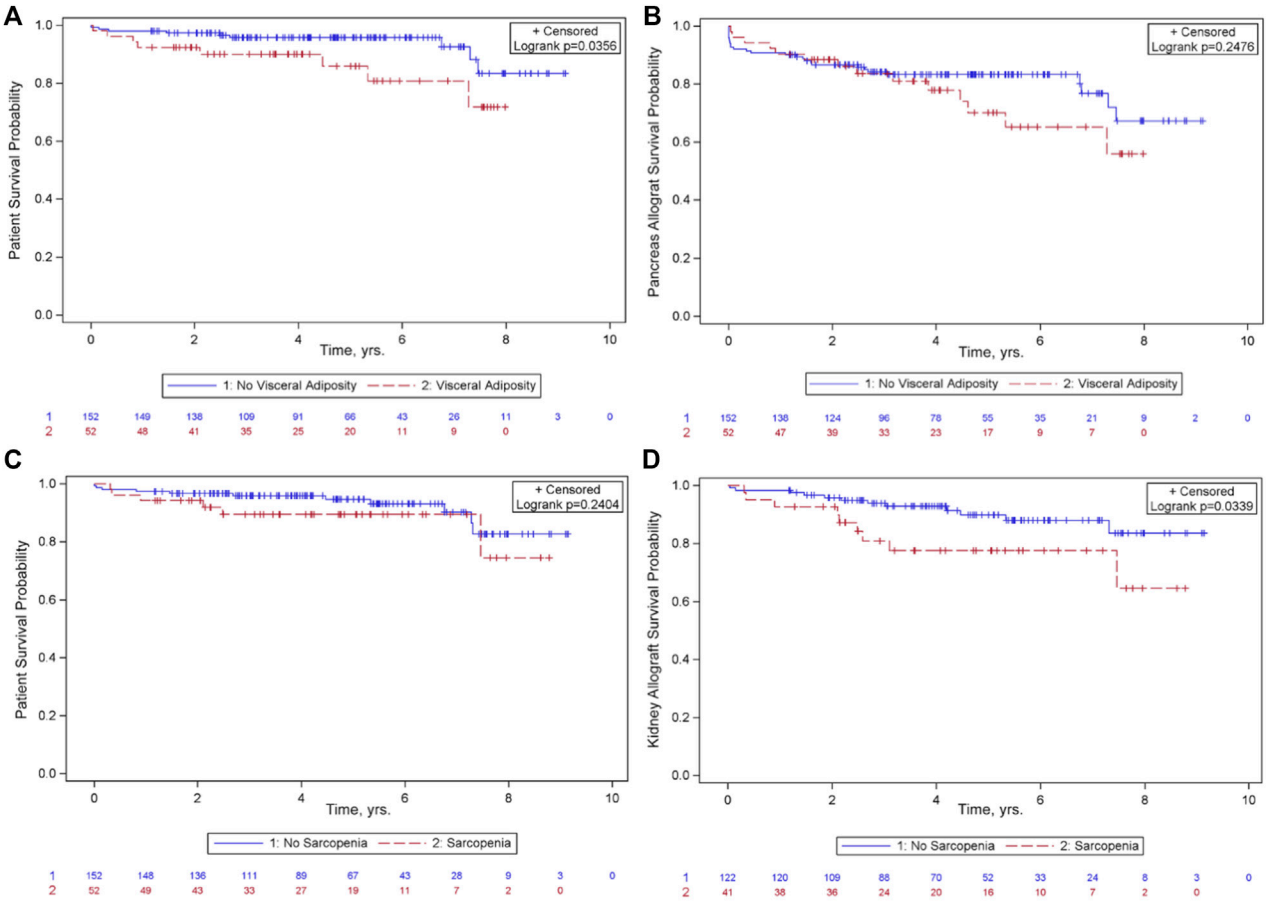
Obesity has traditionally been a relative contraindication to pancreas transplantation due to concerns about the association between obesity and elevated peri-operative risk as well as development of post-transplant insulin resistance [1]. However, studies have shown equivalent outcomes between overweight and non-overweight simultaneous pancreas and kidney transplant (SPK) patients based on the low body mass index (BMI) cutoff of 28 [2, 3]. The impact of more pronounced obesity, and how that is classified, on pancreas transplant outcomes remains unknown. Although easy to calculate, BMI does not account for differences in fat distribution between ethnicities, genders, sex, age, and genetic backgrounds. Cross-sectional imaging allows more granular evaluation of a patient's body composition, including direct measurement of visceral and subcutaneous adiposity and assessment of associated sarcopenia. Individual variation in adipose distribution may be particularly important to assessing risk in pancreas transplant recipients because of the prominence of visceral adiposity in the metabolic syndrome and the development of insulin resistance [4].

Studies incorporating CT-based metrics have associated visceral adiposity with poor outcomes following many types of surgery, including liver and kidney transplantation [5–7]. The only prior study assessing CT metrics of body composition in pancreas transplantation described a protective effect of adipose tissue on the risk of postoperative complications but was limited by a small sample size of both obese (n = 6) and overall (N = 40) patients [8]. Therefore, the impact of body composition on pancreas transplant outcomes remains unknown.

