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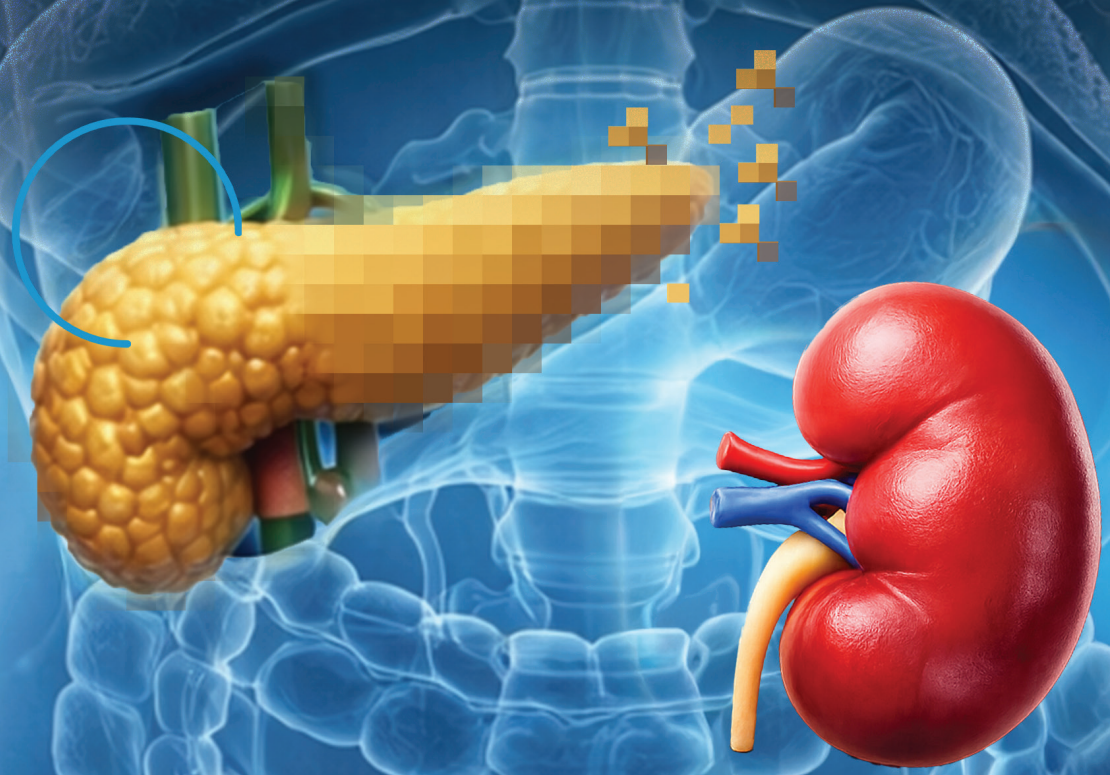

Simultaneous pancreas-kidney transplantation under scrutiny

Transplant International

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Transplant International

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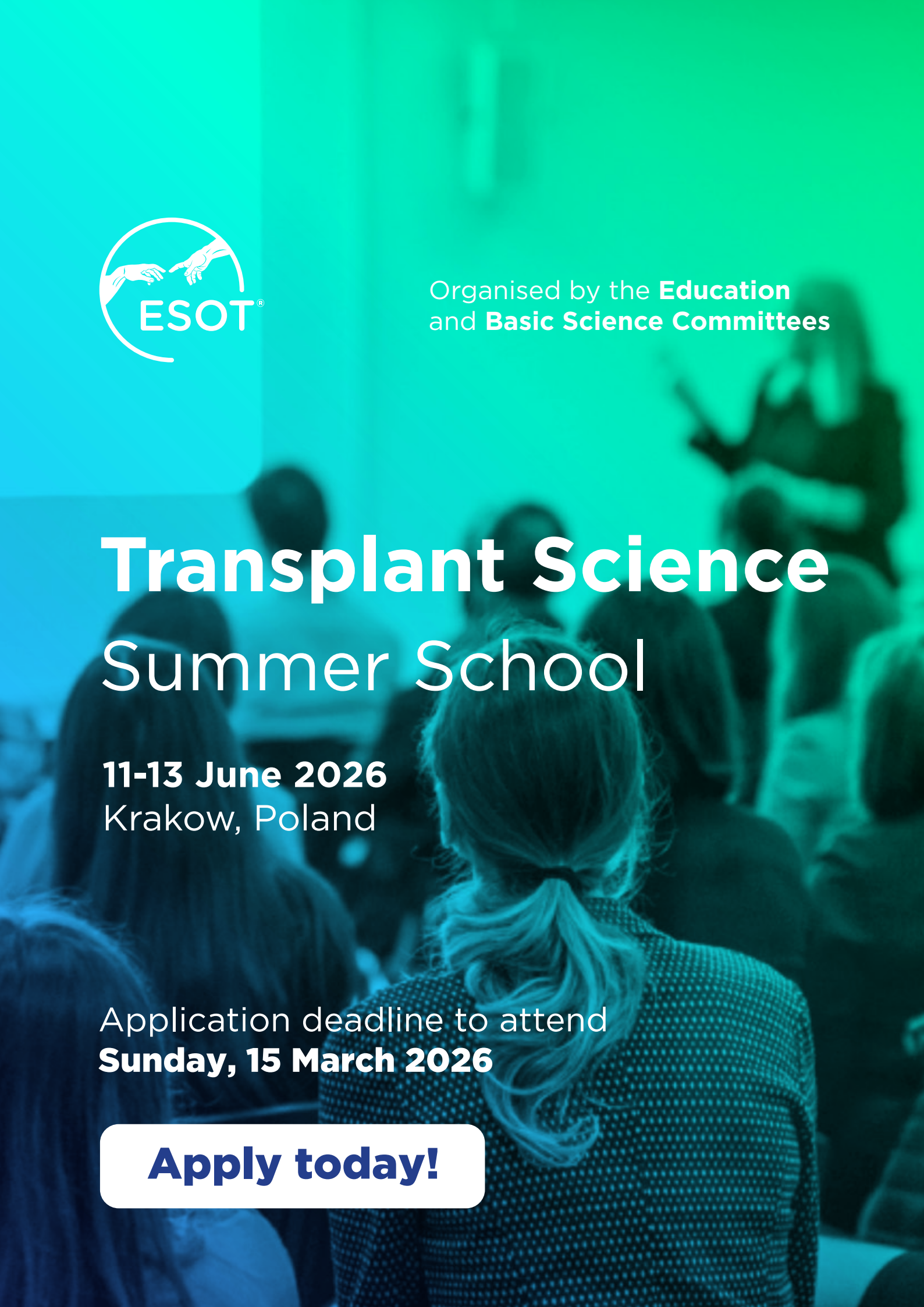

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EDITORIAL
published: 08 January 2026
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Organ Donation: An Act of Individual Generosity and Civic Solidarity

*Thierry Berney**

Editor-in-Chief, Transplant International

Keywords: allocation systems, communication, information, organ donation, promotion of organ donation

When the editorial board received a few days ago the letter written by Reg Green [1], it only took the time to read it to make the decision to publish it in this issue of Transplant International. The letter reminds us of the story of a young boy from the United States, Nicholas Green, who was fatally shot during a robbery while on a family vacation in Italy. In spite of the tragedy that brutally hit the family, they rapidly made the decision to donate Nicholas organs, which allowed to perform transplants in a foreign country in 7 individuals battling illness.

Although this occurred 31 years ago, in the times of my surgical residency, I remember quite vividly this tragic event, the response the Green family decided to oppose to the immense grief and sense of injustice to which they had brutally been confronted and the enormous media coverage it received.

The "Nicholas effect" that ensued is not an overstatement. This act of generosity and solidarity had such a huge impact on the Italian society, that the rate of organ donation in the burgeoning Italian transplant program of the time was multiplied by 3 in the wake of the press coverage of these events [2]. A similar story occurred in the UK in 2017, when a young girl named Keira Ball was killed in a car accident. Her donated heart saved the life of Max Johnson, then 9 years of age. A successful campaign followed in the British press to support a change of the consent legislation from an "opt-in" to an "opt-out" policy, resulting in what is now known as the "Max and Keira law" [3, 4].

These two striking examples demonstrate how individual acts of generosity, not only have the power of bringing solace to a grieving family but can also bring about changes in the national consciousness of a population and in their appraisal of the importance of organ donation. It also shows the importance of communication and information campaigns to translate these acts into tangible results for individuals waiting for an organ.

According to the latest figures published by the Council of Europe, 167′000 organ transplants were performed worldwide in 2024, as reported to the Global Observatory on Organ Donation and Transplantation [5]. This impressive number pales in comparison to the 725′000 patients inscribed on waiting lists, not considering the unknown and, in all likelihood, masive numbers of individuals living with organ failure and no access to transplantation [6, 7].

Organ transplantation is a very particular medical activity. Not only does it shift the usual paradigm of a "contract" between a patient and a doctor, to a three-way relationship in which the organ donor is a crucial component, but it goes much beyond in integrating the notions of a "pool" of organ donors and a community of individuals waiting, sometimes for a very long time, for life-saving surgery. It implies a responsibility of states toward their populations to make every effort to maximize access to donor organs, of course in a total respect of ethical and legal principles [8, 9].

A European working group recently developed a conceptual framework for the planning and development of organ donation programs. They identified several domains of importance in 4 categories [10]. Structural and operational elements (national transplant organization, registries, structured transplant programs, ...) are of course essential, but can only thrive thanks to actions -such as the training of hospital personel to approach potential donor families [4] and the building and maintainance of public support and trust [10]- that are based on communication and must be taken on a continuously ongoing basis. In this regard, it is a remarkable thing that, over the

Editorial

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

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years, Reg Green has tirelessy pursued the endeavour of championing organ donation as a public health necessity. The message he is conveying in his letter [1] is that the acceptance of organ donation by the population should never be taken for granted and that communication and information campaigns never get the luxury of being put to rest even for a short while.

The "Spanish model" has been the epitome of a successful system resulting in the highest rate of organ donation and transplantation in the world [11]. Spain ticks every single box in the conceptual framework [10, 11], starting from a strong political support from the state, which has remarkably survived government changes, to strong structured infrastructures, an efficient program of donor identification [11–13], ethically acceptable incentives [14], thoughtful training of transplant coordinators to approach and speak with potential donor families [4] and regular information campaigns that begin in schools [8, 15]. "The success of the Spanish donation and transplantation program can most likely be attributed to policies that focus on trust and transparency. These include policies that support training opportunities for healthcare professionals that are focused on communication skills, family consultation, and consent, direct communication with the media, including educational programs for journalists, and round-the clock availability for consultation" [11]. It should come as no surprise that in this age of information and communication such policies should be the pillars of a successful organ donation model that boasts the highest rates of organ donation (54 per million population) and organ transplantation (132 per million population) from deceased donors in the world.

It has been reported and calculated that in a 25-year period (1987–2012), more than 500'000 persons had received an organ transplant in the USA, resulting in over 2 millon life-years saved [16]. In addition to saving lives, organ transplantation has the potential to improve quality of life [17, 18] and there is clear and sustained evidence that kidney transplantation is the most cost-effective therapeutic option for end-stage kidney disease, which actualy saves money to healthcare systems compared to dialysis [19]. Governments have therefore both a human and economic duty to maintain effective channels of information and promotion of organ donation. It could also be argued that citizens have a civic duty to consider becoming organ donors, thus participating in an act of national solidarity.

In Spain, in 2024, 6′310 patients received organs from 2′278 deceased donors, with 11′908 patients on an organ waiting list. Meanwhile, in Germany 3′618 patients received organs from 953 donors, with 13′945 on the waiting list. Depending on country of residence, the risk of being transplanted is 3–4 times higher than that of becoming an organ donor, and the risk of being on a waiting list for a life-saving organ that may never arrive is 5–15 times higher [5] ! A provocative question in campaigns aiming at increasing the number of potential organ donors -rather than asking if they would be willing to donate their organs after their death-could therefore be: "would you agree to become an organ recipient ?", make the logical personal choice it implies and thus participate to what is a beautiful act of individual generosity and civic solidarity.

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LETTER TO THE EDITOR
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A Small Boy Makes Medical History

*Reg Green**

Nicholas Green Foundation, La Canada Flintridge, CA, United States

Keywords: bereaved families, media campaign, nicholas effect, organ donation, transplantation

Dear Editors,

In the history of medicine how many patients, thirty years after their death, have been influencing the life-and-death decisions of thousands of bereaved families around the world every year? Perhaps only one, my seven-year-old son, Nicholas, who was shot in a bungled robbery while we were on vacation in the far south of Italy in 1994 and whose organs and corneas my wife, Maggie, and I donated to seven very sick people there.

The story is so alive for millions of Italians that a new 90-min documentary called *Effetto Nicholas* on the results of that decision was recently shown by Italy's publicly-owned RAI television channel and may soon be available in English.

Given that the shortage of donated organs is the biggest obstacle to expanding transplantation, I hope readers will find of interest some of the steps taken by a small informal group of people, 'the Nicholas Effect' team, unpaid and without official backing of any kind that turned a sordid crime in a remote place into a worldwide movement that pushed many millions of people toward organ donation, saved many thousands of lives and has given hope to patients everywhere.

Without them, all experience suggests the likely result would have been a spike of good resolutions to donate organs and a fairly quick return to the norm.

That this time could be different arose from our realization that although, like us, the mass of people normally give little if any thought to organ donation, the subject is potentially of interest to, literally, everyone. Anyone might need a transplant, even a world-class athlete; anyone might have to decide whether or not to donate a loved one's organs; and anyone might be close to someone who will die without a transplant. Surprisingly then, it is in fact one of the few subjects of any kind that can command truly universal attention.

Our first conclusion from that realization was that, if presented innovatively enough, the mass media could be brought to see that their audience would find stories about transplantation riveting, not repellent. The second: the only way to reach enough people to change the donation rates significantly is through the mass media and, nowadays, their rapidly growing sibling, social media. Third, telling the story once is not enough. Like any campaign to change public opinion it has to be continuous, imaginative and adaptable.

Why is donating organs so difficult? Many reasons, but having experienced it for myself, let's fasten on a key one. Brain death is sudden death. Families arrive at hospitals to find one of their members who was in perfect health a few hours earlier and to whom they said "Don't be late for dinner" or "Be careful to look both ways when you cross the road" is dead or dying. Its enormity wipes out all other thoughts and even families who have been strong supporters of organ donation often falter. To this day, I remember one image that kept recurring when the doctors told us Nicholas was brain dead: never again would I hear him say "Goodnight, Daddy."

So from the beginning we held nothing back, sharing our feelings with the world's biggest publications and television shows -- and struck a nerve. News outlets that knew virtually nothing about organ donation -- as their questions showed -- flocked to hear more.

We also shaped the story to interest every sliver of opinion we could think of: magazines for the oldest readers (who are thrilled to know they can still do something that important when they had feared they were losing their usefulness) and the youngest (whose idealism is electrified by the thought of saving other children) women's magazines with their huge readership, religious

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***Correspondence**
Reg Green,
rfdgreen@gmail.com

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publications of every persuasion, sports of every kind, political groups from far left to far right and so on and on.

Reaching large audiences, we found out, is infectious. In Italy, where organ donation rates were the next to the lowest in the European Union when Nicholas was killed, they have quadrupled. Far from being horrified by the thought of diminishing the little American boy by taking away his body parts, the whole country, from Pope to peasant, thought it enhanced him. Streets, schools, parks and hiking trails have been named for him: 154 of them (!) at last count.

So by constant repetition, the hitherto scarcely believable act of removing the organs of someone already dead, putting them into people who are dying and getting several healthy people out of it became real for viewers and readers from Venezuela to Siberia. Even now, hardly a day goes by without us reminding anyone who will listen that the fate of several families could be in their hands at any time.

As the years have rolled by transplantation has shown itself to be transformative, not simply a prolongation of sickly lives: 31 years after the transplants both Nicholas' corneal recipients are still alive, two of the organ recipients lived gratefully for 15 and 22 years before dying and the three others, though once at death's door, are still alive. One of them has done what was once impossible, given birth to two children, the first named Nicholas -- and in a family with a history of liver disease he is fit enough to be in the Italian navy.

To urge this along I wrote two books, *The Nicholas Effect* and *The Gift that Heals*; Maggie and I were part of the team that made the Jamie Lee Curtis television movie, *Nicholas' Gift,* that has now been seen by more than 70 million people; and we made several 12-min educational documentaries that can be downloaded free from our website[1]. Hospitals around the world have shown them to the public and for training their own medical students and nurses. Schools and colleges have included them as part of civics or biology lessons.

Saving lives is, of course, the purpose of organ donation but it has a secondary result, a demonstration that if tragedy strikes people needn't turn inward in bitterness or despair but can save on average three or four desperate strangers, the vast majority of donor families finding some solace, knowing that when the crisis of their lives hit with full force they lived up to their own highest values.

Organ donation doesn't take the pain away -- what could? -- But it can give us all the strengthened hope for a better world.

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.

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RG conceived, wrote, and reviewed the content of the manuscript.

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[1]http://nicholasgreen.org/

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FORUM
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Simultaneous Pancreas–Kidney Transplantation versus Kidney Alone: Interpreting Neutral Survival and Persistent Metabolic Advantages

Lorenzo Piemonti[1,2]*

[1]Unit of Regenerative Medicine and Organ Transplants, IRCCS Ospedale San Raffaele, Milan, Italy, [2]Università Vita-Salute San Raffaele, Milan, Italy

Keywords: kidney transplantation, simultaneous pancreas–kidney transplantation, pancreas transplantation, long-term outcomes, real-world data

A Forum discussing

Reassessing Simultaneous Pancreas Kidney Vs. Kidney Transplant Alone: A Propensity-Weighted Analysis of Survival and Morbidity
by Budhiraja P, Lopez R, Arrigain S, Schold J (2025). Transplant International. doi: 10.3389/ti.2025.14934

Simultaneous Pancreas–Kidney Versus Kidney Transplant Alone: Real-World Outcomes in a Propensity-Matched Global Cohort
by Catarinella D, Williford S, Rusconi F, Caldara R and Piemonti L (2025). Transpl. Int. doi: 10.3389/ti.2025.15709

Forum

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***Correspondence**
Lorenzo Piemonti,
piemonti.lorenzo@hsr.it

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For patients with diabetes and end-stage kidney disease, transplantation is the most effective therapy to restore renal function and improve long-term outcomes. The choice between kidney transplant alone and simultaneous pancreas–kidney transplantation has, however, remained complex. The combined procedure offers the possibility of eliminating insulin dependence and achieving stable glycaemic control, while kidney transplant alone represents a technically simpler operation with a well-established safety profile. For many years, reports from individual centres suggested that simultaneous pancreas–kidney transplantation might also provide a survival advantage, reinforcing the idea that it was not only metabolically superior but also prognostically preferable.

Recent analyses from two large datasets invite us to reconsider this narrative. One, based on the global TriNetX real-world network, and the other derived from the U.S. Scientific Registry of Transplant Recipients, both compared outcomes between simultaneous pancreas–kidney and kidney-alone recipients using modern propensity-based methods. Despite differences in design and endpoints, their conclusions align: when baseline characteristics are properly balanced, the survival benefit of simultaneous transplantation is not evident, although the metabolic advantage remains clear and the risk of early complications is somewhat greater. It is worth noting, however, that a survival signal appears to re-emerge within more selected subgroups—particularly among recipients with type 1 diabetes and a leaner phenotype.

The TriNetX analysis included adults aged 18–59 years who received deceased-donor grafts, excluding living donor and multi-organ recipients. One-to-one propensity score matching was used to create comparable cohorts. Outcomes were examined over short- and long-term horizons, ranging

TABLE 1 | Comparison of SRTR and TriNetX studies on SPKT vs. KTA.

Comparison item	TriNetX analysis	SRTR registry study
Data source	Global, multicenter real-world EHR database	U.S. national transplant registry (2014–2023)
Population	Adults 18–59 with diabetes and ESRD; deceased-donor only; multi-organ excluded	Adults 18–59 with diabetes and ESRD; deceased-donor only; multi-organ excluded
Balancing method	1:1 propensity score matching (caliper 0.1)	Overlap propensity score weighting
Outcomes analysed	Patient survival, kidney graft survival, MAKE, cardiovascular events, infections, malignancies, metabolic outcomes (HbA1c), early complications	Patient survival, kidney graft survival (primary endpoints); 1-year acute rejection and hospital readmission (secondary endpoints)
Time windows	Analyses from day 10 (1-year outcomes) and day 90 (5- and 10-year outcomes)	Kaplan–Meier/Cox at 5 and 10 years; 1-year analyses for rejection and readmission
Patient survival	Pre-matching: SPKT appeared superior. Post-matching: Neutral. Sensitivity: Neutral also in T1D-only and non-obese subgroups	Pre-matching: SPKT appeared superior. Post-matching: Neutral overall. Sensitivity: Survival advantage for SPKT in T1D + lean phenotype subgroup
Kidney graft survival	Pre-matching: apparent advantage for SPKT Post-matching: neutral	Pre-matching: Apparent advantage for SPKT Post-matching: Neutral
Acute rejection (1y)	Pre-matching: higher in SPKT. Post-matching: neutral	Higher in SPKT (owOR ~2.8)
Hospital readmission (1y)	Pre-matching: Higher in SPKT. Post-matching: Slightly higher in SPKT.	Higher in SPKT (owOR ~2.0)
Other complications	Early reduction in MAKE; long-term MAKE neutral; cardiovascular endpoints neutral	Not assessed
Metabolic outcomes	HbA1c consistently lower in SPKT (superior glycaemic control)	Not available
Overall conclusion	No survival advantage overall after adjustment; early morbidity higher; clear metabolic superiority	No survival advantage overall after adjustment; higher early rejection and readmission; survival benefit in specific subgroups (T1D + lean phenotype)

from the first post-transplant year to five and ten years. TriNetX's strength was its breadth of endpoints, which extended beyond survival to include major adverse kidney events, cardiovascular complications, infections, malignancies, and, crucially, glycated haemoglobin. The SRTR analysis, in contrast, drew on the completeness of a national registry, applying overlap propensity score weighting to balance populations. Outcomes focused on patient and graft survival at five and ten years, together with acute rejection and hospital readmission within the first year. Although narrower in scope, SRTR provides a highly reliable picture of transplant-specific endpoints.

Despite these methodological contrasts, both studies delivered consistent findings [1, 2]. Neither identified a survival difference between the two strategies once adjustment was applied. In SRTR, patient survival at five and ten years was almost identical between groups, and TriNetX confirmed this neutrality. Kidney graft survival followed the same pattern. An important nuance is that, within the subset of recipients with type 1 diabetes and a leaner phenotype, SRTR did identify a statistically significant survival advantage for simultaneous transplantation, whereas TriNetX showed a trend in the same direction but without reaching statistical significance. Both studies also highlighted a higher frequency of early complications among simultaneous recipients. In the registry analysis, treated acute rejection during the first year was nearly tripled and hospital readmissions doubled, while the real-world analysis showed a similar though slightly attenuated pattern after matching. In terms of composite renal outcomes, TriNetX suggested a modest early reduction in adverse kidney events for simultaneous recipients, but this advantage was not sustained at later time points. Cardiovascular outcomes were largely neutral. What clearly distinguished the simultaneous group in TriNetX was better metabolic control, with lower glycated haemoglobin consistently observed even after matching. This confirms what is biologically expected: the presence of a functioning pancreas graft translates into restored normoglycemia. To facilitate a more granular comparison across methods and endpoints, the key results of the two studies are summarized in **Table 1**.