We performed a retrospective, single-center study analyzing the preoperative CT scans of adult, first-time pancreas transplant recipients between 2012–2020 to determine the relationship between visceral adiposity, sarcopenia, and post-transplant outcomes. Visceral adiposity was defined separately in men and women as the quartile of patients with the highest visceral adipose tissue-to-subcutanoues adipose tissue ratio (≥0.84 in men and ≥0.51 in women). Sarcopenia was defined similarly as the quartile of patients with the lowest SMI (<51.2 cm^2/m^2 in men and <43.1 cm^2/m^2 in women). Detailed Materials and Methods can be found in the **Supplementary Data**.

The study included 204 pancreas transplant recipients, 146 (71%) with type 1 diabetes mellitus (T1DM) and 58 (29%) with type 2 diabetes mellitus (T2DM). The mean follow-up was

Abbreviations: BMI, body mass index; HR, hazard ratio; PTA, pancreas transplant alone; PTDM, post-transplant diabetes mellitus; SMI, skeletal muscle index; SPK, simultaneous pancreas and kidney transplant; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.



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Hazard of adverse outcomes in subgroup analyses						
	T1DM SPK		T2DM SPK		T1DM PTA	
	HR (95% C.I.)	p	HR (95% C.I.)	p	HR (95% C.I.)	p
Patient Mortality						
Visceral adiposity	**3.60 (1.16 - 11/19)**	**0.03**	1.00	0.99	4.89 (0.37 - 64.18)	0.22
Sarcopenia	2.65 (0.84 - 8.36)	0.10	2.6 (0.16 - 41.67)	0.50	1.00	0.99
Pancreas Graft Failure						
Visceral adiposity	2.11 (0.97 - 4.61)	0.06	1.78 (0.25 - 12.63)	0.57	0.42 (0.05 - 3.38)	0.42
Sarcopenia	1.85 (0.83 - 4.13)	0.13	0.81 (0.08 - 7.83)	0.86	0.71 (0.15 - 3.33)	0.66
Kidney Graft Failure						
Visceral adiposity	2.07 (0.82 - 5.27)	0.13	1.00	0.99	NA	
Sarcopenia	**2.69 (1.08 - 6.71)**	**0.03**	2.76 (0.17 - 44.28)	0.47	NA	
PTDM						
Visceral adiposity	0.82 (0.29 - 2.64)	0.82	2.99 (0.83 - 10.81)	0.09	1.43 (0.38 - 5.29)	0.6
Sarcopenia	1.52 (0.59 - 3.9)	0.39	1.37 (0.38 - 4.93)	0.63	0.55 (0.12 - 2.51)	0.44

CI: confidence interval; HR: hazard ratio; PTDM: post-transplant diabetes mellitus; SPK: simultaneous pancreas and kidney transplant; PTA: pancreas transplant alone; T1DM: type 1 diabetes mellitus

FIGURE 1 | Kaplan-Meier survival curves demonstrating the impact of **(A)** visceral adiposity on patient survival, **(B)** visceral adiposity on pancreas allograft survival, **(C)** sarcopenia on patient survival, and **(D)** sarcopenia on kidney allograft survival. **(E)** Subgroup analysis of hazard ratios of adverse outcomes following pancreas transplantation.

4.9 ± 2.4 years. Patients with visceral adiposity were older (50.7 ± 10.0 vs. 46.6 ± 10.0, p = 0.01) and had a higher incidence of T2DM (20/52 vs. 38/152, p = 0.046). Fifteen patients (7%) met criteria for both visceral adiposity and sarcopenia. Patients with visceral adiposity received organs from younger donors (23.3 ± 11.9 vs. 27.6 ± 25.6, p = 0.02). Donor sex, age, donation after circulatory death status, pancreas donor risk index, cold ischemic time, hospital length of stay, readmission within 30 days, and incidence of delayed graft function were similar between the groups (**Supplementary Table S1**).

Visceral adiposity was associated with decreased patient survival post-transplant (p = 0.04, **Figure 1A**) but not decreased pancreatic graft survival (p = 0.25, **Figure 1B**).

Sarcopenia did not impact patient (p = 0.24) or pancreatic graft survival (p = 0.49). Among SPK recipients, sarcopenia was associated with decreased kidney allograft survival (p = 0.03, **Figure 1C**). Post-transplant diabetes mellitus (PTDM) was not impacted by either exposure (p = 0.49 for visceral adiposity and p = 0.53 for sarcopenia).

Because the end-organ effects of diabetes are different in patients based on type of diabetes and in those receiving SPK versus pancreas transplant alone (PTA), we hypothesized that body composition may impact these patients differently. We therefore performed subgroup analysis based on type of diabetes and transplant type. In SPK recipients with T1DM, visceral adiposity remained associated with decreased patient survival (hazard ratio [HR] 3.60, p = 0.03, **Figure 1E**) and sarcopenia remained associated with decreased kidney allograft survival (HR 2.69, p = 0.03, **Figure 1E**). Neither visceral adiposity nor sarcopenia impacted outcomes in SPK recipients with T2DM or in PTA recipients with T1DM.

This eight-year experience represents the largest examination of the impact of body composition on pancreas transplant outcomes and has two principal findings. First, visceral adiposity is associated with decreased patient survival following pancreas transplant. Second, sarcopenia is associated with worse kidney allograft survival in SPK recipients. In subgroup analysis, these findings were restricted to SPKs recipients with T1DM.

The general association of visceral adiposity and sarcopenia with worse outcomes following pancreas transplant is consistent with results reported following other varieties of surgery. More surprising is the lack of impact of visceral adiposity on either pancreatic allograft survival or PTDM given the well-reported correlation between visceral adiposity, metabolic syndrome, and insulin resistance and the previously reported association of visceral adiposity and PTDM in kidney transplant recipients [9]. The finding that the adverse impacts of visceral adiposity and sarcopenia were confined to recipients with T1DM suggests that the impact of body composition may vary based on type of diabetes. This conclusion is consistent with recent work suggesting that genetic subtypes of adipose distribution have a differential impact on T2DM risk [10].

This analysis has several limitations. First, there are not consensus definitions of visceral adiposity and sarcopenia in this patient population. We attempted to mitigate this limitation by analyzing our data with different thresholds including median values of each sex and other published criteria and saw only minor differences. Second, the sample size is relatively small and may be underpowered for subtle differences. Finally, the study is retrospective and only captures results from patients who were robust enough to complete the pancreas transplant evaluation process. Patients with severe visceral adiposity and/or sarcopenia may have been excluded through other related criteria, including BMI cutoffs and frailty assessments.

This study underscores that visceral adiposity and sarcopenia adversely impact pancreas transplant outcomes. Evolving technology, including the use of artificial intelligence to rapidly and objectively calculate metrics of body composition, can facilitate assessment of these variables in pancreas transplant candidate evaluation and may help define more concrete thresholds. Moreover, these metrics can trigger effective steps to help patients with visceral adiposity or sarcopenia reduce their post-transplant risks through measures like anti-obesity medication and proactive physical rehabilitation. Shifting evaluation criteria toward assessment of body composition instead of BMI might allow more patients to qualify for pancreas transplantation while safeguarding excellent post-transplant results.

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 University of Wisconsin Institutional Review Board. 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

CS, TW, and DA conducted the review of cross-sectional imaging. CS, GL, and DA performed chart reviews. GL provided statistical expertise during analysis. 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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Managing Cytomegalovirus Infection in Lung Transplant Recipients in Real Life: Results of a French Multicenter Survey

Tiphaine Goletto[1†], Kinan El Husseini[1,2†], Antoine Roux[3], Mathilde Briard[4], Gaelle Dauriat[5], Benjamin Renaud-Picard[6], Claire Merveilleux du Vignaux[7], Loic Falque[8], Benjamin Coiffard[9,10], Thomas Villeneuve[11], Xavier Demant[12], Adrien Tissot[13], Domitille Mouren[1], Francois M. Carlier[14], Sophie Alain[15], Jonathan Messika[1] and Vincent Bunel[1,2] on behalf of the SPLF Lung Transplant Group*

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Dear Editors,

Cytomegalovirus (CMV) infection remains a major cause of morbidity and mortality following lung transplantation (LTx), with lung recipients facing particularly high risk due to substantial lung-associated lymphoid tissue harbouring latent CMV [1]. Beyond direct effects, CMV infection increases risks for acute rejection, chronic allograft dysfunction, and opportunistic infections. While international guidelines provide recommendations for CMV management [2–4], real-world adherence in LTx centres remains poorly characterized, particularly given that they represented only 15% of transplant centres in recent broader surveys despite bearing the highest CMV burden [5].

We conducted a cross-sectional survey of 10 French-speaking LTx centres [9 out of 11 French centres (82%) and 1 out of 4 Belgian centres (25%)] between September 2022 and February 2023, using a comprehensive questionnaire addressing CMV prevention, diagnosis, treatment, and resistance management. Fifteen physicians participated, with 13 of 15 (86%) reporting adherence to centre-specific protocols that varied between institutions. All physicians surveyed were pulmonologists and lung transplant specialists, who routinely manage LTx patients and CMV infection in this population. Details regarding our methodology, the questionnaire in itself, as well as the full responses, are available in our **Supplementary Material**.

Our findings revealed substantial heterogeneity in CMV management practices with significant deviations from established guidelines (**Figure 1**). Most strikingly, prophylaxis duration showed concerning variability: in seropositive recipients (R+), 5 of 15 respondents (33%) used only 3 months of prophylaxis despite guidelines recommending 6–12 months [3, 4], while 9 of 15 (60%) used 6 months and 1 of 15 (7%) used 12 months. For high-risk donor-positive/recipient-negative