The disappearance of the survival advantage often reported in earlier work can be explained by several factors. Historical analyses were strongly influenced by selection bias, as patients chosen for simultaneous transplantation were frequently younger and healthier than those who underwent kidney transplant alone. Once like is compared with like, the curves converge. In addition, the combined procedure carries higher short-term risks linked to its surgical complexity and immunologic challenges, offsetting some of the long-term benefits. Outcomes after kidney transplant alone have also improved over time, narrowing gaps that might previously have been more evident. Finally, it is possible that the vascular and metabolic protection conferred by pancreas transplantation requires a longer time horizon than that captured in current datasets. Many patients remain at substantial risk of death from competing causes, which may obscure benefits that emerge only after decades.

At the same time, both studies must be interpreted with caution. Neither can be considered conclusive, and each has important limitations. Registry analyses such as SRTR excel in completeness but cannot account for metabolic or quality-of-life outcomes, which are highly relevant in this population. Real-world networks like TriNetX provide broader clinical detail but are vulnerable to coding variability and incomplete follow-up. Propensity methods reduce but cannot eliminate residual confounding. Moreover, both analyses exclude living donor transplantation, which in practice remains an important

comparator, and neither captures patient-reported outcomes such as hypoglycaemia burden, psychological wellbeing, or daily functioning. A further consideration is that SPKT and KTA recipients are not always fully interchangeable, meaning that even extensive adjustment may not completely resolve baseline differences. Earlier single-centre series—conducted in periods with different standards of diabetes management—consistently reported a survival advantage for SPKT, and the remarkable effort made over decades to refine surgical techniques, perioperative care, and immunosuppression has transformed pancreas transplantation into an increasingly safe and effective procedure. In parallel, contemporary improvements in exogenous insulin therapy and kidney-alone outcomes may have contributed to narrowing the observable survival gap in recent datasets. Subgroup analyses still suggest a possible survival signal in specific phenotypes, such as recipients with type 1 diabetes and lower BMI, although the magnitude and statistical robustness of this effect vary across sources. Together, these considerations highlight that current findings should be viewed as important contributions to an evolving evidence landscape rather than definitive conclusions.

Taken together, these findings should not be viewed as discouraging simultaneous transplantation but rather as refining our understanding of its value. While simultaneous pancreas–kidney transplantation may not consistently demonstrate a survival advantage over kidney-alone transplantation in contemporary adjusted analyses, it continues to provide superior metabolic control and the possibility of insulin independence—outcomes that remain highly meaningful for many patients. For a young adult with type 1 diabetes, the restoration of stable, physiological glycaemic regulation may justify the higher early risks, particularly in the context of a procedure that has become steadily safer and more effective through sustained surgical and perioperative improvements. In addition, emerging subgroup analyses indicate that a survival benefit may persist in specific phenotypes—most notably in recipients with type 1 diabetes and a leaner metabolic profile—suggesting that the value of SPKT is not uniform across all patient categories. For others—especially those with greater comorbidity, different metabolic profiles, or access to living donation—kidney transplant alone may represent the more appropriate strategy. Ultimately, counselling must be individualized, integrating the survival neutrality observed in overall populations with dimensions that registries cannot fully capture, including quality of life, hypoglycaemia burden, and the broader impact of insulin freedom on daily living.

Importantly, these results should in no way diminish the commitment to performing pancreas transplantation or its role within multidisciplinary care. On the contrary, they highlight the need to further strengthen timely referral to high-volume, specialised centres capable of accurately assessing appropriateness and delivering the procedure with the highest standards of safety and expertise. In current practice, a substantial proportion of individuals who could benefit—not only in terms of metabolic restoration but also, for selected subpopulations, in terms of survival—are neither identified nor referred, resulting in missed opportunities for clinically meaningful improvement. Ensuring that eligible patients are correctly evaluated and managed therefore remains an essential priority for the field.

For the field at large, these studies highlight the need for more evidence rather than less. Registries must evolve to incorporate metabolic and patient-centred endpoints, and real-world datasets require further validation and harmonization. International collaborations that combine the completeness of registry data with the granularity of electronic health records could provide a more comprehensive picture of outcomes. Only through such integrated approaches will it be possible to determine whether the metabolic advantage of simultaneous transplantation ultimately translates into reduced vascular complications, preserved organ function, and better long-term health. This need for robust and refined evidence is even more pressing given that a randomized trial comparing SPKT and KTA is neither feasible nor ethically justifiable in this context, making high-quality observational data the only realistic path forward.

The debate between simultaneous pancreas–kidney transplantation and kidney transplant alone is therefore not settled but reframed. The survival benefits once attributed to the combined procedure is less clear under modern analytic methods, yet its metabolic superiority remains unquestionable. More and better evidence is required to fully understand how these dimensions balance over the decades of life after transplantation. Until then, the value of simultaneous transplantation should be appreciated not only through survival curves but also through its potential to transform the daily lives of carefully selected patients.

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2. Budhiraja P, Lopez R, Arrigain S, Schold J. Reassessing Simultaneous Pancreas Kidney Vs Kidney Transplant Alone: A Propensity-Weighted Analysis of Survival and Morbidity. *Transpl Int* (2025). doi:10.3389/ti.2025.14934

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Simultaneous Pancreas-Kidney Transplantation Vs. Deceased Donor Kidney Transplantation in Patients With Diabetes Mellitus – An Ongoing Controversy

A. C. Gruessner[1] and R. W. G. Gruessner[2]*

[1]SUNY Downstate Health Sciences University Department of Medicine, New York, NY, United States, [2]SUNY Downstate Health Sciences University College of Medicine, New York, NY, United States

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The debate about the benefits of simultaneous pancreas-kidney transplantation (SPK) versus deceased donor kidney transplantation alone (DDKTA) has persisted since the inception of SPK in 1966 [1].

In this issue of *Transplant International*, the study entitled "*Reassessing Simultaneous Pancreas-Kidney* vs. *Kidney Transplant Alone: A propensity-weighted Analysis of Survival and Morbidity*" seeks to re-address this topic through a retrospective registry (SRTR) analysis. The authors use this type of analysis to produce real-world evidence to support clinical policy and decision making.

In their study, the authors challenge the survival benefit for all diabetes types for SPK vs. DDKTA and, consequently, question any prioritization for SPK. However, their conclusions are problematic due to the nature of their study design and methodology.

Randomized controlled trials (RCT) are the gold standard for establishing causal relationships. Unfortunately, RCTs in the context of SPK vs. DDKTA are deemed infeasible due to ethical concerns. If a qualified SPK candidate wishes to undergo a simultaneous transplant to become not only dialysis-free but also diabetes-free, why should this candidate be denied an SPK based solely on a randomization protocol that would give him/her only a 50% vs. a 100% chance to become insulin-independent?

Due to the infeasibility of a definitive RCT, the authors employed a propensity-weighted analysis. Undoubtedly, this is a sophisticated statistical method designed to simulate the balance of an RCT by adjusting for confounding variables. However, propensity-weighted analysis should only be performed if all relevant factors are available.

Hence, the central question is: are the SPK and DDKTA groups in this study truly comparable? As evidenced in Table 1 of this article, the two groups differ significantly across all included baseline characteristics. This imbalance raises concerns about residual confounding and the validity of direct outcome comparisons, even after sophisticated statistical adjustment.

The majority of SPK recipients had type 1 diabetes and met stringent listing criteria for pancreas transplantation. In contrast, DDKTA recipients either did not qualify, were declined, or opted out of a

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OPEN ACCESS

***Correspondence**
A. C. Gruessner,
angelika.gruessner@downstate.edu

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simultaneous pancreas transplant. For this reason alone, the two groups represent fundamentally different populations. The significant disparities in donor and recipient characteristics, as well as the unweighted survival outcomes, further underscore this deficiency. Therefore, applying weighted propensity scoring to estimate the probability of receiving an SPK among DDKTA recipients introduces bias, as the counterfactual scenario is not clinically feasible for most candidates. This methodological shortfall may cause misrepresentation of this study's true comparative effectiveness of SPK vs. DDKTA and will lead to wrong conclusions [2].

The study's overall comparative analysis between SPK and DDKTA recipients is challenged by significant cohort imbalances. There are fewer SPK recipients, and they have predominantly type 1 diabetes, whereas DDKTA recipients are more numerous and more often have type 2 diabetes. This disparity introduces inherent confounding, as the diabetes type is closely linked to disease progression, secondary complications, comorbidity profiles, and transplant eligibility.

Moreover, several potentially influential patient characteristics were not accounted for in the authors' analysis, including age at disease onset, duration of diabetes, severity of disease and the severity of secondary complications, regional variations in treatment practices as well as transplant center volume. Almost all transplant centers in the United States transplant kidneys but not all centers transplant pancreata. These variables may have influenced both treatment selection and outcomes, further complicating interpretation of the study's results using incomplete registry data.

Statistical adjustments cannot fully mitigate these confounders, especially when donor quality and transplant criteria vary across groups. As the authors showed, a more robust approach with stratified analyses within homogenous subgroups—such as limiting comparisons to patients with type 1 diabetes to reduce heterogeneity and enhance interpretability -- revealed a lower mortality rate for SPK recipients in this study. This result was confirmed by previous studies which evaluated highly selective cohorts specifically for patients stratified either for type 1 or type 2 diabetes. The reason for these stratifications was to assess the differences in those groups and minimize the selection bias [3].

An SPK transplant is clearly a more difficult procedure than a DDKTA since two organs are transplanted. This naturally carries a higher risk of surgical morbidity and graft rejection. Hence, this finding in the present study was to be expected. Yet importantly, it did not have an impact on patient and kidney graft survival.

The authors challenge the overall benefit of an SPK in general but do not take into consideration that the patient who only receives a DDKTA remains diabetic. After all, diabetes is the main reason for their end-stage renal disease. The DDKTA transplant is only a treatment for one secondary diabetic complication but not for the underlying reason of the patient's end-stage kidney disease. Post transplant, SPK recipients are usually completely off insulin while DDKTA recipients must continue insulin treatment [4]. While both SPK and DDKTA recipients require lifelong maintenance immunosuppression, the impact on diabetes management diverges significantly between the two. In DDKTA recipients, immunosuppressive agents - especially corticosteroids and calcineurin inhibitors – can worsen insulin resistance, exacerbate hyperglycemia, and complicate insulin dosing and glucose monitoring.

As there has been mounting evidence in the literature that diabetic complications in an SPK recipient with a functioning pancreas transplant can be halted, improved or even reversed, this severe disease is ongoing in the DDKTA recipient and, as mentioned, will be even harder to manage due to the side effects of immunosuppression. Cardiac disease, retinopathy, and neuropathy continue to progress and may get worse in DDKTA recipients. There is no question that early restoration of kidney function is essential for patient survival. Yet the real impact of a functioning pancreas graft can only be detected after several years as demonstrated in various studies [5].

The authors also question the advantages of improvement in quality of life for SPK recipients. However, there is a plethora of evidence in the literature demonstrating more significant quality of life improvement after SPK vs. DDKTA [6].

For labile diabetic patients, it is important to emphasize that SPK still remains the best treatment option to become fully insulin independent [4]. It is now apparent that despite great technological improvements through smart pumps, artificial pancreas and other forms of beta-call replacement therapy such as islet and stem cell transplants, these modalities do not consistently result in total freedom from insulin injections. Hence, the currently available new technologies along with DDKTA do not substitute for an SPK as patient surveys have shown [7].

In their summary, the authors challenge listing of any qualified diabetic and uremic patient for an SPK over a DDKTA. They recommend careful counseling regarding higher morbidity and rejection episodes in SPK recipients. However, even in their methodologically flawed study with a higher early complication rate, it is important to emphasize that the mortality rate in SPK vs. DDKTA was not any higher.

Unfortunately, there is a clear disconnect between the study results and the authors' conclusions. How can they possibly advocate against SPK if neither graft survival nor mortality was negatively impacted in their own study? It is obvious that the authors completely disregard that an SPK recipient after a successful dual transplant will be entirely insulin-free and enjoy a higher quality of life.

We agree with the authors about appropriate pretransplant counseling, but with one caveat. We feel strongly that qualified SPK candidates should always be referred to centers offering both SPK and DDKTA. Centers with experience in pancreas transplantation will provide better comprehensive patient counseling than centers without experience in pancreas transplantation.

Aside from the fact that in the US only 2.4% of all kidneys in 2024 were used for SPK, a prioritization of an SPK should continue. After all, the present study shows no inferior outcome for patient and kidney graft survival between the two groups.

In summary, the authors bolster distorted conclusions in their potentially influential publication based on a inappropriate study design and methodology. An equally contentious study in 2004 which falsely reported significantly worse patient survival and higher mortality after solitary pancreas transplantation

resulted in a marked decline in solitary pancreas transplant activity [8]. A subsequent analysis of the original data revealed substantial flaws in methodology [9, 10]. Although the results and conclusions of the original study were subsequently proven wrong, the later publication with corrected data received far less attention. The damage was done: the field of solitary pancreas transplantation almost vanished [11]. It is our hope that the benefits of an SPK are not judged on the basis of the present publication in *Transplant International*.

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

AG and RG both contributed to this opinion piece. All authors contributed to the article and approved the submitted version.

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Response to Commentary on "Reassessing Simultaneous Pancreas Kidney Vs. Kidney Transplant Alone: A Propensity Weighted Analysis of Survival and Morbidity"

Pooja Budhiraja[1]*, *Rocio Lopez*[2,3†], *Susana Arrigain*[2,3†] and *Jesse D. Schold*[2,3†]

[1]Department of Medicine, Mayo Clinic Arizona, Phoenix, AZ, United States, [2]Department of Surgery, University of Colorado Anschutz Medical Campus, Aurora, CO, United States, [3]Department of Epidemiology, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

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***Correspondence**
Pooja Budhiraja,
budhiraja.pooja@mayo.edu

†ORCID:
Rocio Lopez
orcid.org/0000-0002-4319-420X
Susana Arrigain
orcid.org/0000-0001-7533-3932
Jesse D. Schold
orcid.org/0000-0002-5341-7286

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We thank Drs. Gruessner for their thoughtful and experienced perspectives on our manuscript. We acknowledge that simultaneous pancreas-kidney transplantation (SPKT) provides important metabolic benefits, including insulin independence, improved glycemic control, and possible mitigation of diabetic complications. These advantages remain central to patient and clinician decision-making. Unfortunately, these outcomes are not captured in national registry data, which lack information on insulin use, degree of beta cell failure, cardiovascular status, or microvascular complications. Accordingly, our analysis focused on outcomes that are uniformly recorded for all transplant recipients, including patient survival, kidney graft survival, treated acute rejection, and hospital readmissions.

We agree that differences between SPKT and deceased donor kidney transplant recipients present challenges for direct comparison. This is the reason why we used overlap propensity weighting, a method designed to reduce bias in scenarios with limited overlap. Although residual confounding cannot be fully eliminated in observational studies, this approach helps reduce the influence of donor and recipient characteristics that historically favor SPKT in unadjusted analyses. Many prior studies showing superior survival with SPKT included younger donors, lower Kidney Donor Profile Index kidneys, shorter dialysis times, and overall healthier baseline characteristics in the SPKT cohort. These differences can amplify survival signals, making it difficult to distinguish the effects of pancreas transplantation from other influencing factors.

Our findings reflect contemporary practice, where advances in surgical techniques, immunosuppression, perioperative monitoring, and postoperative care have improved kidney-only transplant outcomes, narrowing historical survival differences. In addition, the landscape of diabetes care has evolved with the wider use of therapies such as glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors, which offer metabolic, cardiovascular, and kidney-protective benefits and are increasingly accessible, particularly among patients with Type 2 diabetes [1, 2]. These

advances support individualized SPKT selection, since metabolic improvement may be achievable in some recipients through medical therapy, while transplantation remains most impactful for those with clear insulin deficiency and appropriate surgical risk.

Our subgroup findings provide meaningful context. Among recipients with Type 1 diabetes and BMI below 30, which aligns closely with physiological rationale and traditional listing criteria, SPKT was associated with superior survival. Outside this phenotype, survival was similar, while early morbidity remained higher for SPKT. These findings support careful, individualized selection rather than broad application of SPKT to all diabetic transplant candidates.

We share the authors' longstanding commitment to ensuring that SPKT remains available to those most likely to benefit. Our intent is not to diminish its role but to provide objective empirical evidence that informs nuanced counseling and allocation practices. Incorporating both metabolic strengths and elevated early clinical risks into shared decision-making encourages balanced patient-centered care. We hope our study contributes to ongoing dialogue and supports thoughtful prioritization of pancreas grafts for candidates who stand to gain the most.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

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

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Organ-Specific Determinants of Tolerance and the Unique Challenge of Vascularized Composite Allotransplantation

Haizam Oubari[1,2,3]*, *Loïc Van Dieren*[1,2], *Curtis L. Cetrulo*[4] and *Alexandre G. Lellouch*[4]

[1]Plastic Surgery Research, Massachusetts General Hospital Center for Transplantation Sciences, Charlestown, MA, United States, [2]Harvard Medical School, Boston, MA, United States, [3]Chirurgie Plastique, Hopital de la Croix-Rousse, Lyon, France, [4]Cedars-Sinai Medical Center, Los Angeles, CA, United States

Keywords: animal models, chimerism, organ specific tolerance, tolerance induction, Vascularized Composite Allotransplantation

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Tolerance Induction Strategies in Organ Transplantation: Current Status and Future Perspectives
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We read with great interest the article Tolerance Induction Strategies in Organ Transplantation: Current Status and Future Perspectives. Transplant International. 2025; 38. [1], by Blein T, Ayas N, Charbonnier S, Gil A, Leon J, Zuber J., which offers a timely and well-organized synthesis of the major tolerance-induction strategies across transplantation. Presenting these diverse approaches, ranging from mixed hematopoietic chimerism to regulatory–cell–based interventions, within a single conceptual framework is valuable for the field, particularly as tolerance research continues to evolve at the intersection of immunology, engineering, and translational science. The authors should be commended for their clear exposition and for stimulating a broader discussion on how these pathways could be accurately integrated into future clinical applications, particularly given that, to date, the only reliably effective approach to tolerance induction has been the chimerism-based strategy. They also appropriately underscore the crucial issue of model selection: large animals, especially nonhuman primates (NHPs) or wild-caught species, more reflect the clinical complexity of tolerance induction than environmentally controlled, antigen-limited laboratory mice, as the latter lack the far richer and more heterogeneous repertoire of potentially alloreactive memory T cells typically present in NHPs and human recipients [2]. These models are increasingly challenging to implement, owing to rapidly escalating costs and heightened regulatory scrutiny aimed at ensuring ethical research. Nevertheless, they remain indispensable for meaningful translational progress. In the spirit of expanding this conversation, we believe it is important to highlight an additional dimension that can profoundly influence the success of tolerance-induction strategies: the organ-specific nature of antigenicity and immunologic permissiveness, briefly addressed in this review. These distinctions have significant implications for the application of chimerism-based and cellular therapies across various graft types.

Preclinical and clinical data demonstrate that solid organs differ markedly in their intrinsic antigenicity, inflammatory profiles, and thresholds for tolerogenic conditioning. Intra-abdominal organs such as the kidneys and liver are inherently more permissive to tolerance, whereas hearts and lungs remain tolerance-resistant. These organ-specific disparities help understand why chimerism-based protocols that reliably induce renal tolerance often fail in thoracic organs, underscoring the

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OPEN ACCESS

***Correspondence**
Haizam Oubari,
houbari@mgh.harvard.edu

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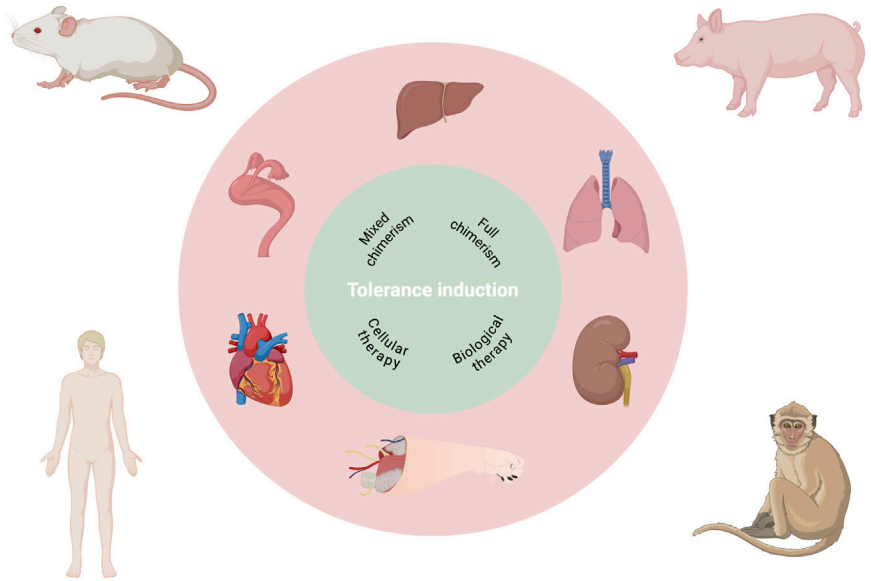

FIGURE 1 | Multilayered complexity for translational research in allotransplantation tolerance.

necessity of interpreting tolerance strategies through an organ-specific rather than organ-agnostic lens [3]. For instance, kidneys are consistently the most amenable organs for tolerance induction: in both NHP models and haplomatched human recipients, mixed hematopoietic chimerism, often transient, has been sufficient to achieve long-term, immunosuppression-free renal allograft survival [4–6]. In fact, kidneys are often considered to possess a protolerogenic potential, a concept further supported by recent MGH findings showing kidney-induced cardiac allograft tolerance in the NHP model [7]. In striking contrast, other solid organs such as the heart [8] and lung grafts remain considerably more refractory, necessitating often stronger immunosuppressive regimens. Cardiac and pulmonary grafts exhibit heightened ischemia–reperfusion injury, stronger innate immune activation, and more proinflammatory tissue-resident leukocyte compartments. These features drive accelerated effector priming, stronger indirect allorecognition, and a limited capacity to sustain donor hematopoietic engraftment, making these organs disproportionately resistant to both chimerism-based and regulatory-cell–based strategies [3]. These mechanistic observations underscore that tolerance induction is fundamentally shaped by organ-intrinsic biology, with mixed chimerism proving far more stable and effective in kidneys and liver than in thoracic organs.