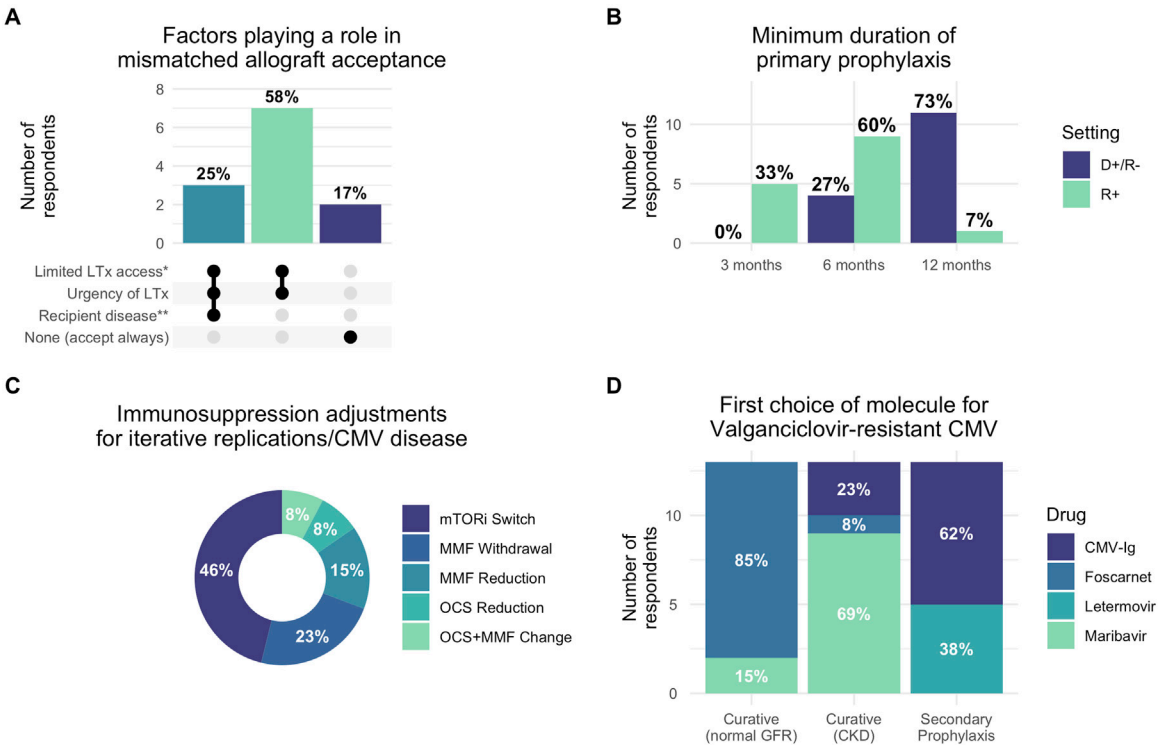

FIGURE 1 | Reported clinical practices for CMV management in lung transplantation. **(A)** Factors influencing acceptance of CMV-mismatched allografts based on responses. Dark dots indicate factors considered by each group. **(B)** Minimum duration of primary CMV prophylaxis by donor/recipient serostatus (D+/R- vs. R+). **(C)** Immunosuppression adjustment strategies preferred for recurrent CMV replication or disease. **(D)** First-choice antiviral therapies for valganciclovir-resistant CMV across different treatment contexts (curative treatment for patients with normal glomerular filtration rate or patients with chronic kidney disease, and secondary prophylaxis). Percentages indicate proportion of responses selecting each factor. *Limited LTx access: recipient factors anticipated to limit access to compatible allografts, such as hyperimmunization, rare ABO group or extreme height, favored mismatched allograft acceptance; **Recipient disease: respondents cited mainly short-telomere syndrome-associated pulmonary fibrosis or systemic sclerosis as situations precluding mismatched allograft acceptance. Abbreviations: D+/R-: donor-positive recipient-negative serostatus; R+: recipient-positive serostatus; CMV: cytomegalovirus; LTx: lung transplantation; CKD: chronic kidney disease; GFR: glomerular filtration rate mTORi: mTOR inhibitor; MMF: mycophenolate mofetil; OCS: oral corticosteroids; CMV-Ig: CMV-specific hyperimmune globulin.

(D+/R-) patients, 11 of 15 (73%) appropriately used 12-month prophylaxis, though 4 of 15 (27%) used shorter durations. In R+ patients with short telomere syndrome, which is associated with impaired CMV immunity and increased treatment toxicity [6], 10 of 13 respondents (84%) used standard valganciclovir prophylaxis, with 2 of 13 (16%) employing alternative approaches such as anti-CMV immunoglobulins or valaciclovir.

Secondary prophylaxis practices diverged markedly from 2018 guidelines that recommended against routine use [3]. After CMV reactivation, 5 of 14 respondents (36%) systematically initiated secondary prophylaxis with an additional 2 of 14 (14%) using it conditionally. Following CMV disease, these proportions increased to 8 of 14 (57%) and 3 of 14 (21%), respectively. All respondents maintained secondary prophylaxis for 3 months. For patients with iterative replications, 11 of 14 (79%) used long-term prophylaxis with durations varying from 3 to 12 months. This widespread adoption likely reflects the clinical reality that LTx recipients experience higher CMV recurrence rates compared to other solid organ transplant recipients.

Post-prophylaxis monitoring also showed substantial variation, with 6 of 15 respondents (40%) performing monthly monitoring in R+ patients, while in D+/R- patients, 5 of 15 (33%) performed monthly monitoring and 4 of 15 (27%) performed weekly monitoring. This heterogeneity emerged despite 2018 guidelines not supporting surveillance after prophylaxis, though updated 2025 guidelines now suggest monitoring in high-risk patients [4]. CMV-specific cellular immune response testing was used by only 4 of 13 respondents (31%), reflecting limited adoption of these newer diagnostic tools despite their potential for personalized management.

Immunosuppression modification was considered by 5 of 13 respondents (38%) for CMV disease and 12 of 13 (92%) for recurrent infections, most commonly involving mTOR inhibitor introduction or antimetabolite reduction. For hematologic toxicity, 10 of 14 (71%) appropriately used hematologic support, though 2 of 14 (14%) modified immunosuppression and 1 of 14 (7%) reduced valganciclovir doses as first-line interventions, potentially increasing resistance risk [7].