These disparities become even more pronounced when considering vascularized composite allotransplantation (VCA). High immunosuppressive requirements have, to date, drastically limited the number of VCA procedures performed worldwide [9], and this translates into a particular complexity when applying tolerance-induction strategies to these grafts. VCAs contain multiple, highly antigenic, leukocyte-rich tissues, including skin and mucosa, as well as ischemia-sensitive components such as muscle. This places them at the extreme end of the tolerance-resistance spectrum. In swine, transient mixed chimerism is insufficient to induce full VCA tolerance, and a characteristic split-rejection phenomenon, marked by acceptance of musculoskeletal elements but rejection of the skin, has been consistently observed [10]. Achieving stable, multilineage chimerism is required for tolerance of all VCA components; this has only been accomplished through intensified conditioning regimens incorporating augmented irradiation, CTLA4-Ig, anti-IL-6R therapy, and vascularized bone marrow, which enabled long-term tolerance of skin-bearing VCAs across class-I barriers in a clinically relevant model [11]. Nonhuman primate data further underscore this divide: prior delayed-tolerance induction protocols in cynomolgus macaques generated robust renal tolerance under identical conditioning yet consistently failed in hand or face VCA models, with early rejection, infectious complications, and absence of chimerism [12]. More recently, our group demonstrated, for the first time in the NHP partial face transplant model, that simultaneous tolerance induction can generate transient myeloid and lymphoid chimerism, allowing for prolonged immunosuppression-free survival of a face allograft, although the graft ultimately underwent split and then full rejection [13]. Collectively, these findings highlight that VCA immunobiology differs substantially from that of solid organs, cautioning against the direct extrapolation of kidney-derived tolerance strategies to the multi-tissue context of VCA. Furthermore, the extreme sensitivity of these grafts to ischemia–reperfusion injury suggests that they may substantially benefit from *ex vivo* preservation, preconditioning and reengineering strategies [14], as also highlighted by Blein et al.

Taken together, these organ- and species-specific distinctions, further magnified in VCA, underscore that tolerance strategies cannot simply be transferred from one graft type to another. They

also outline multiple conceptual layers that shape tolerance-induction research and its clinical translation (**Figure 1**). Against this backdrop, the authors' effort to synthesize cross-organ tolerance mechanisms and to delineate shared versus organ-specific barriers is both timely and necessary, and their work represents a highly relevant contribution to the field.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

All authors (HO, LV, CC, and AL) contributed to the conception of the article, interpretation of the literature, critical analysis of the data discussed, and review of the manuscript. HO drafted the initial version of the manuscript. LV contributed to the editing of the draft and structuring of the literature. CC provided expertise in tolerance-induction strategies and nonhuman primate VCA models. AL supervised the scientific framing of the article, contributed to interpretation across organ systems, and critically revised the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Simultaneous Pancreas–Kidney Versus Kidney Transplant Alone: Real-World Outcomes in a Propensity-Matched Global Cohort

Davide Catarinella[1], *Sarah Williford*[2], *Francesca Rusconi*[3], *Rossana Caldara*[1] *and Lorenzo Piemonti*[1,4]*

[1]Diabetes Research Institute, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ospedale San Raffaele, Milan, Italy, [2]TriNetX LLC, Cambridge, MA, United States, [3]TriNetX Europe BV, Sint-Martens-Latem, Belgium, [4]Diabetes Research Institute, Universita Vita Salute San Raffaele, Milan, Italy

The true comparative effectiveness of simultaneous pancreas–kidney transplantation (SPKT) versus kidney transplantation alone (KTA) in patients with diabetes and end-stage renal disease remains incompletely defined. Using the TriNetX Global Collaborative Network (2010–2024), we identified 3,679 SPKT and 27,062 KTA recipients aged 18–59 years. In unmatched comparisons, SPKT recipients showed lower mortality, fewer cardiovascular events, and improved kidney graft survival relative to KTA recipients, but also higher early rejection, infection, and readmission rates. After 1: 1 propensity score matching, the cohorts were well balanced across all measured covariates, and long-term estimates for survival (HR 1.00, 95% CI 0.90–1.10), kidney graft failure (HR 0.99, 95% CI 0.94–1.04), and cardiovascular events (HR 0.99, 95% CI 0.94–1.05) no longer differed over 10 years. In contrast, SPKT recipients maintained significantly lower HbA1c levels throughout follow-up (mean 6.2% vs. 6.6% at 5 years; $p < 0.001$), reflecting sustained physiologic glycaemic control and a high probability of insulin independence. Sensitivity analyses restricted to type 1 diabetes and non-obese recipients yielded consistent results. After accounting for measured differences between recipients, we did not detect a long-term survival advantage of SPKT over KTA, whereas durable metabolic benefits persisted. Because key donor and immunologic characteristics were not available, a modest intrinsic survival benefit cannot be excluded. These findings highlight the major role of patient selection and support individualised use of SPKT for metabolic indications and quality-of-life improvement rather than survival gain alone.

Keywords: simultaneous pancreas–kidney transplantation, kidney transplantation, diabetes mellitus, end-stage renal disease, patient survival

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***Correspondence**
Lorenzo Piemonti,
piemonti.lorenzo@hsr.it

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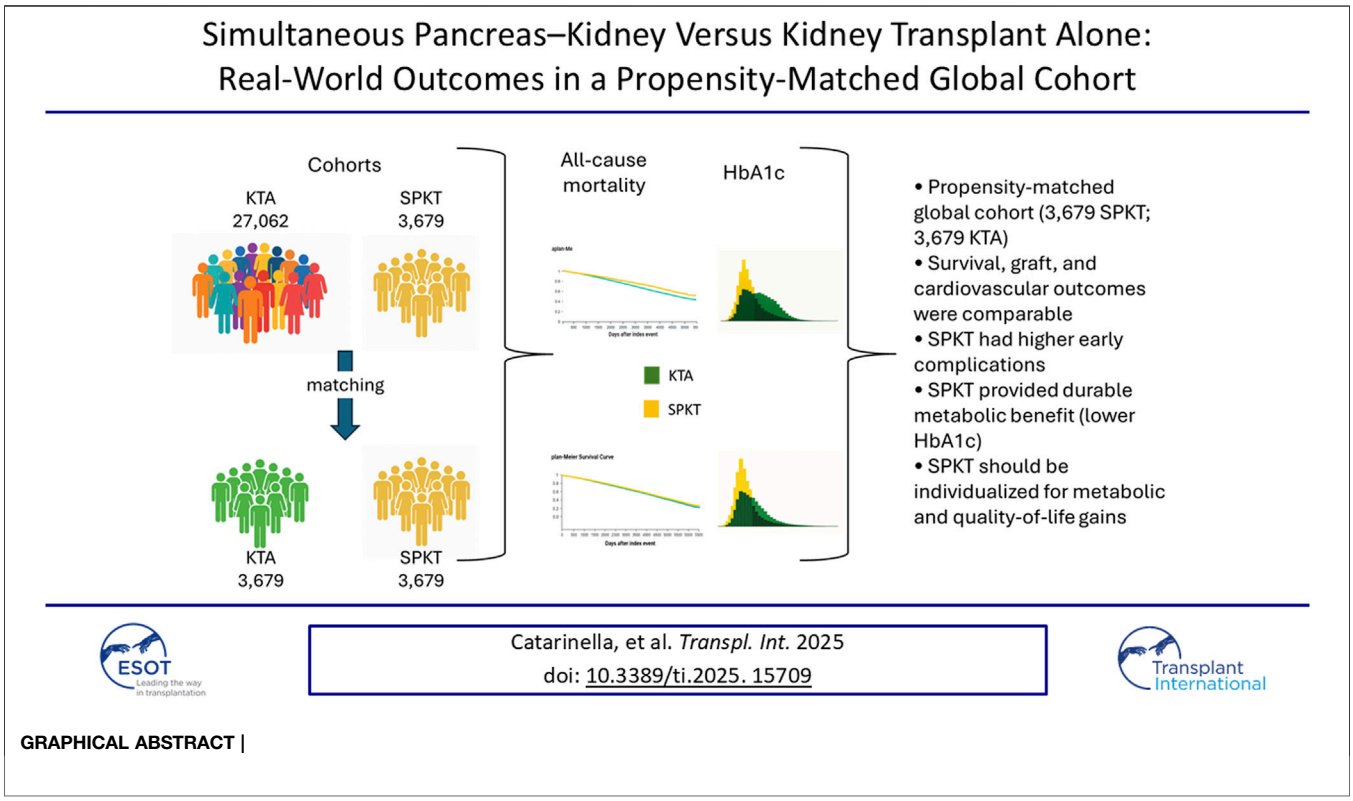
Abbreviations: AR, absolute risk; CI, confidence interval; DDKT, deceased donor kidney transplantation; EHR, electronic health records; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HbA1c, glycated haemoglobin; HR, hazard ratio; KTA, kidney transplantation alone; KM, Kaplan–Meier; MACE, major adverse cardiovascular events; MAKE, major adverse kidney events; OR, odds ratio; PS-matched, propensity score–matched; PTLD, post-transplant lymphoproliferative disorder; RD, risk difference; RR, relative risk; SMD, standardized mean difference; SPKT, simultaneous pancreas–kidney transplantation; T1D, type 1 diabetes; T2D, type 2 diabetes.



GRAPHICAL ABSTRACT |

INTRODUCTION

Simultaneous pancreas–kidney transplantation (SPKT) is a consolidated therapeutic option for patients with diabetes mellitus and end-stage renal disease (ESRD) who are eligible for pancreas transplantation [1–3]. By replacing both organs simultaneously, SPKT provides restoration of renal function together with endogenous insulin secretion, offering the potential for insulin independence and durable metabolic control [4–7]. Kidney transplantation alone (KTA) remains the most common approach worldwide due to its broader applicability, lower surgical complexity, and higher availability of organs, but it does not address the underlying diabetes or its long-term complications [8]. The theoretical advantages of SPKT extend beyond kidney graft survival and patient longevity [9]. Normalization of glycaemic control after successful pancreas transplantation improves HbA1c and reduces glycaemic variability, thereby decreasing the risk of acute metabolic decompensation and potentially preventing or slowing the progression of microvascular and macrovascular complications of diabetes [10–15]. Several observational studies have suggested that SPKT recipients achieve superior metabolic outcomes and quality of life compared with patients undergoing KTA, who remain insulin-dependent and often face suboptimal glucose control despite advances in medical therapy [16]. Despite these potential benefits, the impact of SPKT on hard clinical outcomes has been debated. Some registry-based analyses and single-centre reports have described lower mortality and cardiovascular events among SPKT recipients [17–22], particularly in type 1 diabetes [23, 24], while others have failed to confirm a survival advantage once differences in baseline risk profiles are accounted for [25–30]. Moreover, SPKT carries higher perioperative morbidity, increased immunosuppression, and greater risk of early complications, raising concerns about the overall balance of risks and benefits [31–33]. In the recent era, with improvements in surgical techniques [34–36], perioperative care [37–40], immunosuppressive strategies [41–43], and diabetes management [44], it remains unclear whether the historical advantages of SPKT over KTA persist in real-world practice. Importantly, while survival and graft outcomes are critical endpoints, the ability of SPKT to provide superior long-term glycaemic control represents a distinctive and clinically meaningful outcome that may translate into downstream benefits for patients. Large-scale real-world data may help clarify these uncertainties. TriNetX, a federated network of healthcare organizations, aggregates longitudinal electronic health records and enables comparative effectiveness research across diverse populations with robust analytic tools, including propensity score methods to mitigate baseline imbalances [45]. The objective of this study was to compare long-term outcomes of SPKT versus KTA in patients with diabetes and ESRD using the TriNetX Global Collaborative Network. We evaluated survival, kidney and pancreas graft outcomes, cardiovascular events, diabetes-related acute and chronic complications, malignancies, and mental health, with a particular focus on

whether the improved glycaemic control achieved by SPKT translates into clinical benefit in the new era of transplantation.

MATERIALS AND METHODS

Data Source and Ethics

We performed a retrospective cohort study using the TriNetX Global Collaborative Network (2010–2024, access date 23 September 2025), which aggregates de-identified EHR data from >150 healthcare organizations worldwide. The network provides demographics, diagnoses, procedures, laboratory values, medications, and vitals. Data are de-identified per HIPAA and GDPR; institutional review board approval and informed consent were not required for analyses of de-identified data.

Study Population

Adults aged 18–59 years with diabetes and end-stage renal disease who underwent either simultaneous pancreas–kidney transplantation (SPKT) or kidney transplantation alone (KTA) were identified by transplant procedure codes. Exclusions: paediatric (<18 years) or older adults (>59 years), living-donor or multi-organ transplants, and records lacking a valid index date. The unmatched cohorts comprised 3,679 SPKT and 27,062 KTA recipients.

Exposure, Index Event and Follow-Up

The exposure was transplant type (SPKT vs. KTA). The index event was the date of transplantation. For survival analyses (Kaplan–Meier and Cox regression), outcomes were assessed from 90 days post-transplant. For fixed-timepoint estimates, 1-year outcomes were calculated including events from day 10 post-transplant, while 5- and 10-year outcomes were calculated including events from day 90 onwards.

Outcomes

Primary outcomes were (i) all-cause mortality, (ii) kidney graft failure, and (iii) death-censored graft failure. Secondary outcomes included: major adverse kidney events (MAKE: dialysis dependence, eGFR <15 mL/min/1.73 m^2, transplant complications, or graft failure), transplant-related complications (ICD-10 T86.x), cardiovascular events (composite and components: acute myocardial infarction, stroke, heart failure, cardiac arrest, revascularization), infections/sepsis, treated acute rejection, 1-year hospital readmission, metabolic complications (hypoglycaemia; ketoacidosis/hyperosmolarity), microvascular complications (new-onset neuropathy; retinopathy), mental health (post-transplant depression/anxiety), and oncologic outcomes (PTLD/other neoplasms). Laboratory endpoints were most recent HbA1c and eGFR.

Detailed definitions of all outcomes, including the exact ICD-10 and procedure code lists used to define exposures, comorbidities and endpoints (e.g., cardiovascular events, rejection, infection, neuropathy), are provided in the Supplementary Methods. These definitions were pre-specified before any outcome analyses.

Statistical Analysis

Comparative analyses between cohorts were performed using risk difference, risk ratio, and odds ratio with 95% confidence intervals, as well as Kaplan–Meier curves with log-rank tests and Cox proportional hazards regression. Propensity score matching (1:1 nearest-neighbour with caliper 0.1) was applied to balance baseline demographic, clinical, and laboratory covariates. For all Cox models we assessed the proportional hazards assumption visually and using Schoenfeld residuals; no major violations were detected. Further details on cohort definitions, index event and time windows, analytic settings, outcome definitions (including ICD, CPT, and laboratory codes), and propensity score methodology are reported in the Supplementary Methods.

RESULT

Baseline Characteristics

A total of 3,679 SPKT and 27,062 KTA recipients were identified. Before matching, SPKT recipients were younger, more often type 1 diabetic, and carried fewer cardiovascular comorbidities, whereas KTA recipients were more frequently of Black or Hispanic ethnicity and more commonly had ischemic heart disease, heart failure, dyslipidaemia, and obesity (**Supplementary Table S1**). After 1:1 propensity score matching, well-balanced pairs were generated with excellent covariate balance (all SMD <0.1; **Supplementary Table S1**; **Supplementary Figures S1–S2**). Median follow-up was ~6 years in both groups. At the most recent assessment, HbA1c values were lower in SPKT compared with KTA recipients, both before matching (6.23% ± 1.68% vs. 7.11% ± 1.77%; $p < 0.0001$) and after matching (6.23% ± 1.68% vs. 6.58% ± 1.78%; $p < 0.0001$), although the difference was attenuated after adjustment. A similar pattern was seen for kidney function: eGFR was higher among SPKT recipients before matching (48.5 ± 29.3 vs. 44.1 ± 28.8 mL/min/1.73 m^2; $p < 0.0001$), with only a modest residual difference after matching (48.5 ± 29.3 vs. 46.7 ± 29.0 mL/min/1.73 m^2; $p = 0.013$).

Primary Outcomes

In the unmatched cohorts, SPKT recipients experienced significantly lower mortality compared with KTA, with hazard ratios well below unity and consistently favourable risk estimates at both 5 and 10 years (**Table 1**; **Supplementary Tables S3–S4**). Kaplan–Meier curves confirmed superior survival in SPKT (**Figure 1**). After propensity score matching, however, survival probabilities became virtually identical, and the risk of death did not differ between groups across all time points (**Supplementary Tables S3–S4**). Unadjusted Kaplan–Meier analysis suggested a modest advantage for SPKT, with lower cumulative incidence of graft loss over time (**Table 1**; **Figure 1**). However, risk estimates at 5 and 10 years indicated only minimal differences between groups, with relative risks close to unity (**Supplementary Tables S3, S4**). After propensity score matching, graft outcomes were fully comparable, with no

TABLE 1 | Longitudinal outcomes (Kaplan–Meier and Cox models): SPKT vs. KTA.

Outcome	Cohort	Hazard ratio (95% CI)	KM log-rank p	Direction
All-cause mortality	PS-matched	1.00 (0.91–1.11)	0.97	Neutral
	Pre-matching	0.76 (0.71–0.83)	<0.001	Favors SPKT
Kidney graft failure	PS-matched	0.97 (0.91–1.04)	0.38	Neutral
	Pre-matching	0.92 (0.87–0.97)	0.001	Favors SPKT
Death-censored graft failure	PS-matched	0.99 (0.92–1.07)	0.79	Neutral
	Pre-matching	1.05 (0.99–1.11)	0.11	Neutral
MAKE	PS-matched	0.96 (0.91–1.01)	0.10	Neutral
	Pre-matching	0.82 (0.79–0.85)	<0.001	Favors SPKT
Post-transplant cardiovascular events	PS-matched	0.98 (0.91–1.05)	0.55	Neutral
	Pre-matching	0.73 (0.69–0.77)	<0.001	Favors SPKT
Treated acute rejection	PS-matched	1.02 (0.95–1.11)	0.57	Neutral
	Pre-matching	1.16 (1.09–1.23)	<0.001	Favors KTA
Acute myocardial infarction (first event)	PS-matched	1.09 (0.94–1.25)	0.26	Neutral
	Pre-matching	0.89 (0.80–0.99)	0.04	Favors SPKT
Heart failure (first event)	PS-matched	0.94 (0.84–1.05)	0.25	Neutral
	Pre-matching	0.70 (0.64–0.76)	<0.001	Favors SPKT
Stroke (first event)	PS-matched	1.05 (0.87–1.25)	0.63	Neutral
	Pre-matching	0.87 (0.76–1.00)	0.05	Favors SPKT
Infection or sepsis	PS-matched	1.00 (0.92–1.08)	0.98	Neutral
	Pre-matching	0.87 (0.82–0.93)	<0.001	Favors SPKT
Hypoglycaemia	PS-matched	1.00 (0.89–1.12)	0.93	Neutral
	Pre-matching	0.89 (0.81–0.97)	0.01	Favors SPKT
Ketoacidosis/hyperosmolarity	PS-matched	0.95 (0.83–1.09)	0.50	Neutral
	Pre-matching	1.20 (1.08–1.33)	0.001	Favors KTA
Depression/Anxiety onset post-Tx	PS-matched	0.99 (0.89–1.11)	0.87	Neutral
	Pre-matching	1.07 (0.98–1.16)	0.13	Neutral
Diabetic neuropathy (new onset)	PS-matched	1.11 (0.99–1.24)	0.06	Neutral
	Pre-matching	1.04 (0.96–1.14)	0.31	Neutral
Diabetic retinopathy (new onset)	PS-matched	1.06 (0.93–1.20)	0.38	Neutral
	Pre-matching	1.11 (1.00–1.22)	0.04	Favors KTA
PTLD/Neoplasm	PS-matched	1.01 (0.92–1.11)	0.87	Neutral
	Pre-matching	0.95 (0.88–1.01)	0.11	Neutral

Abbreviations. SPKT, simultaneous pancreas–kidney transplant; KTA, kidney transplant alone; KM, Kaplan–Meier; HR, hazard ratio; CI, confidence interval; PS-matched, propensity-score matched; MAKE, major adverse kidney events; PTLD, post-transplant lymphoproliferative disorder.

evidence of a significant difference at any time point (**Supplementary Tables S3, S4**). In contrast, death-censored analyses showed less favourable outcomes for SPKT. In the unmatched population, the risk of death-censored graft failure was slightly higher in SPKT, particularly in the early post-transplant period, with relative risks favouring KTA (**Supplementary Tables S3, S4**). Kaplan–Meier curves showed largely overlapping trajectories (**Figure 1**). After matching, the differences disappeared, with similar risks of death-censored graft loss between groups (**Table 1**; **Supplementary Tables S3, S4**).

Secondary Outcomes

A consistent pattern was observed across early peri-transplant endpoints. In the unmatched cohorts, SPKT recipients had higher rates of treated acute rejection, kidney transplant–related complications, and hospital readmission within the first year, all favouring KTA (**Supplementary Tables S2–S4**). After propensity score matching, the excess risk of acute rejection was no longer significant, whereas kidney transplant complications remained more frequent in SPKT, though with reduced effect sizes (**Supplementary Tables S3-S4**). Conversely, major adverse kidney events (MAKE) consistently favoured SPKT before adjustment, with hazard ratios and relative risks below unity across all time horizons (**Table 1**; **Supplementary Tables S2–S4**). After propensity score matching, however, this advantage was limited to the first post-transplant year, with neutral risks thereafter (**Supplementary Table S2**). In the unmatched cohorts, SPKT recipients showed lower risks of post-transplant cardiovascular events, with the advantage predominantly driven by a reduced incidence of heart failure (**Table 1**; **Supplementary Tables S3–S4**). Myocardial infarction and stroke occurred less frequently in SPKT as well, but the effect size was smaller. Kaplan–Meier analyses confirmed fewer cumulative cardiovascular events in SPKT, largely attributable to the divergence in heart failure risk (**Figure 1**). After propensity score matching, however, all differences were attenuated, and risks for the composite endpoint as well as for myocardial infarction, stroke, and heart failure became comparable between SPKT and KTA (**Supplementary Tables S2–S4**). In the unmatched cohorts, the profile of diabetes-related events was mixed. Diabetic ketoacidosis and hyperosmolar states were more frequent in

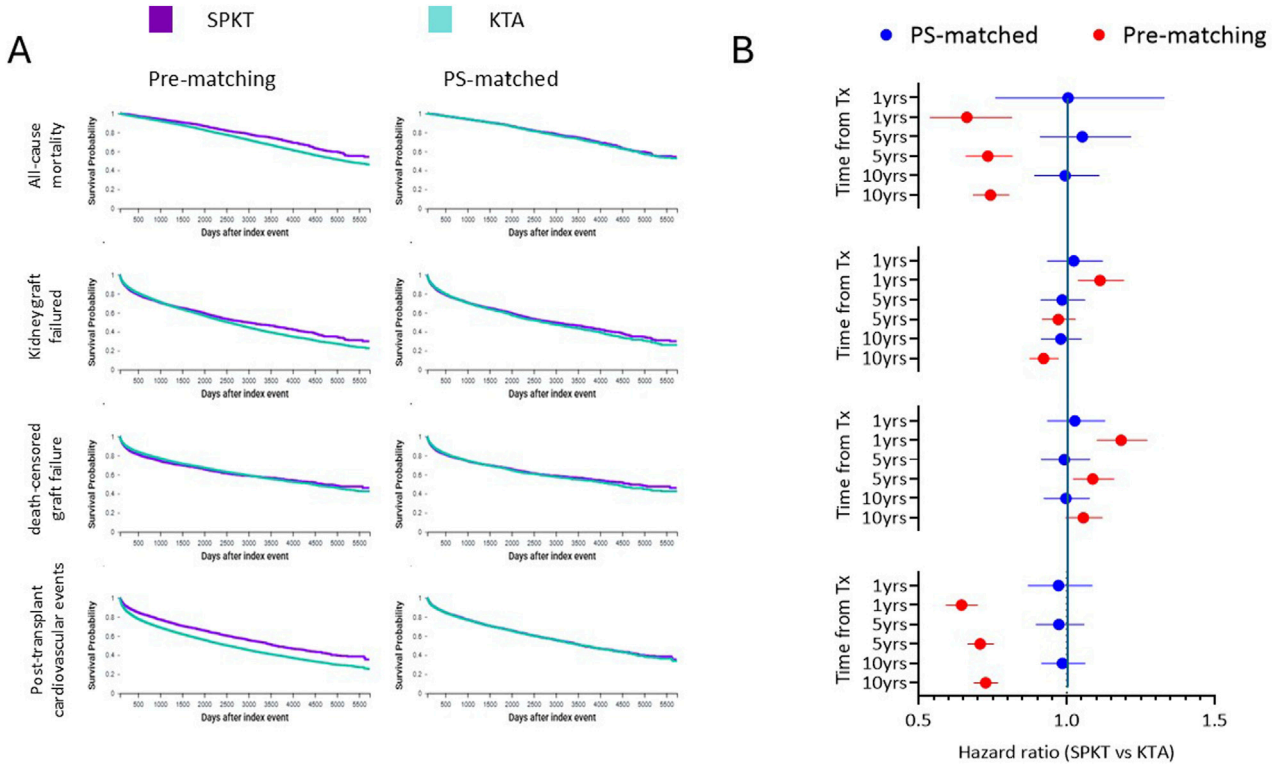


FIGURE 1 | Kaplan–Meier survival curves and hazard ratios for SPKT versus KTA. **(A)** Kaplan–Meier estimates are shown for patient survival, overall graft survival, death-censored graft survival, and cardiovascular outcomes (major adverse cardiovascular events, myocardial infarction, stroke, and heart failure), comparing simultaneous pancreas–kidney transplantation (SPKT, purple) and kidney transplant alone (KTA, light blue). Curves are presented for unmatched cohorts (left column) and after 1:1 propensity score matching (right column). Follow-up extended up to 10 years. **(B)** The forest plot summarizes hazard ratios (HR, dots) with 95% confidence intervals (bars) for each outcome, calculated at prespecified timepoints (1, 5, and 10 years) in unmatched (red) and matched (blue) populations. HR values <1 indicate lower risk with SPKT, whereas HR values >1 indicate lower risk with KTA.

SPKT, with relative risks favouring KTA (**Supplementary Tables S3–S4**). By contrast, severe hypoglycaemia occurred less often in SPKT, indicating a modest advantage for SPKT in this acute complication (**Supplementary Tables S3–S4**). For chronic complications, new-onset diabetic neuropathy and retinopathy were more frequent in SPKT, with risk estimates favouring KTA (**Supplementary Tables S3–S4**). After propensity score matching, however, all these differences were attenuated, and risks of acute decompensation, hypoglycaemia, neuropathy, and retinopathy became largely comparable between groups (**Supplementary Tables S2–S4**). Patterns of infection and sepsis varied according to the time horizon. In the unmatched cohorts, Kaplan–Meier estimates suggested slightly lower cumulative infection risk in SPKT over long-term follow-up (**Supplementary Tables S3, S4**). In contrast, early events within the first year were more common in SPKT, favouring KTA. After propensity score matching, the survival curves became largely overlapping, but the excess of early infections in SPKT persisted, while long-term risks converged toward neutrality (**Supplementary Table S2**). The incidence of post-transplant lymphoproliferative disease and other neoplasms was consistently similar between SPKT and KTA, both before and after adjustment (**Supplementary Tables S3, S4**). As a proxy of quality of life, new-onset depression or anxiety was slightly less frequent in KTA before matching, but this apparent difference was not confirmed after adjustment. In the matched cohorts, risks were virtually identical (Neutral; **Supplementary Tables S2–S4**).

Sensitivity Analyses

To assess the robustness of our findings, we repeated all analyses in two restricted subgroups: (i) recipients with a primary diagnosis of type 1 diabetes (**Supplementary Table S5**), and (ii) type 1 diabetes recipients with a body mass index <30 kg/m^2 at the time of transplantation (**Supplementary Table S6**). Across both sensitivity analyses, the direction and magnitude of risk estimates were consistent with those observed in the overall study population.

DISCUSSION

In this large, real-world analysis, SPKT recipients achieved consistently better glycaemic control than KTA recipients, as reflected by lower HbA1c levels both before and after

propensity score matching. Despite this clear metabolic advantage, long-term patient survival, kidney graft survival, and cardiovascular outcomes were indistinguishable between SPKT and KTA once baseline differences were accounted for. The initial signals of improved survival and reduced cardiovascular risk in the unmatched cohorts were largely attributable to selection bias, with SPKT recipients being younger, predominantly affected by type 1 diabetes, and carrying fewer comorbidities at baseline. Importantly, SPKT was associated with higher early risks—including treated acute rejection, hospital readmission, perioperative complications, and infection/sepsis within the first post-transplant year. These excess short-term risks did not translate into inferior long-term outcomes. The only remaining clinical difference was a modest reduction in MAKE during the first post-transplant year, suggesting a possible short-term renoprotective effect of improved glycaemic control, although without sustained long-term impact on major endpoints. Our findings differ from the earliest registry-based and single-centre reports, which consistently suggested a survival and cardiovascular advantage of SPKT over KTA [46–49] particularly among younger recipients with type 1 diabetes [7, 21, 47, 49–51]. However, they align more closely with subsequent analyses that applied more comprehensive multivariable adjustment or propensity-based methods and reported attenuation or disappearance of these differences [25, 52, 53]. This pattern supports the interpretation that much of the apparent survival benefit of SPKT in historical cohorts may have reflected differences in recipient selection, donor quality, and the clinical context of earlier eras.

A notable result from our study is the persistently lower HbA1c observed in SPKT recipients after matching, despite the relatively small absolute difference (6.2% vs. 6.6%). Based on landmark trials such as DCCT/EDIC [54] and UKPDS [54], a 1% reduction in HbA1c corresponds to a 15%–20% reduction in microvascular risk and a 10%–15% reduction in cardiovascular events. Accordingly, the 0.3%–0.4% difference in our study would be expected to confer only a 4%–6% reduction in microvascular risk and a 3%–5% reduction in cardiovascular risk—an effect size insufficient to produce detectable long-term differences in survival or major cardiovascular outcomes in heterogeneous, real-world cohorts. This helps explain why improved glycaemic control after SPKT, while clinically relevant, did not translate into measurable survival advantages at a population level. These short-term risks associated with SPKT—including perioperative morbidity, treated rejection, infections, and early hospital readmissions—are well documented [31, 32, 36, 55, 56] and represent a recognised trade-off against the metabolic benefits. Furthermore, the therapeutic landscape has evolved substantially. Advances in continuous glucose monitoring, automated insulin delivery systems, and the availability of new agents such as SGLT2 inhibitors and GLP-1 receptor agonists have markedly improved glycaemic profiles and cardiovascular risk in patients with diabetes after kidney transplantation. These innovations have likely narrowed the incremental advantage of SPKT over KTA, further contextualising our findings of long-term similarity in hard outcomes.

This finding warrants further clinical interpretation. In SPKT recipients, an HbA1c in the low-to-mid 6% range reflects physiological insulin secretion, typically associated with minimal risk of severe hypoglycaemia and lower glycaemic variability. In contrast, similar HbA1c values in insulin-treated KTA recipients may mask substantial hypoglycaemia burden, glycaemic fluctuations, and the cognitive and emotional load of intensive insulin management. Because our dataset did not include continuous glucose monitoring metrics—such as time-in-range, glucose excursion indices, or asymptomatic hypoglycaemia—the true metabolic benefit of SPKT is likely underestimated. These considerations reinforce that the metabolic advantage of SPKT remains clinically meaningful even in the absence of detectable long-term survival differences. Our findings should also be interpreted in the context of prior evidence, which for decades has consistently shown a survival advantage of SPKT over KTA. Several factors likely explain why our real-world findings differ from these earlier observations. First, historical cohorts reflect an era of higher dialysis mortality and less effective diabetes and cardiovascular management. Second, donor and recipient selection practices have evolved: SPKT recipients typically receive younger, lower-risk organs and enter transplantation earlier in the course of diabetic complications, whereas KTA recipients accumulate greater comorbidity and longer pre-transplant dialysis exposure. These factors likely amplified earlier survival signals. Third, improvements in perioperative care, modern immunosuppression, and cardiovascular therapy have narrowed the survival gap. Finally, because our dataset lacked key transplant-specific variables—such as donor quality indices, HLA matching, cold ischaemia time, and immunosuppression—an intrinsic survival benefit of SPKT cannot be excluded and may be masked by unmeasured confounding. Together, these considerations reconcile our findings with the broader literature and suggest that, in current practice, the dominant advantage of SPKT lies in its metabolic and quality-of-life benefits rather than in large differences in long-term survival.

This study has several important limitations First, despite rigorous propensity score matching, residual confounding is unavoidable because the TriNetX platform lacks key transplant-specific variables. Donor quality metrics such as Kidney Donor Profile Index (KDPI) and Pancreas Donor Risk Index (PDRI), which strongly influence kidney outcomes and differ systematically between SPKT and KTA, were not available. Similarly, no information was provided on HLA matching, panel reactive antibodies, donor-specific antibodies, cold ischaemia time, centre experience or detailed immunosuppression protocols. These unmeasured factors may attenuate or obscure a true intrinsic survival benefit of SPKT or, conversely, magnify early procedural risk. Second, exposures, comorbidities and outcomes were identified using ICD-10 and procedure codes. The complete lists of codes used in this study are provided in the Supplementary Methods. Although these coding-based definitions follow established conventions, they remain prone to misclassification, under-reporting and variability across institutions—particularly for complex outcomes such as cardiovascular events, rejection, infection or neuropathy, for which clinical adjudication would be preferable. Third, the

database does not capture patient-reported outcomes, continuous glucose monitoring metrics or hypoglycaemia burden—elements that represent the most meaningful clinical benefits of SPKT for many patients [57, 58]. As a result, the metabolic advantage observed in this study likely underestimates the full quality-of-life impact of successful pancreas transplantation [59, 60]. Fourth, diabetes type was defined using diagnosis codes, which may misclassify insulin-treated type 2 diabetes as type 1. Although sensitivity analyses restricted to patients coded as type 1 diabetes and to non-obese recipients were performed, some residual misclassification may persist. Finally, because SPKT by definition requires a deceased donor, our comparison group included only deceased-donor KTA recipients. These findings cannot be extrapolated to living-donor kidney transplantation, which often provides superior survival and represents a distinct clinical pathway.

Taken together, these limitations suggest that while our findings demonstrate no detectable long-term survival advantage of SPKT after adjustment for measured variables, a modest true benefit cannot be excluded. Rather, our results underscore the extent to which survival outcomes are shaped by patient selection, donor quality, and centre-level variation. In this context, the principal justification for SPKT in contemporary practice lies in its profound metabolic and quality-of-life benefits, balanced against higher early procedural risks.

In summary, this large, contemporary real-world analysis shows that the apparent survival advantage of SPKT over KTA disappears after balancing for measurable clinical covariates. Because donor quality and other key transplant-specific factors were not captured, a residual survival benefit cannot be excluded. Nevertheless, SPKT provides durable metabolic benefits, including excellent glycaemic control and freedom from insulin. In the setting of comparable observed survival, decisions about SPKT should be individualised, considering each patient's preference for insulin independence, glycaemic stability, and quality-of-life improvement, as well as willingness to accept higher short-term risks. These findings also highlight a broader issue: despite clear metabolic and quality-of-life benefits, SPKT remains underutilised, and many eligible patients are not systematically referred to transplant centres. Variability in referral pathways, limited awareness among non-transplant clinicians, and the absence of structured evaluation frameworks likely prevent equitable access. In light of our results—showing that the decision for SPKT increasingly centres on metabolic benefit and patient preference—timely and systematic referral becomes critical. Strengthening referral pathways and enhancing collaboration between diabetologists, nephrologists, and transplant teams will be essential to ensure that all suitable candidates are appropriately evaluated.

DATA AVAILABILITY STATEMENT

Individual participant data will not be made available. Study protocol, statistical analysis plan, and analytical code will be available from the time of publication in response to any reasonable request addressed to the corresponding author.

ETHICS STATEMENT

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LP conceived and supervised the study, had full access to all data, and takes responsibility for the integrity and accuracy of the analyses. DC and LP performed the data extraction and statistical analyses. FR, SW, RC, and DC contributed to study design, data interpretation, and manuscript drafting. All authors contributed to the conception, critical revision, and final approval of the manuscript, and agree to be accountable for all aspects of the work.

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FR and SW were employed by TriNetX at the time of the study.

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GENERATIVE AI STATEMENT

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

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.15709/full#supplementary-material

SUPPLEMENTARY FIGURE S1 | Standardized mean differences (SMD) for baseline characteristics between SPKT and KTA recipients before (red circles) and after propensity score matching (blue squares). Variables include demographics, comorbidities, and diabetes type. Dashed vertical lines at ±0.1 indicate the threshold for acceptable balance. Matching achieved excellent covariate balance across all variables, with all post-matching SMDs <0.1.

SUPPLEMENTARY FIGURE S2 | Distribution of propensity scores, follow-up time, HbA1c, and eGFR before and after matching. The figure displays cumulative distribution curves of propensity scores (top panels), histograms of follow-up time (middle panels), and histograms of last available laboratory values for HbA1c (bottom left) and eGFR (bottom right) in SPKT and KTA recipients, shown separately for unmatched and propensity score–matched cohorts.

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ORIGINAL RESEARCH
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Reassessing Simultaneous Pancreas-Kidney Vs. Kidney Transplant Alone: A Propensity-Weighted Analysis of Survival and Morbidity

Pooja Budhiraja[1]*, *Rocio Lopez*[2,3†], *Susana Arrigain*[2,3] and *Jesse D. Schold*[2,3†]

[1]Department of Medicine, Mayo Clinic Arizona, Phoenix, AZ, United States, [2]Department of Surgery, University of Colorado Anschutz Medical Campus, Aurora, CO, United States, [3]Department of Epidemiology, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

This study compares outcomes between Simultaneous Pancreas-Kidney Transplantation (SPKT) and Deceased Donor Kidney Transplantation (DDKT) in recipients with diabetes, assessing survival benefits against surgical and immunological risks. We analyzed Scientific Registry of Transplant Recipients data (2014–2023) to assess patient and kidney graft survival. Overlap propensity score weighting was applied to adjust for group differences. Kaplan-Meier and Cox proportional hazards models were used to estimate survival outcomes in unadjusted, covariate-adjusted, and weighted analyses. Among 22,545 recipients with diabetes (25% SPKT), those receiving SPKT were younger (41 vs. 52 years), predominantly non-Hispanic white, had type 1 diabetes, lower BMI, shorter dialysis duration, and higher preemptive transplant rates (all $p < 0.001$). Overlap-weighted (ow) analyses showed no significant differences in 5- and 10-year patient (SPKT: 86%, 71%; DDKT: 87%, 74%) and kidney graft survival (SPKT: 80%, 66%; DDKT: 83%, 62%). SPKT recipients with graft survival at 1 year experienced higher 1-year treated acute rejection (owOR: 2.80, 95% CI: 1.75–4.49) and hospital readmissions (owOR: 2.05, 95% CI: 1.62–2.60). However, among recipients with type 1 diabetes and BMI <30, SPKT was associated with lower mortality compared to DDKT. After adjustment for selection bias, SPKT did not improve long-term survival compared to DDKT and was associated with greater early morbidity.

Keywords: allocation system, SPKT, DDKT, patient survival, allograf survival

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***Correspondence**
Pooja Budhiraja,
budhiraja.pooja@mayo.edu

†ORCID:
Rocio Lopez
orcid.org/0000-0002-4319-420X
Jesse D. Schold
orcid.org/0000-0002-5341-7286

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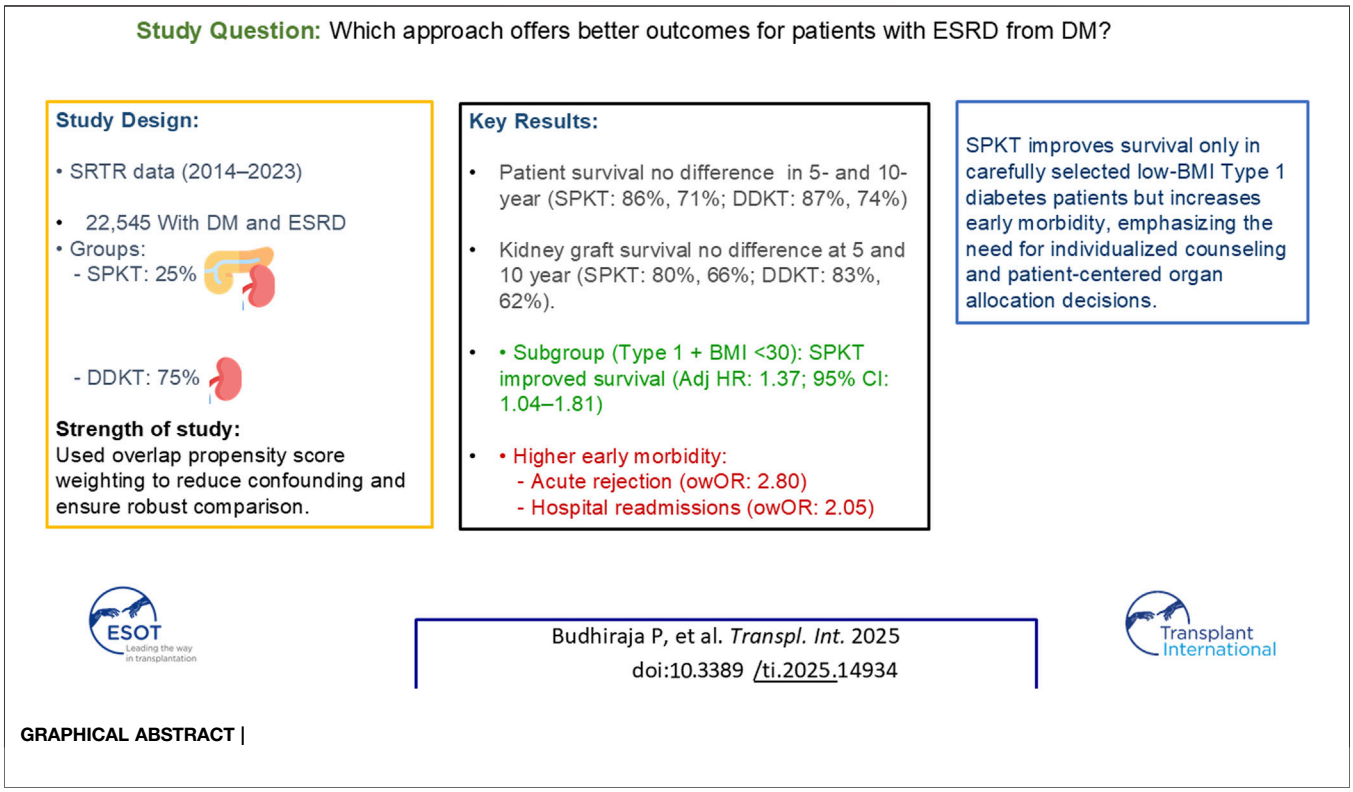
Abbreviations: BMI, Body mass index; CI, Confidence Interval; CMV, Cytomegalovirus; DDKT, Deceased Donor Kidney Transplant; HCV, Hepatitis C virus; HR, Hazard ratio; HRSA, Health Resources and Services Administration; KDPI, Kidney Donor Profile Index; OPTN, Organ Procurement and Transplantation Network; OR, Odds ratio; SPKT, Simultaneous Pancreas-Kidney Transplantation.



GRAPHICAL ABSTRACT |

INTRODUCTION

Kidney transplantation is a standard therapeutic intervention for chronic and end-stage renal disease (ESRD). In select patients with diabetes and kidney failure, a simultaneous pancreas and kidney transplant (SPKT) also restores euglycemia. It normalizes glycosylated hemoglobin levels, further improving quality of life and reducing diabetic complications in this select recipient candidate population [1–3].

Despite its many benefits, SPKT carries notable challenges, including a 5%–10% increased risk of early pancreas graft loss, higher early postoperative complications, a greater rate of early hospital readmissions, and a higher incidence of combined graft rejection compared to kidney-alone transplants [4].

Previous studies comparing SPKT with Deceased Donor Kidney Transplantation (DDKT) have suggested potential survival and metabolic advantages of SPKT, particularly among recipient with type 1 diabetes. SPKT is associated with a lower incidence of major adverse cardiovascular events, enhanced left ventricular function, and improved metabolic control associated with euglycemia, which are critical for patients with diabetes and end-stage renal disease [5–7]. Recent literature highlights the protective effects of SPKT on cardiac function and vascular health, likely due to the restoration of insulin production and improved glycemic control [8, 9]. Furthermore, SPKT recipients experience improved quality of life metrics and metabolic control, which help delay or reverse diabetic complications and improve long-term survival [5–7]. Additionally, there is growing consideration for expanding SPKT criteria to patients with type 2 diabetes, reflecting evolving clinical practice trends [10].

Despite these benefits, SPKT is associated with higher surgical morbidity, increased early complications, and higher acute rejection rates. Survival rates in successful SPKT recipients are reportedly higher when the pancreas functions effectively, yet the trade-off between risk and benefit remains debatable [11, 12].

Previous studies assessing outcomes after SPKT primarily evaluated highly selected cohorts, specifically patients with type 1 or type 2 diabetes, separately, highlighting significant survival benefits associated with early pancreas graft function. However, such analyses did not fully account for critical donor and recipient selection biases or incorporate comprehensive adjustments for minimal overlap scenarios between SPKT and DDKT cohorts [1]. Moreover, most earlier studies did not robustly quantify surgical morbidity, including acute rejection rates and hospital readmissions, which may have led to an incomplete picture of overall clinical benefits.

The comparative benefits of SPKT versus DDKT remain challenging to assess due to inherent differences in recipient selection practices, variability in donor organ quality, and the trade-offs between surgical and immunological risks versus potential metabolic improvements and quality-of-life gains from pancreas transplantation. Our study uniquely addresses these critical gaps by employing advanced overlap propensity score weighting techniques designed to mitigate selection bias across a broader recipient cohort with diabetes, rigorously

evaluating multiple outcome measures beyond pancreas graft function alone and reflecting contemporary surgical practices and immunosuppression protocols. By precisely matching SPKT and DDKT recipients on critical donor and recipient characteristics, we provide a more accurate comparative assessment of the true benefits and risks associated with SPKT.

Assessing the risks versus benefits of SPKT is essential for informed patient counseling. It weighs surgical risks against metabolic control and quality of life, helping patients choose between SPKT and DDKT. This study aims to illuminate these considerations, thereby improving patient guidance and optimizing organ allocation policies to maximize the advantages of these critical transplants.