Resistant CMV management revealed evolving practices influenced by new therapeutic options, highlighting both opportunities and challenges in this complex clinical scenario. For patients with normal renal function, 11 of 13 (85%) preferred foscarnet over maribavir (2 of 13, 15%), while in renal impairment, maribavir was preferred by 9 of 13 (69%). Anti-CMV immunoglobulins were used by 8 of 12 respondents (67%) for secondary prophylaxis in resistant cases, with letermovir usage varying widely (8 of 13 (61%) never used it, while others employed it in specific scenarios).

The availability of maribavir through compassionate use programs during our survey period and its subsequent broader approval likely influenced these preferences [8]. Nearly all respondents would test for ganciclovir resistance in case of reactivation despite preventive treatment (11 of 13, 85%) or failure of curative treatment (12 of 13, 93%). These findings underscore the challenges clinicians face when managing resistant CMV, particularly the need to balance efficacy against drug-specific toxicity profiles in an already immunocompromised population with limited access to resistance testing.

The widespread practice variation we observed is particularly significant given that participating centres employ similar immunosuppression protocols and serve comparable populations. Our sample comprised nearly all French LTx centres, suggesting these findings reflect national practice patterns. Similar variability has been reported in Italian programmes [9] and broader European surveys [10], indicating these challenges transcend national boundaries.

The clinical implications are concerning. Santos et al. demonstrated that delayed-onset CMV disease following prophylaxis discontinuation occurs in up to 14% of LTx recipients with associated mortality risk [2]. Our finding that one-third of respondents use only 3-month prophylaxis in R+ patients may have significant clinical consequences, particularly when considering that breakthrough infections may increase resistance risk, impacting long-term allograft survival. Encouragingly, many practice variations we documented have been partially addressed in updated 2025 guidelines [4], which incorporate more aggressive secondary prevention strategies and suggest post-prophylaxis monitoring in high-risk patients, reflecting growing recognition of LTx-specific challenges.

While our study has limitations, including modest sample size and focus on French-speaking centres, our comprehensive coverage of French centres provides valuable insights into an underrepresented but high-risk population. The documented practice heterogeneity, particularly deviations from evidence-based recommendations, highlights critical gaps in CMV management standardization. The fact that 86% of respondents follow centre-specific protocols suggests local guidelines themselves diverge from international recommendations. The higher CMV burden in LTx recipients compared to other solid organ transplant populations necessitates specialized management approaches addressing unique challenges including optimal prophylaxis duration and management of patients with conditions like short telomere syndrome. These findings underscore the need for enhanced education, practice standardization initiatives, and generation of LTx-specific evidence to support future guideline development.

In conclusion, this survey reveals significant heterogeneity in CMV management among French-speaking LTx centres, with notable deviations from international guidelines. Given CMV's substantial impact on LTx outcomes, addressing these variations through enhanced education, standardized protocols, and LTx-specific evidence generation should be a priority for the transplant community.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Conceptualization: TG and VB; Data curation: TG; Formal analysis: TG and KH; Investigation: TG, KH, AR, MB, GD, BR-P, CM, LF, BC, TV, XD, AT, DM, FC, SA, JM, VB; Methodology: TG, KH, and VB; Project administration: TG and VB; Resources: AR, MB, GD, BR-P, CM, LF, BC, TV, XD, AT, DM, FC, SA, and JM; Supervision: VB and JM; Validation: All authors; Visualization: KH; Writing – original draft: TG and KH; Writing – review and editing. 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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Against All Odds: Why a Lung Donor Score Does Not Add Up

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Keywords: lung transplant, risk factors, clinical prediction model, lung donor score, statistical modeling

Dear Editors,

The Eurotransplant Lung Donor Score (LDS) [1] is a prediction model to assess the risk of donor lung discard due to medical reasons. A logistic regression model was fitted using data from over 5,000 donor lungs, and the resulting odds ratios were translated into a risk score ranging from 6 to 19 points, with higher scores indicating poorer donor lung quality. The LDS was found to be significantly associated with 1-year survival. The authors concluded that the LDS accurately reflects the likelihood of organ acceptance and is predictive of patient mortality. Furthermore, its implementation at the time of donor reporting may support more informed donor risk assessment and improve recipient selection. The LDS is used to study the quality of transplanted lungs in Eurotransplant [2], but it's unclear to what extent it is actually used in clinical practice to define an extended-criteria donor lung.

However, we believe the Eurotransplant LDS has some methodological limitations. The scoring system is presented in Table 2 of the original report. Odds ratios from the logistic regression model were rounded to the nearest whole number to construct a risk score. For example, donor age between 45 and 54 years was assigned 1 point (odds ratio 1.33), a history of smoking was assigned 2 points (odds ratio 1.53), and the presence of inflammation on donor bronchoscopy was assigned 3 points (odds ratio 2.83). Finally, individual points were summed into an overall risk score. We identified four limitations in the construction of the LDS, discussed in detail below.