MATERIALS AND METHODS

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. We used the September 2024 standard analysis files to identify subjects who received kidney or simultaneous kidney-pancreas transplantation between 1 January 2014, and 30 November 2023. The following exclusions were applied: recipients younger than 18 or older than 59 years at time of transplant, non-diabetic recipient, primary diagnosis other than diabetes, prior kidney or pancreas transplant, multi-organ transplant other than kidney-pancreas, living donor, en-bloc or sequential kidney transplant, donor younger than 18 or older than 59 (**Supplementary Figure S1**).

Our primary outcomes were time to kidney allograft failure and patient death. We defined kidney allograft survival time as the number of months from transplantation to irreversible graft failure, indicated by a return to dialysis, kidney re-transplantation, or patient death [13]. We censored at the earliest of the recipient censoring cohort date or the last graft follow-up date. For our cohort, we defined patient survival as the number of months from transplantation until death or the recipient censoring cohort date, which was 1 June 2024. We truncated follow-up at 10 years.

Secondary outcomes included risk for treated acute kidney graft rejection either prior to discharge or during the first year post-transplant. Rejection events reflect treated acute kidney rejection. Biopsy confirmation is not consistently performed or coded across centers in the registry, so we relied on treatment-based indicators. Therefore, we chose to use acute treated kidney rejection as a practical alternative. While this may slightly overstate rejection incidence, treated episodes are likely to reflect clinically significant cases, minimizing overestimation.

We also assessed hospital readmission during the first year post-transplant. To ensure equal time risk when examining outcomes in the first-year post-transplant, we restricted the analysis to the subset of subjects with a 1-year post-transplant follow-up form who had not experienced graft loss within the first post-transplant year. Additionally, we examined 90-day pancreas graft failure among the SKPT group, defined as the number of days from transplantation to irreversible graft failure, as indicated by documented graft failure, pancreas re-transplantation, or death. Additionally, we calculated the Pancreas Donor Risk Index (PDRI) using the formula presented by Axelrod et al. [14].

We calculated the Kidney Donor Profile Index (KDPI) using the 2014 reference values, as this was the midpoint of our cohort [15].

Data were missing for the following variables: education (1.4%), donor history of hypertension (1.2%), donor history of diabetes (1.1%), KDPI (0.74%), BMI (0.72%), donor eGFR (0.71%), cold ischemia time (0.49%), donor BMI (0.29%), dialysis duration at transplant (0.16%), peak cPRA (0.13%), pancreas procedure type (0.04%), donor race/ethnicity (0.02%), and primary insurance (0.009%).

Continuous variables were summarized using means and standard deviations (SD), and categorical factors were summarized using frequencies and percentages. We used t-tests and Pearson's chi-square tests to compare continuous and categorical variables between the DDKT and SPKT groups. Post-transplant length of stay was summarized with median, 25th, and 75th percentiles and compared with Wilcoxon rank sum tests due to its skewed distribution.

We used multivariate imputation by chained equations to impute 5 datasets with complete data. The multiple imputation included the following characteristics: age, sex, race/ethnicity, BMI, education, insurance, dialysis duration, insurance, diabetes type, time of on the waitlist, dialysis duration, cPRA, cold ischemia time, donor sex, donor age, donor race/ethnicity, donor BMI, donor history of diabetes, donor history of hypertension, KDPI, deceased donor type, donor cause of death, transplant type, kidney transplant type, graft loss, and graft survival time. All models were fitted on each of the 5 imputed datasets, and parameter estimates were combined.

We utilized overlap propensity score weighting to address potential confounding factors arising from the significant differences in recipient and donor characteristics between DDKT and SPKT. To estimate the propensity score for receiving a SPKT, we employed a multivariable logistic regression model that included recipient age, sex, race/ethnicity, BMI, education, insurance, dialysis duration, diabetes type, blood type, time of on the waitlist, cPRA, cold ischemia time, left vs. right kidney transplant, donor sex, donor age, donor race/ethnicity, donor BMI, donor history of diabetes, donor history of hypertension, donor blood type, KDPI, deceased donor type (DBD vs. DCD), donor cause of death, and transplant year. **Supplementary Figure S2** illustrates the distributions of propensity scores based on transplant type. The overlap propensity score weighting method assigns each patient's weight based on the probability of that patient receiving the alternative transplant type [16] and has been shown to outperform inverse probability of treatment weighting (IPTW) in cases of minimal overlap [17].

TABLE 1 | Recipient and procedure characteristics by transplant type.

Factor	Overall (N = 22,545)		DDKT (N = 16,793)		SPKT (N = 5,752)		p-value
	N missing	Statistics	N missing	Statistics	N missing	Statistics	
Age at transplant (years)	0	48.2 ± 8.4	0	50.4 ± 7.0	0	41.6 ± 8.6	*<0.001*[a]
Age at transplant (years)	0		0		0		***<0.001***[c]
18–39		4,058 (18.0)		1,530 (9.1)		2,528 (43.9)	
40–49		6,782 (30.1)		4,793 (28.5)		1,989 (34.6)	
50–59		11,705 (51.9)		10,470 (62.3)		1,235 (21.5)	
Sex	0		0		0		***<0.001***[c]
Female		8,077 (35.8)		5,847 (34.8)		2,230 (38.8)	
Male		14,468 (64.2)		10,946 (65.2)		3,522 (61.2)	
Race/ethnicity	0		0		0		***<0.001***[c]
Non-hispanic white		6,639 (29.4)		3,870 (23.0)		2,769 (48.1)	
Non-hispanic black		8,500 (37.7)		6,793 (40.5)		1,707 (29.7)	
Non-hispanic other and Multi-racial		1,992 (8.8)		1,711 (10.2)		281 (4.9)	
Hispanic		5,414 (24.0)		4,419 (26.3)		995 (17.3)	
Education	312		216		96		***<0.001***[c]
High school or less		11,102 (49.9)		8,711 (52.5)		2,391 (42.3)	
Some college		6,321 (28.4)		4,552 (27.5)		1,769 (31.3)	
College or more		4,810 (21.6)		3,314 (20.0)		1,496 (26.4)	
Primary insurance	2		0		2		***<0.001***[c]
Private		5,662 (25.1)		3,387 (20.2)		2,275 (39.6)	
Medicare		14,886 (66.0)		11,925 (71.0)		2,961 (51.5)	
Medicaid		1,587 (7.0)		1,146 (6.8)		441 (7.7)	
Other		408 (1.8)		335 (2.0)		73 (1.3)	
BMI	163	29.5 ± 5.4	140	30.8 ± 5.2	23	25.8 ± 4.0	***<0.001***[a]
BMI	163		140		23		***<0.001***[c]
<18.5		172 (0.77)		71 (0.43)		101 (1.8)	
18.5–24.9		4,784 (21.4)		2,323 (13.9)		2,461 (43.0)	
25–29.9		7,343 (32.8)		5,005 (30.1)		2,338 (40.8)	
30–34.9		6,359 (28.4)		5,591 (33.6)		768 (13.4)	
≥35		3,724 (16.6)		3,663 (22.0)		61 (1.06)	
Diabetes type	0		0		0		***<0.001***[c]
Type I		6,512 (28.9)		1,959 (11.7)		4,553 (79.2)	
Type II		16,033 (71.1)		14,834 (88.3)		1,199 (20.8)	
Blood type	0		0		0		***<0.001***[c]
A		8,016 (35.6)		6,060 (36.1)		1,956 (34.0)	
AB		1,330 (5.9)		1,106 (6.6)		224 (3.9)	
B		3,188 (14.1)		2,476 (14.7)		712 (12.4)	
O		10,011 (44.4)		7,151 (42.6)		2,860 (49.7)	
Dialysis duration at transplant (months)	37		21		16		***<0.001***[c]
Preemptive		1,586 (7.0)		704 (4.2)		882 (15.4)	
>0–11.9		2,307 (10.2)		1,156 (6.9)		1,151 (20.1)	
12–23.9		3,129 (13.9)		1,625 (9.7)		1,504 (26.2)	
24–47.9		5,512 (24.5)		4,059 (24.2)		1,453 (25.3)	
48–71.9		4,767 (21.2)		4,276 (25.5)		491 (8.6)	
≥72		5,207 (23.1)		4,952 (29.5)		255 (4.4)	
Peak cPRA	30		29		1		***<0.001***[c]
0		13,130 (58.3)		9,272 (55.3)		3,858 (67.1)	
1–19		2,604 (11.6)		1,918 (11.4)		686 (11.9)	
20–79		4,250 (18.9)		3,314 (19.8)		936 (16.3)	
80–97		1,528 (6.8)		1,294 (7.7)		234 (4.1)	
97–100		1,003 (4.5)		966 (5.8)		37 (0.64)	
Transplant year	0		0		0		***<0.001***[c]
2014		1,646 (7.3)		1,143 (6.8)		503 (8.7)	
2015		1,593 (7.1)		1,065 (6.3)		528 (9.2)	
2016		1,840 (8.2)		1,283 (7.6)		557 (9.7)	
2017		1,958 (8.7)		1,410 (8.4)		548 (9.5)	
2018		2,096 (9.3)		1,498 (8.9)		598 (10.4)	
2019		2,450 (10.9)		1,805 (10.7)		645 (11.2)	
2020		2,571 (11.4)		1,973 (11.7)		598 (10.4)	
2021		2,800 (12.4)		2,187 (13.0)		613 (10.7)	
2022		2,899 (12.9)		2,294 (13.7)		605 (10.5)	
2023		2,692 (11.9)		2,135 (12.7)		557 (9.7)	

(Continued on following page)

TABLE 1 | (*Continued*) Recipient and procedure characteristics by transplant type.

Factor	Overall (N = 22,545)		DDKT (N = 16,793)		SPKT (N = 5,752)		p-value
	N missing	Statistics	N missing	Statistics	N missing	Statistics	
Kidney procedure type	0		0		0		**<0.001[c]**
Left kidney		12,339 (54.7)		8,082 (48.1)		4,257 (74.0)	
Right kidney		10,206 (45.3)		8,711 (51.9)		1,495 (26.0)	
Time on wait list (months)	0		0		0		**<0.001[c]**
0–5.9		7,969 (35.3)		4,994 (29.7)		2,975 (51.7)	
6–11.9		3,055 (13.6)		1,983 (11.8)		1,072 (18.6)	
12–23.9		3,665 (16.3)		2,643 (15.7)		1,022 (17.8)	
24–47.9		4,206 (18.7)		3,664 (21.8)		542 (9.4)	
≥48		3,650 (16.2)		3,509 (20.9)		141 (2.5)	
Cold ischemia time (hours)	111		48		63		**<0.001[c]**
<6		1,306 (5.8)		586 (3.5)		720 (12.7)	
6–11.9		5,763 (25.7)		2,584 (15.4)		3,179 (55.9)	
12.0–23.9		11,269 (50.2)		9,528 (56.9)		1,741 (30.6)	
≥24.0		4,096 (18.3)		4,047 (24.2)		49 (0.86)	

Statistics presented as Mean ± SD or N (column %).p-values: a = t-test, c = Pearson's chi-square test.
BMI: Body mass index; cPRA: calculated panel reactive antibody; DDKT: deceased donor kidney transplant; SPKT: simultaneous pancreas-kidney transplant.
Bold values denote statistically significant results at the prespecified significance level (P < 0.05).

We plotted unweighted and overlap-weighted Kaplan-Meier estimates to visualize the cumulative rates of kidney allograft failure and patient mortality. Additionally, we employed Cox proportional hazards models to assess three scenarios: 1) the unadjusted association, 2) the covariate-adjusted association (using the same variables as the propensity score model), and 3) the overlap-weighted association between transplant type and the cumulative outcomes of kidney allograft failure and patient mortality. We examined the interaction between transplant type and age group in covariate-adjusted and overlap-weighted models.

We utilized logistic regression to evaluate the association between transplant type and treated acute rejection and hospital readmissions. These models were built under the same three scenarios as the Cox models using the subset of subjects with the 1-year post-transplant follow-up form who had not experienced graft loss within the first post-transplant year. We also calculated the cumulative 90-day pancreas graft survival in the SKPT group and used a log-rank test to evaluate differences by age group.

Lastly, we conducted sensitivity analyses restricted to recipients with Type 1 diabetes to assess the robustness of our findings in a subgroup more closely aligned with SPK listing criteria. We performed two subgroup analyses: 1) recipients with Type 1 diabetes, and 2) recipients with Type 1 diabetes and BMI <30, comparing outcomes for DDKT versus SPKT.

All tests were two-tailed and performed at a significance level of 0.05. Analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

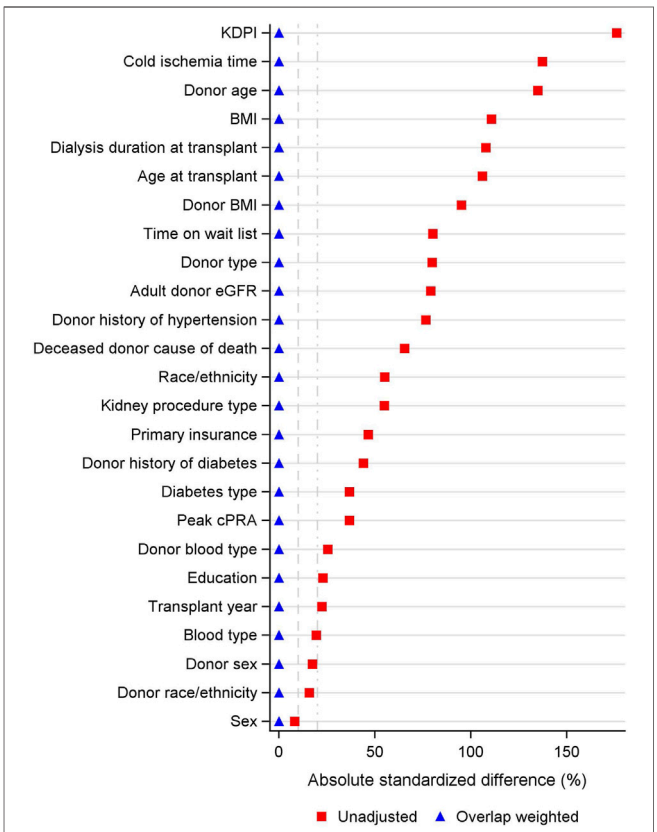


FIGURE 1 | Covariate Balance Across SKPT vs. DDKT. BMI: body mass index; cPRA: calculated panel reactive antibody; eGFR: estimated glomerular filtration rate; KDPI: kidney donor profile index.

RESULTS

This analysis included 22,545 transplant recipients with diabetes, 25% of whom received a SPKT. SPKT recipients were younger than DDKT recipients (mean ± SD: 42 ± 9 vs. 50 ± 7 years, p < 0.001) (**Table 1**). Additionally, a higher percentage of SPKT recipients were female (39% vs. 35%, p = 0.003) and non-Hispanic white (48%

TABLE 2 | Donor characteristics by transplant type.

Factor	Overall (N = 22,545)		DDKT (N = 16,793)		SPKT (N = 5,752)		p-value
	N missing	Statistics	N missing	Statistics	N missing	Statistics	
Donor age (years)	0	37.4 ± 11.6	0	41.0 ± 10.7	0	26.8 ± 6.9	*<0.001*[a]
Donor age (years)	0		0		0		***<0.001***[c]
18–39		12,878 (57.1)		7,418 (44.2)		5,460 (94.9)	
40–49		5,269 (23.4)		5,000 (29.8)		269 (4.7)	
50–59		4,398 (19.5)		4,375 (26.1)		23 (0.40)	
Donor sex	0		0		0		***<0.001***[c]
Female		8,069 (35.8)		6,363 (37.9)		1,706 (29.7)	
Male		14,476 (64.2)		10,430 (62.1)		4,046 (70.3)	
Donor race/ethnicity	5		5		0		***<0.001***[c]
Non-hispanic white		14,630 (64.9)		11,155 (66.4)		3,475 (60.4)	
Non-hispanic black		3,629 (16.1)		2,491 (14.8)		1,138 (19.8)	
Non-hispanic other and Multi-racial		828 (3.7)		639 (3.8)		189 (3.3)	
Hispanic		3,453 (15.3)		2,503 (14.9)		950 (16.5)	
Donor blood type	0		0		0		***<0.001***[c]
A		8,617 (38.2)		6,539 (38.9)		2,078 (36.1)	
AB		902 (4.0)		819 (4.9)		83 (1.4)	
B		2,690 (11.9)		1,970 (11.7)		720 (12.5)	
O		10,336 (45.8)		7,465 (44.5)		2,871 (49.9)	
Donor BMI	65	28.0 ± 6.7	65	29.3 ± 7.1	0	24.2 ± 3.7	*<0.001*[a]
Donor BMI	65		65		0		***<0.001***[c]
<18.5		541 (2.4)		300 (1.8)		241 (4.2)	
18.5–24.9		7,962 (35.4)		4,690 (28.0)		3,272 (56.9)	
25–29.9		7,057 (31.4)		5,173 (30.9)		1,884 (32.8)	
30–34.9		3,831 (17.0)		3,511 (21.0)		320 (5.6)	
≥35		3,089 (13.7)		3,054 (18.3)		35 (0.61)	
Donor history of diabetes	253	1,493 (6.7)	224	1,489 (9.0)	29	4 (0.07)	***<0.001***[c]
Donor history of hypertension	267	5,625 (25.2)	235	5,360 (32.4)	32	265 (4.6)	***<0.001***[c]
Donor eGFR (CKD-EPI 2021)	159		151		8		***<0.001***[c]
120+		5,135 (22.9)		2,610 (15.7)		2,525 (44.0)	
105–119		4,417 (19.7)		3,476 (20.9)		941 (16.4)	
90–104		2,570 (11.5)		1,846 (11.1)		724 (12.6)	
75–89		2,422 (10.8)		1,802 (10.8)		620 (10.8)	
60–74		2,279 (10.2)		1,795 (10.8)		484 (8.4)	
≥60		5,563 (24.9)		5,113 (30.7)		450 (7.8)	
Donor type	0		0		0		***<0.001***[c]
DBD		17,239 (76.5)		11,654 (69.4)		5,585 (97.1)	
DCD		5,306 (23.5)		5,139 (30.6)		167 (2.9)	
Deceased donor cause of death	0		0		0		***<0.001***[c]
Anoxia		10,137 (45.0)		8,164 (48.6)		1,973 (34.3)	
Cerebrovascular/Stroke		4,544 (20.2)		3,973 (23.7)		571 (9.9)	
Head trauma		7,105 (31.5)		4,037 (24.0)		3,068 (53.3)	
Other		759 (3.4)		619 (3.7)		140 (2.4)	
KDPI	166		157		9		***<0.001***[c]
0–19		6,037 (27.0)		1,963 (11.8)		4,074 (70.9)	
20–39		6,888 (30.8)		5,532 (33.3)		1,356 (23.6)	
40–59		5,481 (24.5)		5,198 (31.2)		283 (4.9)	
60–79		3,973 (17.8)		3,943 (23.7)		30 (0.52)	

Statistics presented as Mean ± SD or N (column %). p-values: a = t-test, c = Pearson's chi-square test.

BMI: Body mass index; cPRA: calculated panel reactive antibody; DDKT: deceased donor kidney transplant; eGFR: Estimated glomerular filtration rate; KDPI: kidney donor profile index; SPKT: simultaneous pancreas-kidney transplant.

Bold values denote statistically significant results at the prespecified significance level (P < 0.05).

vs. 23%, p < 0.001). Regarding insurance, 51% of SPKT and 71% of DDKT recipients had Medicare. SPKT recipients had a lower BMI (26 ± 4 vs. 31 ± 5 kg/m^2, p < 0.001) and were more likely to have type 1 diabetes (79% vs. 12%, p < 0.001) than DDKT recipients. SPKT recipients had a higher rate of preemptive transplants (15% vs. 4% in DDKT, p < 0.001), shorter durations of dialysis, and waitlist time (52% vs. 30% in the <5-month category, p < 0.001). Due to the large sample size, many comparisons reached statistical significance. The absolute standard differences between the groups can be seen in **Figure 1**.

The cold ischemia time was shorter for SPKT than DDKT (69% vs. 19% in the <12 h category, p < 0.001). Notably, 74% of SPKT recipients received a left kidney compared to 48% of DDKT recipients.

SPKT donors were younger than DDKT donors (27 ± 7 vs. 41 ± 11 years, p < 0.001) (**Table 2**). Additionally, a higher percentage of

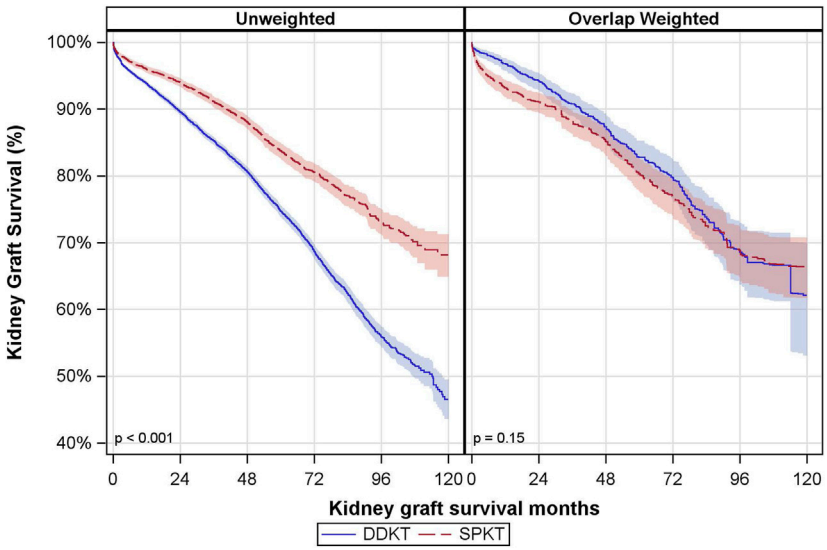


FIGURE 2 | Unadjusted and Overlap Weighted Cumulative Kidney Graft Survival Rates. DDKT: deceased donor kidney transplant; SPKT: simultaneous pancreas-kidney transplant.

TABLE 3 | The association of DDKT vs. SPKT with patient mortality and kidney graft failure.

Model	DDKT vs. SPKT HR (95% CI)	
	Kidney graft failure	Patient mortality
Unadjusted	1.76 (1.63, 1.90)	2.06 (1.88, 2.26)
Covariate-adjusted[a]	1.03 (0.91, 1.17)	1.07 (0.92, 1.24)
Overlap weighted	0.86 (0.66, 1.11)	0.85 (0.64, 1.13)

[a]*Adjusted for recipient sex, age, race/ethnicity, education, insurance, blood type, BMI, dialysis months; cPRA, diabetes type, transplant year, left vs. right kidney transplant, months on wait list, CIT, donor sex, donor age, and KDPI.*
CI: confidence interval; DDKT: deceased donor kidney transplant; HR: hazard ratio; SPKT: simultaneous pancreas-kidney transplant.