First, rounding odds ratios such as 1.53, 1.87, and 2.40 all to a score of 2 points is suboptimal, as it obscures important differences in risk. These values represent varying levels of association with organ discard: a donor smoking history corresponds to a 1.5-fold increase in the odds of organ discard, purulent secretions observed on bronchoscopy to a 1.9-fold increase, and a PaO_2/FiO_2 ratio of 301–350 mmHg to a 2.4-fold increase. Grouping them under the same score point may discard a vast amount of information, which may harm discrimination and the predictive accuracy of the model.

Second, the construction relies on adding odds ratios, a practice that is statistically not valid. For example, consider a 20-year-old donor with purulent secretions observed on bronchoscopy. The donor is assigned the level of donor age <45, resulting in an odds ratio of 1 (reference level), indicating neither a decrease nor an increase in the odds of organ discard. Then, the odds ratio for purulent secretions is nearly 2, reflecting a 2-fold increased chance of discard. Combining these two odds ratios would result in a $1 \times 2 = 2$-fold increase in the odds of organ discard. If these two odds ratios were combined by summing them, it would result in a 3-fold increase in the odds of organ discard, which is incorrect. Odds ratios multiply; they do not add up. This is a basic mathematical property of ratios.

Third, caution is warranted when using binary indicators to denote the presence or absence of missing data. In the current model, nearly all donor risk factors include a category specifically representing missing values, which may introduce bias and compromise the validity of the predictions [3]. A single imputation model may be considered when the missing data are low. Advanced methods, such as multiple imputations, are not always practical when applying a model in clinical practice. Predictors with substantial missingness are generally poor candidates, as they are also likely to be missing in future patients. When only a small proportion (less than 5%) of data is missing, complete case analysis may be acceptable, though it remains important to always investigate potential reasons for missingness. Strong

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TABLE 1 | Our revised score along with the original results by Eurotransplant (we preserved the ordering of the risk variables). The revised score is the log OR multiplied by a factor of 4 and rounded to a whole number. For example, a visualized tumor in the bronchoscopy gets 4 × 1.68 ~ 7 points.

Factor	OR	log OR	Original score	Revised score
Donor age (y)				
<45	1.00	0.00	1	0
45–54	1.33	0.29	1	1
55–59	1.77	0.57	2	2
60+	2.68	0.99	3	4
Donor history				
compromised	3.90	1.36	4	5
uncompromised	1.00	0.00	1	0
Smoking history				
yes	1.53	0.43	2	2
no	1.00	0.00	1	0
missing	1.18	0.17	1	1
Chest X-ray				
clear	1.00	0.00	1	0
edema	1.28	0.25	1	1
shadow	1.65	0.50	2	2
atelectasis	1.31	0.27	1	1
consolidation	1.58	0.46	2	2
missing	1.23	0.21	1	1
Bronchoscopy				
clear	1.00	0.00	1	0
nonpurulent	1.48	0.39	1	2
purulent	1.87	0.63	2	3
inflammation	2.83	1.04	3	4
visualized tumor	5.34	1.68	5	7
missing	1.26	0.23	1	1
PO2/FiO2 (mmHg)				
>450	1.00	0.00	1	0
351–450	1.26	0.23	1	1
301–350	2.40	0.88	2	4
<=300	2.97	1.09	3	4
missing	2.35	0.85	2	3
		Range	6–19	0–24

candidate predictors are objective measures that are consistently and widely available. In organ transplantation, in particular, key clinical information is mandatory, as an organ cannot be allocated without it. Thus, it is often possible to retrieve missing data from the medical records and databases.

Fourth, the primary outcome used in the model was organ discard. As it stands, the model predicts the probability of discard rather than clinically meaningful endpoints such as graft failure or patient death. Even if organ discard is correlated with these outcomes, the primary endpoint should ideally reflect a patient-centered outcome following transplantation.

We propose the following simple solution: we calculated the log odds ratios from Table 2 of the original publication. We then multiplied these values by a factor of 4 and rounded them to whole numbers. This preserved sufficient accuracy while aligning more closely with the original score for easier comparison. Using a multiplicative factor of 5 would also work, but it would increase the maximal score to 30. This new risk score system avoids data loss due to rounding of small numbers. Moreover, adding the values on the log scale is statistically appropriate. The new risk score ranges from 0 to 24, and is shown in **Table 1**. **Supplementary Figure 1A** shows the distribution of the original and revised scores, while **Supplementary Figure 1B** compares them directly. The revised score, however, cannot address the issues with how missing data were handled and with the choice of the primary outcome.

Medical statisticians warned against the flawed practice of adding up ratios decades ago [4] but the problem seems to persist. A risk score for donation after cardiac death (DCD) liver transplants combined hazard ratios in a similarly incorrect manner [5]. Summing odds ratios (or hazard ratios) not only lacks any meaningful interpretation, but may also produce misleading results. For instance, an odds ratio of 0.8 from a logistic model, which indicates a 0.8-fold risk reduction, would paradoxically increase the overall risk score if added. On the log scale, however, ratios smaller than 1 have a negative sign.

The LDS continues to be used today, for instance, a recent study used it as a benchmark to compare with their newly developed risk score [6]. Had the LDS been constructed using a statistically appropriate approach, the resulting score may have offered more accurate and evidence-based weighting of clinical donor risk factors in lung transplants. We hope our approach offers a constructive refinement of the LDS that could improve its accuracy and interpretability.