SPKT donors were male (70% vs. 62%, p = 0.003) and non-Hispanic Black (20% vs. 15%, p < 0.001). SPKT donors were also less likely to have a history of diabetes or hypertension and had significantly higher eGFR. Additionally, SPKT individuals were more likely to be DBD and had lower KDPI.

The median post-transplant hospital stay was 8 days [P25, P75: 6, 11] for SPKT recipients compared to 5 days [P25, P75: 4, 7] for DDKT recipients (p < 0.001).

Figure 1 illustrates the covariate balance before and after overlap weighting. The propensity score was estimated using logistic regression, allowing overlap weighting to create exact balance on the mean of every measured covariate. **Supplementary Figure S3** displays the relative contribution of each covariate to the propensity score model. Variables with the strongest influence on treatment assignment included recipient blood type, BMI, dialysis duration, and diabetes. Donor characteristics such as blood type, BMI, KDPI, and cold ischemia time were also among the most imbalanced between groups and contributed substantially to the propensity score model to ensure covariate balance, even though they do not directly influence treatment assignment.

Kidney Graft Survival The median follow-up time for kidney graft survival was 36 months (P25, P75: 12, 60 months). There was a notable difference in the unadjusted kidney graft survival between the groups, but this did not remain significant after overlap weighting (**Figure 2**). In the DDKT group, the overlap weighted 5- and 10-year graft survival rates were 83% and 62%, respectively. Compared to the SPKT group, the overlap weighted graft survival rates were 80% at 5 years and 66% at 10 years.

In covariate-adjusted and overlap weighted analyses, there was no significant difference between SPKT vs. DDKT recipients in terms of kidney graft failure (overlap weighted hazard ratio (owHR: 0.86; 95% CI: 0.66, 1.11) (**Table 3**). The interaction between transplant type and age group was not statistically significant. Results were consistent when looking at death-censored kidney graft failure.

Findings remained consistent in the subset of recipients with Type 1 diabetes, both across all BMI ranges and among those with BMI <30 (**Supplementary Table S1**).

Patient Survival

The median follow-up time for patient survival was 46 months (P25, P75: 24, 72 months). There was a notable difference in the unadjusted patient survival between the groups, but this did not remain significant after overlap weighting (**Figure 3**). In the DDKT group, the overlap-weighted 5- and 10-year patient survival rates were 87% and 74%, respectively. Comparatively, the SPKT group had overlap-weighted patient survival rates of 86% at 5 years and 71% at 10 years.

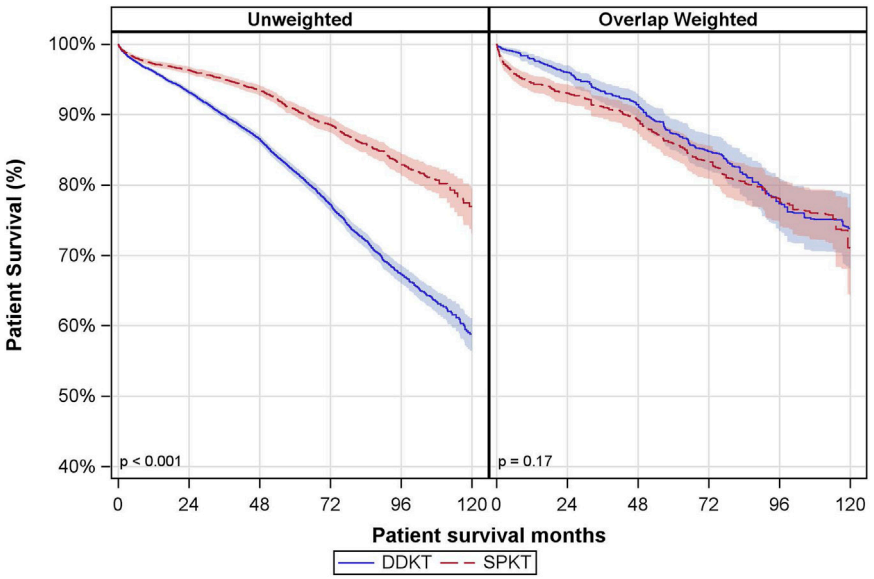


FIGURE 3 | Unadjusted and Overlap Weighted Cumulative Patient Survival Rates. DDKT: deceased donor kidney transplant; SPKT: simultaneous pancreas-kidney transplant.

TABLE 4 | The association of SPKT vs. DDKT with treated acute rejection and hospital readmission.

Model	SPKT vs. DDKT OR (95% CI)		
	Treated acute Rejection prior to discharge (N = 22,543)	Acute treated Rejection within 1 Year of transplant[a] (N = 19,072)	Hospital Readmission Within 1 Year of transplant[a] (N = 19,009)
Unadjusted	1.00 (0.71, 1.41)	2.35 (2.09, 2.64)	1.45 (1.36, 1.55)
Covariate-adjusted[b]	1.51 (0.82, 2.79)	2.96 (2.35, 3.72)	1.77 (1.58, 1.99)
Overlap weighted	1.49 (0.32, 6.94)	2.80 (1.75, 4.49)	2.05 (1.62, 2.60)

[a]Restricted to the subset of subjects with the 1-year post-transplant follow-up form who had not experienced graft loss within the first post-transplant year.
[b]Adjusted for sex, age, race/ethnicity, education, insurance, blood type, BMI, dialysis months; cPRA, diabetes type, transplant year, kidney transplant type, months on wait list, CIT, donor sex, donor age, and KDPI.
CI: confidence interval; DDKT: deceased donor kidney transplant; OR: odds ratio; SPKT: simultaneous pancreas-kidney transplant.

In covariate-adjusted and overlap weighted analyses, there was no significant difference in patient mortality between SPKT vs. DDKT recipients (owHR: 0.85; 95% CI: 0.64, 1.13) (**Table 3**). The interaction between transplant type and age group was not statistically significant.

In the subset of recipients with Type 1 diabetes across all BMI ranges, findings remained consistent with the main analysis. However, among recipients with Type 1 diabetes and BMI <30, those who received DDKT had a significantly higher hazard of death compared to SPKT recipients (adjusted HR: 1.37; 95% CI: 1.04, 1.81) (**Supplementary Table S1**).

Treated Acute Rejection and Hospital Readmission

16,793 DDKT and 5,750 SPKT recipients had information regarding treated acute rejection before hospital discharge. Treated acute rejection was documented for 0.78% of each group.

In covariate-adjusted and overlap weighted analyses, there was no significant difference between SPKT and DDKT recipients in terms of treated acute rejection before discharge (overlap weighted odds ratio (owOR): 1.49; 95% CI: 0.32, 6.94) (**Table 4**).

A total of 14,107 DDKT and 4,965 SPKT recipients who were alive with a functioning graft 1-year post-transplant had data regarding treated acute rejection within the first year following transplant. Treated acute rejection was documented for 11% of SPKT and only 5% of DDKT. In the covariate-adjusted and overlap-weighted analyses, SPKT recipients were significantly more likely to experience treated acute rejection within 1 year of transplantation than DDKT recipients (owOR: 2.80, 95% CI: 1.75, 4.49) (**Table 4**).

A total of 14,066 DDKT and 4,943 SPKT recipients who were alive with a functioning graft 1-year post-transplant had data

regarding hospital readmissions within a year of transplant. At least one hospital readmission was documented for 62% of SPKT and 52% of DDKT. In the covariate-adjusted and overlap weighted analyses, SPKT recipients were significantly more likely to have hospital readmissions within 1 year of a transplant than DDKT recipients (owOR: 2.05, 95% CI: 1.62, 2.60) (**Table 4**).

The findings for treated acute rejection and hospital readmission during the first year post-transplant were consistent in the subset of recipients with Type 1 diabetes who remained alive with a functioning graft 1 year after transplantation, across all BMI ranges as well as among those with a BMI less than 30 (**Supplementary Table S2**). Even among recipients with Type 1 diabetes and BMI under 30, SPKT was associated with an increased risk of treated acute rejection (adjusted OR: 2.08; 95% CI: 1.33–3.25) and hospital readmissions (adjusted OR: 1.62; 95% CI: 1.28–2.04) during the first year following transplant (**Supplementary Table S2**).

Pancreas Graft Failure Among SPKT Recipients

Overall, cumulative 90-day pancreas graft survival in the SPKT group was 93% (95% CI: 92, 94), with those aged 50–59 having higher pancreas graft failure rates (**Supplementary Figure S4**).

DISCUSSION

The ongoing discussion about the survival benefits of SPKT versus DDKT is inherently complex, compounded by differences in the selectivity of recipient candidates, donor organ quality, and the trade-offs between surgical and immunological risks versus metabolic and quality-of-life benefits of pancreas surgery [1–3, 18]. Additionally, there is growing consideration for expanding SPKT criteria to patients with type 2 diabetes, reflecting evolving clinical practice trends [10].

Historical analyses, particularly using SRTR data, have often indicated superior kidney graft and patient survival rates for SPKT recipients, which were typically attributed to the younger, healthier donor kidneys with lower KDPI scores [4, 11, 12, 19, 20]. Moreover, SPKT's survival benefits hinge on avoiding early pancreas graft loss [12]. There is a noted risk of 5%–10% for such losses [4]. Also, a pancreas transplant has a higher risk of other surgical complications, such as thrombosis, infections, and leaks, and a higher risk of rejection [21–23].

A significant strength of our study was the robust statistical approach, which employed advanced overlap propensity score weighting, enabling precise balancing of SPKT and DDKT recipients on crucial donor and recipient characteristics, such as donor age, health conditions, and KDPI scores. This meticulous method has been shown to outperform IPTW in cases with minimal overlap [17] and significantly mitigated confounding due to selection bias, providing a more accurate comparative assessment of SPKT outcomes.

Our analysis also highlights key demographic and clinical differences between SPKT and DDKT recipients that may influence transplant outcomes, including insurance coverage, dialysis duration, and racial distribution. SPKT recipients were more likely to have private insurance, shorter dialysis exposure, and to be non-Hispanic white. Among these, shorter dialysis duration prior to transplant is particularly relevant, as it is strongly associated with improved post-transplant survival. Given the large sample size, even small differences between groups may reach statistical significance, and should be interpreted with consideration of their clinical relevance. These findings reinforce the importance of early referral and timely evaluation for transplantation, especially in patients with diabetes, who face high mortality rates while on the waitlist [22].

Although the main analysis demonstrated no significant overall survival benefit for SPKT compared with DDKT, our sensitivity analyses revealed important differences in specific patient subgroups. Among recipients with Type 1 diabetes and BMI <30, SPKT was associated with significantly lower mortality compared to DDKT. This suggests that the survival benefits of SPKT may be most evident in carefully selected, lower-risk patients who meet traditional listing criteria. In contrast, among broader groups that included higher BMI patients or mixed diabetes types, no survival difference was observed. These findings highlight the critical role of patient selection in determining which individuals are most likely to benefit from SPKT.

While this subgroup experienced a survival benefit, SPKT was also associated with higher early morbidity, including treated acute rejection and hospital readmissions, highlighting the need to weigh these risks during transplant decision-making.

SPKT is a more complex surgical procedure than kidney-alone transplantation, with longer operative times and a greater risk of perioperative complications such as thrombosis, infection, and technical graft failures. These early risks may offset the potential survival advantage expected from shorter waitlist times by contributing to higher early postoperative morbidity and mortality. In our study, we observed that 1-year post-transplant outcomes, including treated acute rejection and hospital readmissions, were more frequent among SPKT recipients. This suggests that the clinical burden during the first year after transplant is greater for SPKT recipients, which may further limit the survival benefit of shorter wait time.

An important novel finding in our study was the significantly increased morbidity among SPKT recipients, evidenced by higher rates of treated acute rejection and hospital readmissions within the first post-transplant year among those who were alive with a functioning graft 1-year post-transplant. Highlighting this increased morbidity, despite a lack of survival advantage, underscores the necessity for cautious patient selection and counseling when considering SPKT.

These findings emphasize the trade-off between potential long-term metabolic and survival benefits and the higher early morbidity associated with SPKT. They underscore the importance of individualized counseling and shared decision-

making when selecting candidates for SPKT, ensuring that patients understand both the risks and potential advantages.mes.

This study presents several limitations. Firstly, notable differences in recipient characteristics were observed, potentially introducing selection bias in the preference for DDKT over SPKT among candidates with higher surgical risks. The study's retrospective nature allows for identifying correlations without establishing causality. Additionally, other recipient characteristics not available in the registry may have also impacted the study results. We employed propensity score weighting to mitigate potential confounding due to the notable differences in characteristics between DDKT and SPKT recipients. However, achieving covariate balance on the mean through overlap weighting may not ensure complete adjustment for confounding across all variables. While propensity score weighting reduces bias from measured covariates, it cannot address unmeasured confounders, which may still influence treatment assignment and outcomes, leaving the potential for residual confounding.

Although biopsy-proven rejection offers greater diagnostic accuracy, it is not consistently performed or reliably documented across transplant centers. Therefore, we used treated acute rejection as a practical alternative, reflecting clinically significant episodes while minimizing overestimation. Additionally, the study's secondary outcomes may not have been consistently captured; however, it is less likely that they were captured in a biased systematic manner between the study groups. Furthermore, these secondary outcomes are assessed using the 1-year follow-up form, and transplant centers are not required to continue follow-up after graft failure. As a result, our analysis is restricted to recipients with 1-year graft survival, which may introduce survivor bias.

The study's scope was constrained by the limitations of the SRTR database, particularly its inability to monitor diabetic complications such as retinopathy and neuropathy, which are critical to quality of life. Additionally, we lack information regarding post-transplant cardiovascular events and metabolic improvements, both of which are increasingly recognized as important benefits of SPKT over DDKT in recent studies. Recent research has highlighted the advantages of SPKT in reducing cardiovascular morbidity and improving long-term metabolic control. Future research focusing on these areas could yield valuable insights. Furthermore, with the advent of new treatments such as Glucagon-Like Peptide-1 receptor agonists, which have demonstrated cardioprotective and metabolic benefits in population with diabetes, it remains unclear how these therapies may influence outcomes in SPKT versus DDKT recipients. Future research should consider the potential impact of these medications on transplant outcomes, as they could alter the risk-benefit profile of SPKT in managing diabetes-related complications. Prospective studies focusing on these areas could yield valuable insights into the full impact of SPKT on quality of life and long-term survival.

The potential for improved quality of life and long-term metabolic benefits with SPKT is a crucial consideration for patient counseling, particularly for individuals seeking to avoid the costs and burdens associated with insulin therapy. To date, there is a gap in research comparing the cost-effectiveness and quality of life between new insulin therapies and the insulin-free lifestyle afforded by SPKT for patients with diabetes and renal failure. Given the data, the choice of SPKT should be shared with the patient, weighing personal preference against the risk of morbidities versus the potential for increased life years in selected patients.

Our study evaluated transplant data extending through 2023, reflecting contemporary practices in surgical techniques, immunosuppression regimens, and postoperative care. This potentially explains differences in outcomes compared to older studies ending earlier. Over recent years, advances in surgical expertise and immunosuppressive management likely contributed to improved outcomes in kidney-alone transplants, diminishing previously seen advantages of simultaneous pancreas transplants.

Future research should prospectively evaluate diabetic complications and patient-reported outcomes post-transplantation, areas insufficiently captured by registry-based studies. Further cost-effectiveness analyses comparing SPKT with contemporary insulin therapies and newer anti-diabetic medications are essential for comprehensive patient counseling and policymaking.

Our findings emphasize the necessity of individualized patient counseling that comprehensively weighs the risks of increased morbidity against the potential metabolic and quality-of-life benefits of SPKT. Ultimately, these insights necessitate careful reconsideration of existing prioritization policies for SPKT to adopt a nuanced, individualized approach to organ allocation. Ensuring equitable and clinically effective transplant strategies will require balancing demonstrated risks with patient-specific potential benefits. Individualized approaches are needed to balance early surgical risks with potential long-term metabolic and quality-of-life benefits, ensuring that SPKT is prioritized for those most likely to benefit.

CONCLUSION

This study adds important context to current organ allocation practices that prioritize SPKT based on presumed survival benefits. Our findings show that, after rigorous statistical adjustment, SPKT recipients face significantly higher early morbidity without clear long-term survival or graft advantages compared to DDKT.

Given these outcomes, organ allocation policies should shift toward individualized approaches, carefully balancing each patient's clinical risks against potential metabolic and quality-of-life improvements. Patient counseling must reflect these considerations, facilitating informed decisions aligned with patient-specific benefits and risks. Future allocation strategies should also integrate ongoing advancements in diabetes management and address disparities in transplant outcomes across diverse patient populations.

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

Statistical analysis was done by JS, RL, and SA. All authors contributed to the concept and writing of the manuscript. JS conceived the idea. All the participants participated in writing the paper.

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CONFLICT OF INTEREST

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

GENERATIVE AI STATEMENT

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

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14934/full#supplementary-material

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REVIEW
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A Brief Review of Artificial Intelligence in Living Kidney Donation

Jasir Nawar[1†], Jennifer D. Motter[1†], Jane J. Long[1], Ritika Sarpal[2], Dorry L. Segev[1,3], Michal A. Mankowski[1†] and Macey L. Levan[1,3†]*

[1]Department of Surgery, NYU Grossman School of Medicine, New York, NY, United States, [2]Department of Computer Science and Engineering, University of California, Merced, CA, United States, [3]Department of Population Health, NYU Grossman School of Medicine, New York, NY, United States

Artificial intelligence (AI) is rapidly transforming healthcare, and the field of kidney transplantation (KT) is no exception. While much of the AI-related work has focused on deceased donor KT, there is a growing body of research applying AI tools to living kidney donation (LKD). This review explores AI's current and potential roles in LKD, focusing on predictive and social applications of AI in LKD. Additionally, we discuss the challenges and limitations of implementing AI in clinical settings and highlight emerging research trends. This review consolidates existing research and provides a foundation for both transplant professionals and data scientists seeking to integrate AI responsibly into living donor programs.

Keywords: AI, living donor, living kidney donation, machine learning, kidney transplantation

INTRODUCTION

Living kidney donation (LKD) remains a vital approach to bridging the gap between supply and demand in kidney transplantation (KT), offering improved graft survival, less delayed graft function, and shorter wait times than deceased donor transplantation [1–3]. Yet, LKD programs confront persistent obstacles: a limited donor pool, intricate immunologic and medical evaluations, and psychosocial factors affecting donor candidacy and retention [1–3].

Artificial intelligence (AI), leveraging modern computational techniques and large-scale data, holds promise for addressing these obstacles. In KT, AI can enhanced risk stratification, optimized organ allocation, and supported recipient management, particularly in deceased donor contexts [4, 5]. However, systematic synthesis of AI's impact on LKD remains limited.

In this review, we examine current applications of AI in LKD, from risk prediction and donor evaluation to patient education and social media analysis. We evaluate model methodologies and discuss clinical integration, ethical implications, and directions for future research. The goal is to offer clinicians, researchers, and policymakers a clear, evidence-based perspective on AI's role in advancing living kidney donation.

METHODS

Literature Search

A comprehensive literature search was conducted across PubMed and Google Scholar to identify studies pertaining to AI in LKD. Search strategies incorporated keywords across two domains: 1) AI and predictive modeling (e.g., generative artificial intelligence, machine learning), and 2) living kidney donation (e.g., live kidney donation, living kidney donor, living donor kidney transplantation

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***Correspondence**
Macey L. Levan,
macey.levan@nyulangone.org

†These authors have contributed equally to this work

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[LDKT]). We excluded studies that were abstracts without full text, non-English publications, or focused on deceased donation in their methods. Only articles that were published from 2008 onward were considered to ensure a focus on contemporary techniques and advancements. Study selection was finalized through iterative discussion among JN, MM, and ML (**Table 1**).

OVERVIEW OF AI METHODS IN LKD RESEARCH

Common Metrics to Assess Model Quality

The studies discussed throughout this review used common machine learning metrics to assess the performance of their models with respect to accuracy, discrimination, calibration (**Table 2**).

Overview of Clinical Problems and Models

We provide an overview the clinical problems addressed in the included studies, the models used to address each problem, and the rationale for the usage of certain models (**Table 3**).

Traditional Machine Learning Models

Traditional machine learning (ML) techniques such as eXtreme Gradient Boosting (XGBoost), K-Nearest Neighbors (KNN) algorithm, and Naïve Bayes (NB) algorithm have been used to create post-operative prediction systems of outcomes such as graft survival and post-operative renal insufficiency. These models aim to better inform LKD donors about their donation risks and support clinicians in counseling potential LKD donors.

XGBoost is an ensemble-learning method that combines multiple smaller models into a single, more accurate one. This is done by building many shallow decision trees sequentially, each one improving upon the errors of the last [21]. The model focuses on efficiency, speed, and high performance, using parallel processing to train models on large datasets. It is a highly effective model for training on tabular clinical datasets across various prediction tasks due to its handling of missing data, ability to automate ranking of variables, and regularization to reduce overfitting, which can reduce model training time compared to manual methods [21]. XGBoost has demonstrated versatility across multiple applications in LKD research. XGBoost was employed for variable selection in the Live-Donor Transplant Outcome Prediction model (L-TOP), leveraging its ability to handle missing values for automated elimination of variables [17]. In the UK, researchers used XGBoost alone to develop a predictive model for graft failure in LKD recipients using data from the UK Transplant Registry, where it was favored due to the presence of nonrandom missing data. Compared to a decision tree approach and a random survival tree approach, XGBoost provided the highest Area Under the Receiver Operating Characteristic (AUROC) score for all time points of its task [7]. In other words, across all time points, the XGBoost based model achieved and maintained the highest ability to distinguish between LKD patients with graft failure and those whose graft survived. Additionally, XGBoost has been applied to predict post-donation eGFR of donors in order to identify individuals at risk for post-donation renal insufficiency [8]. The XGBoost-based model achieved the highest AUROC and showed the strongest correlation between predicted and observed pre- and post-donation eGFR values. These findings suggest that the model may offer a reliable tool for forecasting postoperative eGFR outcomes, potentially assisting clinicians in the evaluation and selection of living kidney donors [8].

XGBoost outcomes are less interpretable than commonly used linear models due to modeling and training methods involving multiple decision trees. One method to create a more interpretable model is to combine multiple, more interpretable algorithms together. In 2019, Atallah et al. combined two model, KNN and NB, to create a model for measuring five-year graft survival of LKD recipients [6]. KNN is a predictive model that categorizes a new sample into a class by identifying the 'k' closest samples and assigning it the most common class among them, making it far more interpretable than XGBoost since model decisions are due to proximity to groups of samples [22]. However, since KNN is directly dependent on the number of samples, its performance degrades as the amount of data, number of variables, or dimensionality increases.

Atallah et al. addressed this by using a Naïve Bayes (NB) algorithm for variable selection, identifying the most relevant inputs for KNN based on probabilistic categorization [6]. Naïve Bayes (NB) is a probabilistic model that assumes independence among variables yet often performs well in medical contexts where interpretability is critical, such as disease and risk prediction [23]. Atallah et al. used NB to iteratively exclude individual variables, retaining those whose removal reduced model accuracy [6]. Given the need to evaluate 44 variables, this approach leveraged NB's computational efficiency. The combination of NB for variable selection with KNN ultimately demonstrated the highest accuracy and mean F1 score compared with nomogram, decision tree, Bayesian network, and neural network models available at the time [6].

Traditional ML techniques are already well established and continue to remain valuable for developing predictive models in LKD. With the availability of more powerful computational hardware, combining multiple ML algorithms in one model has become increasingly easier to do. As these combined models are composed of multiple, interpretable pieces, these models can potentially improve predictive performance, while maintaining the interpretability needed for clinical decision-making.

Neural Networks

Neural Networks (NN) are being used to gather insights from high-dimensional inputs where regular variable selection is not feasible. NNs are used to mimic the decision-making manner of the human brain and consist of layers of interconnected nodes acting akin to connected neurons [24]. Basic neural networks are early examples of deep learning, capable of capturing complex nonlinear patterns. Deep learning is a natural evolution of early NNs, where more layers of nodes could be trained to capture far more nuanced patterns due to increased computational ability in the past decade [25]. Early predictive models in LKD include efforts to use basic NNs for five-year survival estimation [9]. In a

TABLE 1 | Summary of AI applications in living kidney donation.

Tool name	Model(s) used	Population	Application	Results	References
Traditional machine learning models					
KNN + naïve bayes	Naïve bayes + KNN	n = 2728	Graft failure prediction (5 years)	80.77% accuracy 73.5% F1 score	Atallah et al. [6]
UK-LTOP	XGBoost	n = 12,661	Graft failure prediction (1–12 years)	5 years: 0.73 AUROC, 0.72 C-statistic 10 years: 0.75 AUROC, 0.72 C-statistic 12 years: 0.79 AUROC, 0.72 C-statistic	Ali et al. [7]
KDNI	XGBoost	n = 823	Post-donation eGFR (6–12 months)	0.900 AUROC, 73.2% sensitivity, 90.3% specificity	Jeon et al. [8]
Neural networks					
Neural network	Neural network	n = 1,900	Graft survival prediction (5 years)	0.88 AUROC, 88.43% sensitivity, 73.26% specificity, 88% accuracy, 82.1% PPV, 82% NPV	Akl et al. [9]
3D DenseNet	DenseNet	n = 1,074	Post-donation eGFR	Donors with higher remnant kidney volume to weight ratio exhibit less change in post donation eGFR	Jo et al. [10]
CNN	CNN	n = 1,930	Segmentation of kidney CT scan and estimation of kidney volume	$p > 0.05$ for all estimated volumes of cortex and medulla	Korfiatis et al. [11]
LSTM	LSTM	n = 203,219	Classification of social media post relation to LKD	60.2% F1 36.8% specificity 77.1% sensitivity 62.9% accuracy	Asghari et al. [12]
Transformer models					
ChatGPT 3.5, BERT	Transformers	n = 3292	Classification of reddit post relation to LKD	78% F1 79% specificity 79% sensitivity 79% accuracy	Nielsen et al. [13]
ChatGPT, MedGPT, gemini	Transformers	n = 35	Evaluation of readability of generated information on LKD	39.42 FRES 10.63 FKGL	Villani et al. [14]
ChatGPT 3.5, ChatGPT 4.0	Transformers	n = 27	Evaluation of readability of generated information on LKD	Reduced FKGL by 4.30 ± 1.71 ($p < 0.001$) 96% reduction of information to eight grade level or below	Garcia Valencia et al. [15]
ChatGPT	Transformers	n = 20	Evaluation of accuracy of generated information on LKD	55% of responses rated to have ≥80% accuracy 85% of responses rated to have ≥66% completeness 85% of responses rated to be ≥75% not harmful	Xu et al. [16]
Specialized models					
L-TOP	XGBoost + deep cox mixtures	n = 66,914	Graft failure prediction (1.5–13 years)	5 years: 0.70 AUROC, 0.70 CTD 10 years: 0.68 AUROC, 0.67 CTD 13 years: 0.68 AUROC, 0.66 CTD	Ali et al. [17]
RAPTO	AutoScore	n = 823	Post-donation eGFR (6–12 months)	0.846 AUROC, 0.965, AUPRC	Jeon et al. [18]
Gia chatbot	Decision tree chatbot	n = 54	APOL1 risk education	82% agreed "neutral and unbiased", 82% agreed "trustworthy", and 85% "words, phrases, and expressions are familiar to the intended audience"	Gordon et al. [19]

APOL1, apolipoprotein 1; AUROC, Area Under the Receiver Operating Characteristic Curve; AUPROC, Area Under the Precision-Recall Curve; CNN, convolutional neural network; CTD, time-dependent concordance index; eGFR, estimated glomerular filtration rate; FKGL, Flesch–Kincaid Grade Level; KDNI, kidney donor network initiative ;KNN, k-nearest neighbors; LKD, living kidney donation; LSTM, Long Short-Term Memory; PPV, positive predictive value; NPV, negative predictive value; RAPTO, Risk Assessment Post-donation Tool Using Outcome-based AutoScore; UK-LTOP, Live-Donor Kidney Transplant Outcome Prediction tool, XGBoost, Extreme Gradient Boosting.

study by Akl et al., NNs were trained on donor-recipient variables to learn patterns associated with successful transplant outcomes [9]. While less complex than modern NN models, this work demonstrated the early potential of in LKD graft survival prediction. Compared to nomogram-based models to predict 5-year graft survival estimation, the NN achieved higher sensitivity and predictive accuracy, and achieved almost twice the positive predictive value [9].

Convolutional neural networks (CNNs) are a type of neural network designed to process image data through convolutional layers that analyze each pixel in the context of its neighbors, enabling effective detection of edges and textures. CNNs are used in facial recognition, object detection, and handwriting recognition [25]. In a study by Korfiatis et al, CNN-based segmentation was used to quantify cortical and medullary kidney volumes from imaging data [11]. The results showed correlations between segmentation with clinical donor characteristics, offering a new biomarker for renal health and transplant planning [11]. Additionally, the segmentation of kidney CTs were achieved in less than 5 min, a great increase in efficiency compared to the 30–90 min that a human observer could take on the same task [11].

TABLE 2 | Common metrics to assess model quality.

Metric	Definition	Clinical interpretation
Sensitivity or recall	Proportion of true positive cases correctly identified by the model [20]	High sensitivity indicates few patients with the condition are missed. This is important for screening or early detection, where failing to identify a case may have deleterious consequences
Specificity	Proportion of true negative cases correctly identified by the model [20]	High specificity minimizes false alarms. This is important for confirmatory testing or when unnecessary treatment should be avoided
Positive predictive value (PPV) or precision	Proportion of predicted positives that are truly positive [20]	High PPV indicates that a positive result reliably suggests that the patient has the condition. This is important when providers rely on positive results to guide diagnosis or initiate treatment; PPV strongly depends on prevalence of the condition
Negative predictive value (NPV)	Proportion of predicted negatives that are truly negative [20]	High NPV indicates that a negative result reliably suggest that the patient does not have the condition. This is important in ruling out the presence of the condition; NPV strongly depends on the prevalence of the condition
F1 score	Harmonic mean of precision and recall [20]	High F1 indicates that the model achieves good balance between false positives and false negatives. Ignores true negatives; may be clinically misleading when false positives carry a substantial burden. This is important when both types of diagnostic errors have clinical consequences (e.g., missing a diagnosis and over-diagnosing are equally undesirable)
Area under the receiver operating characteristic curve (AUROC)	Measures a model's ability to discriminate between patients with and without the condition across all thresholds. AUROC values range from 0.5 (0.5 is random chance) to 1.0 [20]	High AUROC indicates that the model can reliably discriminate between patients with and without the condition, independent of the specific decision cutoff. Disscrimination only; does not indicate PPV/NPV at a working threshold or calibration
Area under the precision-recall curve (AUPRC)	Measures the tradeoff between precision and recall across all thresholds. AUPRC values range from 0 (poor performance) to 1.0 (perfect performance) [20]	High AUPRC indicates that the model correctly identifies most patients with the condition while rarely misclassifies patients without the condition as positive. Baseline depends on prevalence; especially relevant for imbalanced outcomes. This is important when the disease is rare, and both false positives and false negatives can be costly

Densely Connected Convolutional Network (DenseNet) is a deep CNN designed for efficient image classification. Unlike other NNs in which each layer shares its output with the next layer, DenseNet connects each layer to every other layer in a feedforward fashion. This improves parameter efficiency and information flow, preventing variables from being lost or ignored [26]. Applications of DenseNet include object recognition for autonomous driving, X-ray analysis, and robot vision. A 3D DenseNet model was developed by Jo et al. to measure kidney volume from CT images in elderly donors [10]. Viewing the model's measured kidney volume against post-donation eGFR revealed significant negative correlations in elderly donors [10].

In general, CNNs have already been applied effectively in image-based LKD prediction tasks. However, despite the strength of NNs to easily deal with high dimensional inputs, less sophisticated techniques with lower variables may be favored for interpretability, especially regarding prediction modeling such as predicting LKD outcomes.

Language Models

Language models are models which specifically process text as input data for tasks. At the time of this writing, language modeling has exploded as one of the most popular areas in the field of AI, particularly due to the creation of transformer models [27]. From this newfound popularity of transformers, text-based tasks in LKD such as donor outreach and communication have enjoyed a recent surge of interest as well [28]. While transformers may be popular now, previous models such recurrent neural networks (RNN) can be relevant to language tasks where simplicity and lower computational cost are a concern.

Transformer Models

Transformer models use self-attention mechanisms to evaluate all words in a sentence simultaneously, identifying key relationships regardless of word position or distance [29]. Bidirectional Encoder Representations from Transformers Models (BERT) consider both previous and subsequent words to better understand the input text [30]. Meanwhile, Generative Pretrained Transformer Models (GPT) generate human-like responses based solely on previous words [27]. BERT models focus on reading comprehension and classification tasks such as search engines and text classification. GPT models focus on writing, chatting, and summarizing and have applications in text generation and translation. A notable aspect of transformer models is the ability to fine-tune them, which involves taking a transformer model previously trained on a general corpus of information and training this pre-trained model on a dataset specific to some tasks, essentially "specializing" the model to the desired task [30]. Nielsen, et al., 2025 fine-tuned BERT and GPT models and used them to determine if Reddit posts were written by users who presently undergoing experiences in LKD, users who previously experienced effects of LKD, and general LKD

TABLE 3 | Key clinical challenges in living kidney donation and potential AI solutions.

Clinical challenge/ Question	Models used	Rationale
Transplant outcome prediction	• Naïve bayes • KNN • XGBoost • Neural network • Deep cox mixtures • AutoScore	• Naïve bayes and KNN are simple methods which can fetch modest results with some tuning. They can also be used as supporting methods in data preprocessing • XGBoost, neural networks, deep cox mixtures, and Autoscore can have very good results in prediction at the cost of some added complexity
Education	• LSTM • Transformers • Decision tree	• LSTM and transformers are well suited in identifying long term dependencies in text sequences • Transformers-based models are currently the state of the art in on-the-fly text generation • Decision trees provide an easy to interpret hierarchy which can be easily explained
Donor risk or perioperative risk	• Deep cox mixtures • Autoscore	• Currently, a deep cox mixtures model has had its results compared to LKDPI • Autoscore is a framework to build customizable risk scores
Image analysis	• CNN • 3D DenseNet	• The internal computation of CNNs and 3D DenseNet, which is called the "convolution" is and has been well established in analyzing image data

news [30]. Gathering these insights into donor anxiety, medical concerns, social support needs, and emotional experiences at scale has only just become possible with current transformer models [13].

In educational applications, GPT-based models have been evaluated for generating materials on LKD, demonstrating the ability to produce accurate and readable content at the college level for public awareness campaigns and patient education [14]. ChatGPT has shown promise in improving patient communication by rewriting FAQs for living donors, where it was found to significantly reduce the reading level of FAQs, enhancing clarity for users with diverse literacy levels [15]. Additionally, ChatGPT's responses to real patient questions about kidney transplantation have been analyzed for accuracy, completeness, and potential harm and has demonstrated the ability to provide accurate and up to date information for most LKD questions which are commonly asked, suggesting its potential as a valuable supplement to human education efforts [16]. However, limitations from model "hallucinations", or the generation of responses which are factually and logically incoherent, remain [31].

Recurrent Neural Networks

RNNs process sequential data retaining previous steps in memory in order to understand current tasks. However, important events from less recent steps are often forgotten. Long Short-Term Memory models (LSTM) are a type of RNN that better retain relevant information across longer time steps, making them well-suited for modeling long-term patterns such as the general populace sentiment with respect to LKD. LSTMs use gating mechanisms which filter events that should be kept, used, and forgotten [32]. Applications of RNNs and LSTMs include autocomplete during typing, speech recognition such as Siri or Google Assistant, and language translation. Asghari et al., 2022 used a deep RNN using LSTM nodes to classify and interpret social media posts, reliably determining whether they were related to LKD [12]. This approach demonstrates the potential for automating the identification of potential LKD donors on a large social media scale [12].

Rule-Based Methods

Despite the very recent advances in language modeling, well designed simple models still work well for very specific tasks while also offering high interpretability for clinicians. Rule-based chatbots occupy this niche, as they rely on decision trees or if-then logic to guide users through structured interactions. They are designed to educate and support patients in their choices. Although they are not as sophisticated as chatbots driven by GPT based models, these models offer greater transparency and consistency. The "Gia" chatbot, a rule-based conversational agent, was developed to educate African American donor candidates about the APOL1 gene, a known genetic risk factor for kidney disease. In testing, users generally found the chatbot to be neutral, unbiased, and trustworthy [19]. Until the extent of racial bias with respect to transformer models is extensively studied and addressed, simple language models such as Gia are best suited to tackle LKD language tasks targeted at specific populations.

Current transformer models and prior RNNs have made it possible for researchers to evaluate how LKD patients respond to their care at a scale previously unimaginable. At the same time, GPT-based models have made it possible to communicate with patients in a new way, creating LKD content automatically and with reasonable accuracy.

Specialized Models

In some studies, some customized models were developed in an attempt to address LKD problems in a more unique way compared to previously discussed models. There are currently few specialized AI architectures which have been deployed to address LKD problems. However, the studies done suggest potential upsides for these approaches in LKD outcome prediction and even building new profiling methods in LKD.

One type of specialized model is Deep Cox Mixtures (DCM), where NNs are used to generate patterns from input patient data and then a combination of Cox models is then used to predict time-to-event outcomes based on the generated NNs patterns. This method enables personalized, flexible risk estimation and uses hazard functions to retain interpretability [17]. Applications

of DCMs include survival estimation of various diseases, such as cancer, as well as variables associated with diseases, such as serum free light chain, for example. DCM was incorporated into the Live-Donor Transplant Outcome Prediction (L-TOP) model to predict death-censored graft failure of LKD recipients. The predictive ability of L-TOP outperformed the live kidney donor profile index on the same population [17]. At the cost of some complexity, DCM was able to elevate the bar for donor profiling.

In addition to elevating clinical scoring, specialized models open the possibility for creating clinical scores. AutoScore is a specialized model that combines multiple models for variable selection, discretization, and logistic regression to produce interpretable risk scores that facilitate clinical decision-making [18]. Autoscore translates the outputs of a combination of multiple models into a simple, point-based scoring system. In LKD, AutoScore has been used to develop models that stratify donor risk based on readily available preoperative factors such as demographic information, kidney volume, GFR, and lab values [10]. Jeon et al. used the AutoScore model to build an interpretable scoring system for renal adaptation, allowing clinicians to stratify donor risk using a simple point-based system [33]. The generated scoring model was able to predict the probability of fair renal adaptation, defined by the study as a post-donation eGFR ≥60 mL/min/1.73 m^2 [33]. Prior to Jeon et. al, few studies existed to predict renal adaptation based on pre-operation variables, let alone a clinical score for renal adaptation. The Autoscore model leverages multiple interpretable and generalizable modules as part of its architecture, potentially allowing risk scores to be generated for other LKD outcomes.

DISCUSSION

Recent developments indicate a shift toward more comprehensive, personalized, and interpretable applications of AI in LKD. Emerging work aims to integrate multiple AI technologies for more robust decision-making, while also addressing ethical, social, and clinical concerns associated with transplantation.

One major trend is the prevalence of simpler AI architectures in clinical tools. More advanced, modern transformer-based and deep learning architectures often function as "black boxes," delivering predictions without clarity on their reasoning [34]. While explainability techniques such as SHAP (SHapley Additive exPlanations) can be used to address this ambiguity; however, it is important to note that still there are limitations to consider when it comes to SHAP in its ability to explain models [34]. To address this challenge, approaches in LKD literature, Atallah et. al., AutoScore and L-TOP aim to balance accuracy with interpretability [6, 17, 33]. These models prioritize transparency, enabling clinicians to understand the rationale behind each prediction, which in turn fosters trust and supports shared decision-making.

Another key trend is the use of large electronic health records (EHRs) datasets to improve generalizability across populations. As highlighted recently, efforts are being made to overcome single-center biases by training models on national data [35]. National and representative data help mitigate the risk of algorithmic bias, ensuring that AI tools perform reliably across diverse demographic and geographic settings.

Finally, AI is increasingly seen not only as a predictive engine, but also as a communication facilitator. Tools like GPT-based chatbots are being adapted to support personalized donor education, provide real-time patient support, and enhance counseling.

Challenges and Limitations

Data Heterogeneity

Despite its promise, the application of AI in LKD faces several persistent challenges. One of the foremost barriers is the heterogeneity of available data. Clinical datasets often vary in format, quality, and completeness across institutions. This results in situations where, for the same problem, certain approaches are non-transferrable due to differences in data collection processes and variable availability, as observed in LTOP and UK-LTOP [7, 17]. Moreover, data missingness within collected variables can create additional challenges for model development and interpretation. While imputation techniques can address missingness in certain contexts, non-random missingness makes imputation inappropriate, as it introduces bias. This constraint influenced model selection in UK-LTOP, where tree-based algorithms were selected over DCM (successfully used in L-TOP) as they handle missing data without imputation. Furthermore, variations in imputation strategies affect evaluation metrics, particularly the AUROC score, which may impact performance comparisons and limit external validity.

Validation

In addition to the heterogeneity of available data, the current lack of scale poses a substantial obstacle. At present, the largest dataset that evaluated LKD transplant outcomes was limited to tens of thousands of patients, with test samples of similar size [17]. Lack of scale and diverse cohorts not only hinders the development of robust models, but it also prevents adequate large-scale external validation–an essential step in establishing generalizability and adoption of prediction models [28, 36, 37]. Although LKD models may report promising results, especially in predicting donor outcomes, their broader applicability is uncertain. It is difficult to ascertain whether a model is prone to overfitting to specific patterns without validating it using data beyond the test set of a study, even when techniques like cross-validation or temporal splits are employed. Therefore, it becomes unclear how susceptible the model is to data drift (i.e., changes in the distribution of input data over time as new data is incorporated) [36]. Along with the need for large-scale external testing, few of the discussed studies compared the predictive performance of their models to current standard models, such as the living kidney donor profile index (LKDPI) [17]. While this comparison may not be relevant for all studies, it would be valuable for graft survival prediction models to understand the benefit of the proposed techniques. Overall,

robust validation methods external testing in diverse cohorts are essential to ensure consistent and reliable performance.

Model Complexity

There is an ongoing tension between model complexity and overfitting, which underscores the challenge of balancing model accuracy and generalizability. Rooted in the bias-variance tradeoff, greater model complexity increases the risk of achieving high performance on inputs that are specific to the training data, but fails to generalize effectively to unseen test data or real-world clinical settings. Additionally, increased model complexity often comes at the cost of reduced explainability, which can introduce undue risk for providers in decision-making. As such, simpler models may be preferred to prevent this from occurring. However, in some instances, such as images or large-scale data, a more complex model is often better suited to capture the increased complexity and scope. When applying complex models to clinical decision-making, it is essential to assess their external validity, calibration, and decision-support usefulness. This can be achieved using standard performance metrics (**Table 1**) alongside evaluations of model transportability and integration into clinical workflows. Ultimately, appropriate model selection requires careful evaluation of the input data, goals, and tradeoffs, ensuring the design of a model that balances performance with explainability and real-world applicability.

Adoption

Despite rigorous validation, numerous barriers persist in the clinical adoption of AI. One key barrier is inconsistent reporting of metrics across models, particularly in outcome prediction models. Standardized reporting of performance metrics (**Table 1**) would enhance comparability and help identify which models are most appropriate for decision support in clinical use.

Another important barrier is the lack of trust in predictive modeling. Providers may be hesitant to rely on models that do not have clear explainability or transparency, especially in the current context of minimal regulatory oversight [38, 39, 40]. Addressing concerns around liability from inaccurate predictions is important for clinical adoption and emphasizes the need for regulations.

Ethical issues also arise when AI tools are used in patient-facing applications like donor or recipient education and social media analysis. Consent, bias, and data safety are key ethical issues that must be considered for the responsible and equitable use of AI tools [28, 36, 39–41]. Experiments involving AI models like ChatGPT require more consideration of their results, as the datasets used for evaluation are often curated from online sources such as community-generated benchmarks and platforms aggregating human activity [42]. This introduces questions about the provenance of data, quality control, and the need for inclusion of diverse perspectives, particularly when vulnerable populations are involved.

Establishing standardized benchmarks to assess these tools, particularly in scenarios such as LKD communication, remains an important challenge. Evaluating AI tools for fairness, especially when vulnerable populations are involved, remains equally important [4, 28, 37, 39]. Addressing these concerns requires robust standards for ethical AI implementation in clinical environments, which will be essential for promoting trust, safety, and equitable outcomes in patient care.

Finally, issues of cost must be addressed when considering integrating AI into clinical practice. Infrastructure requirements like data storage, data maintenance, and security add significant expenses. From a modeling perspective, substantial costs arise from training predictive models and deploying them across health systems, which is necessary to ensure quick, reliable, and easily accessible model outputs for clinical decision-making.

CONCLUSION

AI is beginning to play a meaningful role in LKD, from predicting outcomes and improving donor-recipient matching to analyzing social media and enhancing patient education. Still, most models require validation with multicenter data, and future work should prioritize interpretability. Usability and fairness must also be addressed to ensure these tools can be effectively and equitably integrated into transplant care. As this field grows, close collaboration among clinicians, data scientists, and ethicists will be essential to realize the full benefits of AI in LKD.

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Association Between Three Lung Donor Scores and Lung Acceptance in DBD and DCD Donors

Fabian Iten[1], Julius Weiss[1]*, Simon Schwab[1], Franziska Beyeler[1], Thorsten Krueger[2], Angela Koutsokera[3], Macé Schuurmans[4], Isabelle Opitz[5], György Lang[5] and Franz Immer[1]**

[1]Swisstransplant, Swiss National Foundation of Organ Donation and Transplantation, Bern, Switzerland, [2]Division of Thoracic Surgery, Lausanne University Hospital, Lausanne, Switzerland, [3]Division of Pneumology, Lausanne University Hospital, Lausanne, Switzerland, [4]Division of Pulmonology, University Hospital Zurich, Zurich, Switzerland, [5]Department of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland

The use of extended criteria donors (ECD) has become increasingly important in lung transplantation to address organ donor shortages. To better assess lung graft quality and optimize donor selection, several scores have been developed. This study assesses whether Swiss lung acceptance practice is associated with three validated lung donor scores — the Oto Score, Eurotransplant Score (ET), and Zurich Donor Score (ZDS) — in both DBD and DCD donors. Due to limited clinical data, certain parameters of the Oto and ET Scores were adapted (aOto and aET). Data from 1515 actual deceased donors between 01.07.2014 and 30.06.2024 were analyzed. Logistic regression and AUC-ROC analysis were used to evaluate the scores' discriminative ability. Results showed that all three scores were associated with lung acceptance, with AUC values indicating acceptable to moderate discriminative ability — 0.75 for aOto, 0.70 for aET, and 0.77 for ZDS — and DCD donors being consistently less likely to be accepted for lung transplantation compared to DBD donors. Nonetheless, all three scores showed limitations as standalone models. Developing a novel, nationally applicable Swiss prediction tool integrating current lung acceptance criteria and recipient factors could improve donor–recipient matching, support more efficient organ utilization, and potentially increase transplant activity.