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

SS wrote the first draft. SS and FI reviewed and commented on the final version. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The SupplementaryMaterial for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14937/full#supplementary-material

Supplementary Figure 1 | (A) Histogram showing the two distributions, and **(B)** scatterplot comparing the original Lung Donor Score (LDS) to our revised score. Donors assigned 6, 7, 8, etc. points in the original model receive more nuanced values in the revised version; this applies across the entire risk spectrum. Data were based on simulations of 10,000 lung donors, representing all theoretically possible combinations of risk factors. The simulations do not accurately reflect real-world distributions and covariances among risk variables, but may be suitable for the purpose of visualizing our argument that a significant amount of information was discarded when constructing the LDS.

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LETTER TO THE EDITOR
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The Impact of an Exceptional Lung Allocation Score on Organ Access of Failing Pulmonary Arterial Hypertension Patients – A Eurotransplant Experience

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Keywords: lung allocation score, pulmonary arterial hypertension (PAH), lung transplant, organ allocation, waiting list

Dear Editors,

PAH patients remain a challenging diagnosis group in lung transplantation. Cardiac decompensation can render patients non-transplantable resulting in higher rates of waitlist deaths. Therefore, timely transplantation is of utmost importance in this patient group. However, capturing the true urgency of PAH patients is challenging in a system primarily designed for parenchymal pulmonary diseases. Patients suffering from pulmonary-vascular diseases usually have low LAS scores due to preserved pulmonary function parameters and gas exchange. The eLAS system was introduced to account for this discrepancy in the ET region. A board of independent judges, reviews clinical parameters as well as trajectories of disease severity for each eLAS application on an individual basis. For PAH patients, eLAS can be granted for patients with cardiac index <2 L/m^2 and right atrial pressure >15 mmHg, a bilirubin increase by 50%/abnormal, a creatinine increase by >50%/abnormal and for PAH patients on awake ECMO. If an eLAS application is accepted by the LAS review board, the patient's conventional LAS is replaced by a score corresponding to the 95-99th percentile of all patients listed in the Eurotransplant region. To assess how this system impacts waitlist mortality and early survival in PAH patients, we analyzed a total of 241 PAH patients receiving double lung transplant using ET data (**Figure 1**). Patients in the eLAS group tended to be younger (median 40y vs. 46y; p = 0.017) and more often female compared to the LAS group (72.1% vs. 59.3%; p = 0.076). Systolic PAP (100 vs. 84.5 mmHg; p = 0.022), mean PAP (65 vs. 54 mmHg; p = 0.011) and central venous pressure (12.5 vs. 10 mmHg; p = 0.017) were significantly higher in the eLAS group. Post-transplant mortality was highest in patients transplanted

Abbreviations: ET, Eurotransplant; PAH, Pulmonary arterial hypertension; LAS, Lung allocation score; eLAS, Exceptional lung allocation score; PAP, Pulmonary artery pressure; IQR, Inter-quartile range.

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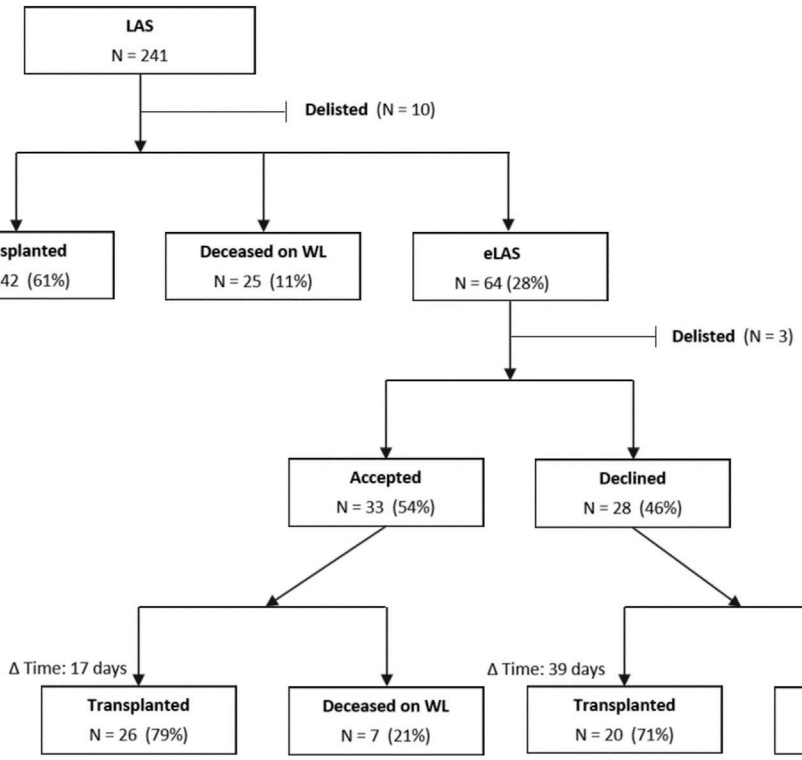

FIGURE 1 | Flowchart of PAH patients through the LAS/eLAS system. (Abbreviations: d, day; Δ Time, Days between listing and event, i.e., either transplantation or death; eLAS, Exceptional lung allocation score; LAS, Lung allocation score; WL, Waitlist; y, Year).

after declined eLAS (90-day: 36.8%) compared to 19.2% in patients with a valid eLAS and 10.1% in the LAS group (p = 0.018). Differences in 1-year-mortality did not reach statistical significance.

The implementation of the ET LAS system in 2011 is generally considered a success. It facilitated cross-border sharing of donor lungs for high-urgent recipients, thus reducing waitlist mortality and median waiting time [1]. Especially patients with restrictive lung diseases profited from a LAS-based allocation. In contrast, PAH patients were the only group showing worse survival after LAS implementation in Germany [1]. In addition, PAH patients have the highest waitlist mortality and second lowest chance of being transplanted within 1 year in the ET region.

One of the important differences between failing PAH patients and patients suffering from parenchymal lung disease is the complexity to bridge patients for a prolonged time. In the majority of cases with non-PAH lung disease, VV-ECMO is sufficient, whereas PAH patients require a VA mode for right ventricle unloading and cardiac support. VV-ECMO is far less invasive and can be performed for extended periods of time, while VA-ECMO is known to entail higher risks for bleeding or thromboembolic complications. Indeed, PAH patients have the lowest transplantation rate of ECLS-bridged patients. Therefore, an ideal organ allocation system should aim to avoid the need for ECLS bridging by assigning higher urgency to PAH patients while they are still stable. It seems that the current eLAS system is only partially successful in this regard, as eLAS can only be requested for PAH patients already in right heart failure.

Recently, important advances have been made in assessing decompensation risk of PAH patients. Parameters suggested by the latest ERS guidelines include WHO-FC, 6MWD, biomarkers and cardiac imaging (e.g., changes of RV dimension, RV fractional area change, RV free wall strain, tricuspid annular plane systolic excursion, tricuspid regurgitation, TAPSE/sPAP, RA area) [2]. With increasing evidence for these factors in the general PAH population, they might also be useful to incorporate in lung allocation scores. This is further underlined by a study by Vicaire et al., showing that high-risk PAH patients according to COMPERA 2.0, REVEAL Lite 2 as well as ESC/ERS guidelines at the time of listing had poor outcomes after LTx, emphasizing the need for early referral to a lung transplant center [3].

Currently, an accepted eLAS request results in scores between the 95th and 99th percentile. This resulted in a timely transplantation of 79% of patients in our analysis. This is unique and underlines the importance of being able to apply for an exceptional score, as the majority of these patients would have died. Of note, in 26/33 patients in very critical situations (based on the eLAS requirements) were rescued with an acceptable 1-year survival. In contrast, almost half of eLAS requests in our cohort were rejected by the LAS-board as they did not meet preset criteria, leaving these patients on the list with a regular LAS. Interestingly, many of them were transplanted, but with almost quadrupled 90-day mortality. This observation aligns

with Wille et al. who found significantly lower 1-year survival for group B patients with denied exceptional LAS requests in the US. [4].

As LAS calculation aims to balance pre-transplant likelihood of death and post-transplant survival, some have argued that therapeutic benefit is not favourable in many PAH patients, not meriting allocation of scarce donor organs. However, PAH patients are currently at an unfair disadvantage on both sides of this equation. It has been shown that the LAS calculation actually underestimates pre-transplant mortality of PAH patients awaiting transplantation [5]. This is especially relevant since risk of waitlist mortality factors into the ET-LAS calculation with twice the weight of post-transplant likelihood of survival. At the same time, post-transplant survival has significantly improved in recent years and is comparable to other underlying diseases in high-volume centers, especially by the use of postoperative ECMO prolongation strategies. Survival conditional on survival to 3 months is well-known to exceed all other diagnosis groups except CF [6]. Taken together, PAH patients make excellent transplant candidates who deserve equity in organ allocation.

Our investigation has several limitations. Being a retrospective analysis based on registry data, it can contain miscoded data or missing values. We lacked clinical information on PAH patients at the time of listing and their trajectories until they were transplanted or died on the waitlist. In addition, it is unknown how often LAS scores have been updated during the waiting time. Detailed measurements of patient hemodynamic impairment are not captured by ET, preventing competing risk analysis of known parameters predicting cardiac failure in PAH. Also, specific reasons for the refusal of an eLAS request by the board were not available. As our cohort includes patients transplanted over the course of almost 8 years, the analysis could also be prone to era effects.

In conclusion, allocation requires a balanced reflection of urgency. Our analysis suggests that the current ET allocation system is not optimal for PAH patients, who are underprivileged compared to other indication groups. The option to grant an eLAS for PAH patients addresses some of the flaws but is not specific enough to reduce waitlist mortality in this highly specific subgroup of patients. Further refinement of the ET-LAS, additional business rules or a revision of the eLAS system are warranted to ensure equal access to life-saving transplantation for PAH patients.

DATA AVAILABILITY STATEMENT

Data not available due to ethical/legal restrictions.

ETHICS STATEMENT

The studies involving humans were approved by Medical University of Vienna Internal Review Board (EK 1776/2023). 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

SS and KH conceived the study; CK, FD, GW, LB, TS, LS, PE, RS, BG, JG, MH, SS, and KH designed the study; SV provided data; SS and KH performed the statistical analysis and interpreted the data; SS and KH wrote the manuscript draft with contribution and important conceptual content from SV, CK, FD, GW, LB, TS, LS, PE, RS, BG, JG, MH, AB, and PJ. All authors contributed to the article and approved the submitted version.

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