Keywords: donation after circulatory death (DCD), donor lung acceptance, extended criteria donor, lung donor score, lung transplantation

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***Correspondence**
Fabian Iten,
fabi.iten@icloud.com
Julius Weiss,
julius.weiss@swisstransplant.org
Franz Immer,
franz.immer@swisstransplant.org

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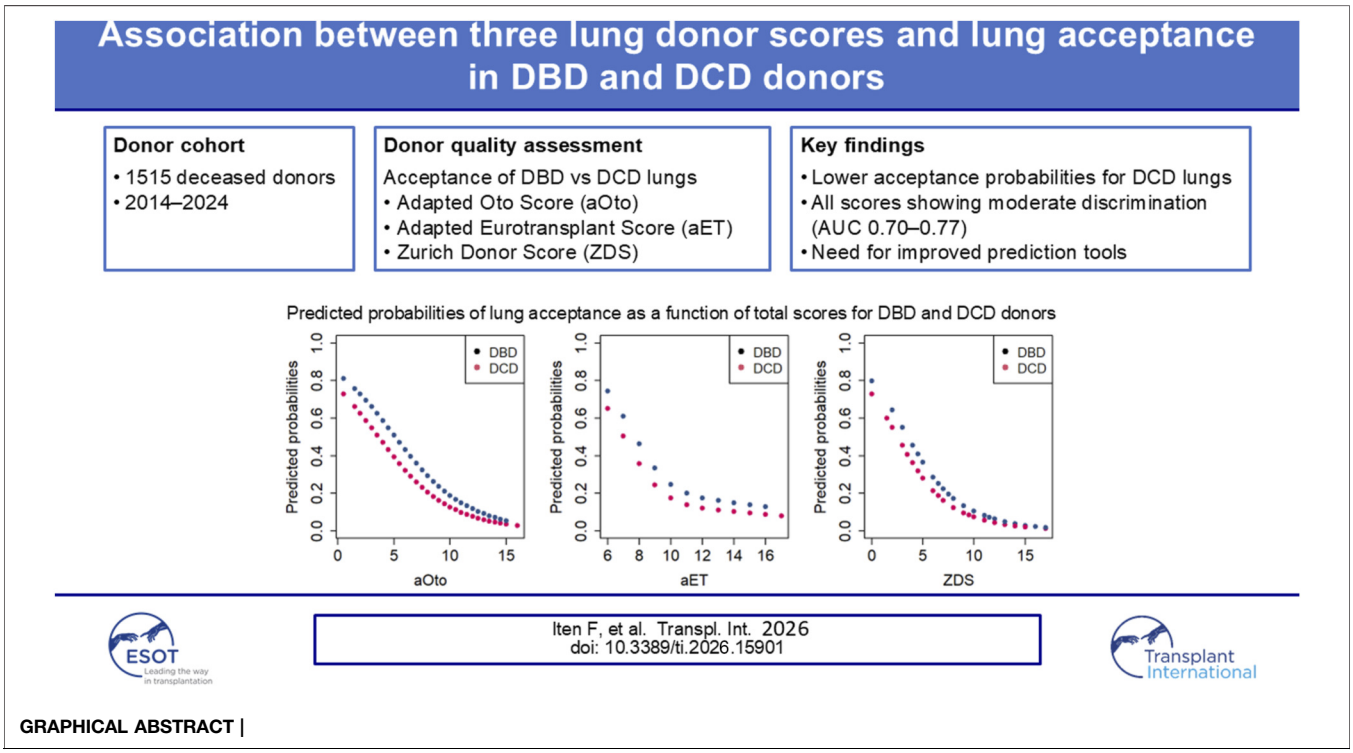
INTRODUCTION

Lung transplantation is a well-established treatment for patients with end-stage lung diseases when all other therapeutic options are depleted. It significantly improves survival and quality of life [1]. These developments are further supported by recent large European series, including the Belgian national experience, demonstrating continued improvements in outcomes and expanding clinical applicability of lung transplantation [2]. However, the scarcity of transplantable donor lungs and the continually expanding waiting lists — as a consequence of broader indications and enhanced bridging options — in most countries remain substantial challenges in lung transplantation [3, 4]. To address this, the use of extended criteria donors (ECD) has increased in recent years, along with a growing use of donation after circulatory death (DCD) [5, 6]. Following a hiatus of 4-years, DCD organ donation was restarted in Switzerland in 2011, thereby enhancing transplant activity and



GRAPHICAL ABSTRACT |

reducing waiting times. By 2023, 41% of transplanted lungs in Switzerland were from DCD donors [7]. However, DCD donors differ in several ways from donation after brain death (DBD) donors. They are typically older, predominantly male, and more likely to have preexisting cardiac comorbidities. They also tend to have higher body mass index (BMI) and lower arterial partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratios, along with increased prevalence of preprocurement pneumonia [8, 9].

Despite the increasing use of ECD for lung transplantation, an international consensus on their uniform definition is lacking. In contrast, to provide a reference for optimal donor lung quality the International Society for Heart and Lung Transplantation (ISHLT) proposed five criteria in 2003 that define an ideal lung donor: age <55 years, smoking history <20 pack years, clear chest X-ray, no purulent secretions on bronchoscopy and a PaO_2/FiO_2 ratio >300 mmHg [10]. Building on these criteria, Oto and colleagues developed a score to numerically assess donor lung quality and predict the probability of organ acceptance [11]. Based on this score, but with certain modifications Smits and colleagues established the Eurotransplant Score (ET) which reliably predicted lung acceptance and 1-year survival [12]. To improve long-term outcome prediction, Ehrsam and colleagues proposed the Zurich Donor Score (ZDS) in 2020, incorporating diabetes and significant pulmonary infection as parameters, replacing bronchoscopy and chest X-ray findings [13].

This study aims to assess how the ZDS and adapted versions of the Oto and ET Scores are associated with lung acceptance practices in Switzerland. Given the increasing number of DCD donations in recent years, it is of particular interest to calculate scores separately for DBD and DCD to evaluate whether they exhibit different probabilities for transplantation.

PATIENTS AND METHODS

Donor Data Collection

In this retrospective cohort study, we analyzed data from all deceased organ donors in Switzerland between 01.07.2014 and 30.06.2024 (n = 1730). Donor data were extracted from the Swiss Organ Allocation System (SOAS). SOAS is primarily designed for donor evaluation and organ allocation and does not systematically capture post-transplant recipient outcome data. Such data were not available for analysis and could not be included in the present study. For this analysis, only actual deceased donors (ADD) were included, whereas not utilized donors (n = 203) and potential donors with a positive SARS-CoV-2 PCR test during the period when SARS-CoV-2 was considered a contraindication for lung transplantation in Switzerland (between 12.03.2020 and 31.03.2023, n = 12) were excluded.

ADD refers to a deceased donor from whom at least one organ was procured for transplantation [14], whereas a not utilized donor is a deceased donor from whom no organs were recovered for transplantation. We categorized lung offers as either "refused" or "accepted," to indicate that it is the transplant center decision whether to accept or not an offered lung graft for transplantation. The category "accepted lung offer" is equivalent to the outcome "lung transplanted," while "refused lung offer" is equivalent to the

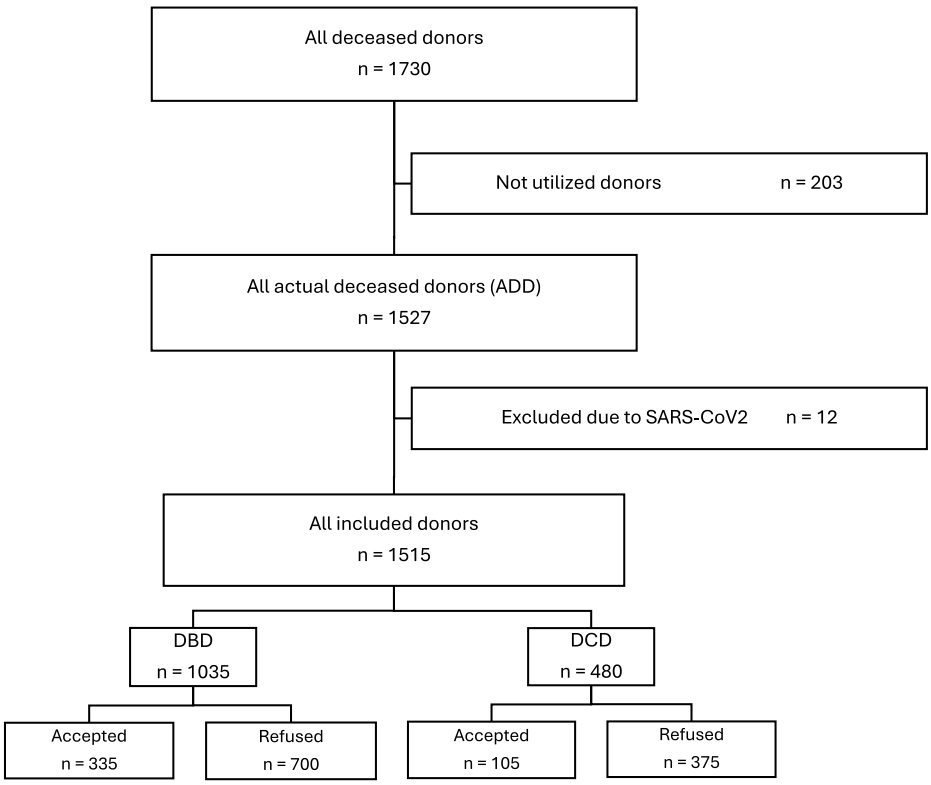


FIGURE 1 | Flow chart of all reported deceased donors in Switzerland in 2014–2024.

outcome "lung not transplanted." This decision can be taken based on the medical information during allocation or onsite during the procurement due to intraoperative findings. Additionally, for donor lungs in which no compatible recipient was on the waiting list are also in the category "refused lung offer." In this study, accepted lung offers from Swiss donors also included lungs transplanted abroad. This occurred under international agreements when no suitable recipient was found on the national waiting list [15].

An overview of the analyzed cases, detailing donor types and exclusion criteria, is presented in **Figure 1**.

Adapted Oto Score (aOto)

Based on the five parameters defined by the ISHLT as ideal lung donor criteria, Oto and colleagues established their score to assess donor lung quality [11]. Lower score values were associated with better organ quality and, subsequently, higher lung acceptance. Since some clinical data relevant to the score calculation are not routinely recorded in the SOAS, we adapted the following parameters for this analysis:

- *Chest X-ray findings*: Due to the lack of qualitative assessment and opacity localization in the SOAS, this parameter was modified using analogous distribution of points as in the adapted ET Score (see below): Clear chest X-ray, atelectasis or edema was weighted 0.5 points; opacity or consolidation was weighted 2.5 points.
- *Secretions in bronchoscopy*: As the amount of bronchial secretions is not recorded in the SOAS, this parameter was simplified into two categories: "no secretions" was assigned 0.5 points, while "secretions" was assigned 2.5 points.
- Parameters with missing data were assigned score values following the methodology used in the ET Score [12].

Resulting from these adaptations, the maximum achievable score was 17, rather than 18 as in the original Oto Score [11].

Adapted Eurotransplant Score (aET)

In the retrospective study by Smits and colleagues, the Eurotransplant Score was defined and empirically validated, building on the Oto Score and adding a parameter for donor history factors [12]. Parameters were weighted based on the odds ratios for lung acceptance or discard, with lower score values indicating better organ quality and, consequently, higher lung acceptance. For our analysis, we adjusted the following parameter:

- Donor history: In the original score, donor history was considered "compromised" in cases of drug abuse, malignancy, sepsis, meningitis or a positive virology status (HBsAg, HBcAb, HCVAb, anti-CMV) [12]. As the criterion "sepsis" is not routinely recorded in the SOAS and HBsAg as well as anti-CMV were rarely measured in the donor cohort of this period, donor history was considered "compromised" only

in cases of drug abuse, malignancy, meningitis or positive virology status (HBcAb and/or HCVAb).

Zurich Donor Score (ZDS)

Ehrsam and colleagues proposed and validated the ZDS on a Swiss donor and recipient cohort between 1992 and 2015 [13], identifying score parameters through univariate Cox regression and international consensus criteria, using more recent studies to determine point distribution compared to the Oto and ET Scores. Parameters with missing data were assigned score values following the methodology used in the ET Score [12]. Similar in the other scores, a lower ZDS indicates better organ quality and improved recipient survival.

Statistical Analysis

The study population was subdivided into four groups: DBD and DCD donors, as well as accepted and refused lung offers. Donor characteristics of the groups were compared using Pearson's Chi-squared test for categorical variables and Wilcoxon rank-sum test for continuous variables. Total aOto, aET and ZDS values were compared between accepted and refused DBD and DCD lung offers using Wilcoxon rank-sum test with p-values adjusted for multiple testing using the Bonferroni correction. Unless otherwise stated, the statistical analyses were performed using a two-sided approach and p-values of <0.05 were considered statistically significant. Multiple logistic regression was used to calculate the odds ratios (OR) for DCD donors and score values in relation to the chance of lung acceptance. To evaluate the discriminative ability of the aET, aOto, and ZDS in determining whether a lung donation is accepted or refused, the area under the receiver operating characteristic curve (AUC-ROC) was calculated. An AUC value of 0.5 signifies discriminative power no better than random guessing, while a value approaching 1 reflects perfect performance in outcome differentiation.

All statistical analyses in this study were performed using R version 4.4.2 [16].

Ethics Approval

This analysis of SOAS data does not fall under the Swiss Human Research Act; legal regulation in Switzerland distinguishes between research (which is subject to approval) and quality assurance (not subject to approval). The Ethics Committee of the Canton of Bern determined the study to be of the quality assurance type and therefore exempt from review and the requirement to obtain informed consent (BASEC-ID: Req-2025-00515).

RESULTS

Donor Characteristics

Of the 1515 included donors, 1035 (68.3%) were DBD donors and 480 (31.7%) were DCD donors. Among DBD donors, 335 lungs (32.4%) were accepted for transplantation, while 700 (67.6%) were refused. In comparison, only 105 lungs (21.9%) from DCD donors were accepted, and 375 (78.1%) were refused. Overall, 408 lungs (26.9%) were transplanted in Switzerland and 32 (2.1%) abroad, resulting in a total of 440 transplants (29.0%), while the remaining 1075 lungs (71.0%) were refused. An overview of DBD and DCD donor characteristics is presented in **Table 1**.

DBD donors whose lungs were accepted were significantly younger, with a median age of 51.0 years (IQR: 34.0–60.0), compared to DCD lung donors whose median age was 58.0 years (IQR: 48.0–65.0; $p < 0.001$). Among donors whose lungs were refused, the age difference was less pronounced: DBD donors had a median age of 60.0 years (IQR: 49.0–72.0), and DCD donors 62.0 years (IQR: 51.0–71.0; $p = 0.322$).

Differences in causes of brain injury were found between DBD and DCD donors: The leading cause of death in DBD donors was cerebral disease or cerebral hemorrhage (54.3% among those whose lungs were accepted vs. 51.0% among those whose lungs were refused), whereas most DCD donors died from anoxic brain injury (43.8% vs. 55.2%, respectively). Preclinical resuscitation was significantly less common in DBD compared to DCD donors, both among those whose lungs were accepted (29.0% vs. 41.9%; $p = 0.011$) and those whose lungs were refused (37.4% vs. 53.1%; $p < 0.001$). Among donors whose lungs were accepted, DBD donors had lower rates of cardiovascular diseases (9.9% vs. 22.9%; $p = 0.001$), arterial hypertension (22.4% vs. 41.9%; $p < 0.001$), and diabetes (4.5% vs. 9.5%; $p = 0.097$) compared to DCD donors.

Score Composition and Donor Distribution

Tables 2–4 present how the aOto, aET, and ZDS are built and how the different parameters are weighted with points. For each parameter, the respective donor distribution is shown.

Association of Scores and Donor Type With Lung Acceptance

The results of the regression analysis and odds ratios for lung acceptance are presented in **Table 5**. There is strong evidence that higher score values in aOto, aET and ZDS are associated with a decreased chance (OR <1) of donor lung acceptance in the analyzed Swiss study population ($p < 0.001$). For example, an increase in the ZDS from 5.0 to 8.5 reduced the odds of donor lung acceptance by a factor of 0.31 (95% CI 0.26–0.37). Similarly, aOto and aET showed odds ratios of 0.23 (95% CI 0.18–0.28) and 0.29 (95% CI 0.24–0.35), respectively. Across all three scores, DCD donors were significantly less likely to be accepted for lung transplantation than DBD donors, with odds ratios of 0.62 (95% CI 0.47–0.82) for aOto, 0.65 (95% CI 0.50–0.84) for aET and 0.68 (95% CI 0.52–0.90) for ZDS. **Figure 2** shows that accepted lungs from DCD donors had significantly higher aOto (2-A), aET (2-B) and ZDS (2-C) compared to those of DBD donors (all $p < 0.001$, Bonferroni-adjusted for multiple testing). In contrast, no significant differences were observed between refused lungs from DBD and DCD donors (aOto: $p = 0.493$ (2-A); aET: $p = 0.343$ (2-B); ZDS: $p = 0.891$ (2-C)).

Predicted probabilities for each score value have been calculated separately for DBD and DCD donors based on the regression models, as shown in **Figure 3**. The predicted probability of a DBD lung donation being accepted was 79.8% at a ZDS of 0 (minimum score), whereas it was 1.6% at a ZDS of 19 (maximum score). Similarly, the predicted probability of a DCD

TABLE 1 | Baseline Characteristics of accepted and refused DBD and DCD lung offers.

Characteristics	Accepted lung offer			Refused lung offer		
	DBD n = 335[a]	DCD n = 105[a]	p-value[2]	DBD n = 700[a]	DCD n = 375[a]	p-value[2]
Sex			<0.001			<0.001
Female	180 (53.7%)	35 (33.3%)		291 (41.6%)	106 (28.3%)	
Male	155 (46.3%)	70 (66.6%)		409 (58.4%)	269 (71.8%)	
Age (years)	51.0 (34.0, 60.0)	58.0 (48.0, 65.0)	<0.001	60.0 (49.0, 72.0)	62.0 (51.0, 71.0)	0.322
Height (cm)	170.0 (165.0, 180.0)	175.0 (165.0, 180.0)	0.111	172.0 (165.0, 180.0)	174.0 (166.0, 180.0)	0.049
Weight (kg)	70.0 (64.0, 80.0)	80.0 (70.0, 88.0)	<0.001	77.0 (66.0, 88.0)	80.0 (68.0, 90.0)	0.055
BMI (kg/m[b])	24.2 (22.0, 26.9)	25.8 (23.7, 28.5)	<0.001	25.5 (23.1, 28.3)	26.0 (23.3, 29.0)	0.168
Blood group			0.101			0.082
A	142 (42.4%)	45 (42.9%)		330 (47.1%)	188 (50.1%)	
AB	3 (0.9%)	3 (2.9%)		22 (3.1%)	15 (4.0%)	
B	34 (10.1%)	4 (3.8%)		58 (8.3%)	43 (11.5%)	
O	156 (46.6%)	53 (50.5%)		290 (41.4%)	129 (34.4%)	
Cause of brain injury			<0.001			<0.001
ANX	67 (20.0%)	46 (43.8%)		209 (29.9%)	207 (55.2%)	
CDE + CHE	182 (54.3%)	37 (35.2%)		357 (51.0%)	97 (25.9%)	
CTR	82 (24.5%)	20 (19.0%)		125 (17.9%)	50 (13.3%)	
OTH	4 (1.2%)	2 (1.9%)		9 (1.3%)	21 (5.6%)	
Resuscitation			0.011			<0.001
Yes	97 (29.0%)	44 (41.9%)		262 (37.4%)	199 (53.1%)	
No	235 (70.1%)	58 (55.2%)		428 (61.2%)	170 (45.3%)	
Missing	3 (0.9%)	3 (2.9%)		10 (1.4%)	6 (1.6%)	
Heart disease			0.001			0.625
Yes	33 (9.9%)	24 (22.9%)		211 (30.1%)	123 (32.8%)	
No	294 (87.7%)	77 (73.3%)		473 (67.6%)	245 (65.3%)	
Missing	8 (2.4%)	4 (3.8%)		16 (2.3%)	7 (1.9%)	
Hypertension			<0.001			0.262
Yes	75 (22.4%)	44 (41.9%)		292 (41.7%)	157 (41.9%)	
No	249 (74.3%)	61 (58.1%)		385 (55.0%)	212 (56.5%)	
Missing	11 (3.3%)	0 (0%)		23 (3.3%)	6 (1.6%)	
Diabetes			0.097			0.157
Yes	15 (4.5%)	10 (9.5%)		84 (12.0%)	43 (11.5%)	
No	317 (94.6%)	95 (90.5%)		602 (86.0%)	330 (88.0%)	
Missing	3 (0.9%)	0 (0%)		14 (2.0%)	2 (0.5%)	

[a]*n (%); Median (Q1, Q3).*

[b]*Pearson's Chi-squared test; Wilcoxon rank sum test.*

Abbreviations: ANX, anoxia; CDE, cerebral disease; CHE, cerebral hemorrhage; CTR, cerebral trauma; OTH, others.

lung donation being accepted was 72.8% at a ZDS of 0, whereas it was 1.1% at a ZDS of 19. Likewise, the aOto and aET returned high predicted probabilities of lung acceptance at low score values and correspondingly lower probabilities at higher values.

The AUC-ROC analysis assessing the discriminative ability of the three lung donor scores yielded a value of 0.75 (95% CI 0.72–0.78) for aOto, 0.70 (95% CI 0.67–0.73) for aET and 0.77 (95% CI 0.74–0.79) for ZDS, indicating an acceptable to moderate performance regarding the association with lung acceptance for DBD and DCD donors. Among the three lung donor scores, the ZDS demonstrated the strongest association with donor lung acceptance, as reflected by its highest discriminatory power.

DISCUSSION

Comparison of DBD and DCD Donors

Our study demonstrated differences in donor characteristics between DBD and DCD donors whose lungs were accepted for transplantation. DCD donors were in median 7 years older and were more likely to be male, have higher BMI, and suffer more often from comorbidities such as heart disease, arterial hypertension and diabetes, compared to DBD donors. Furthermore, DCD donors whose lungs were accepted, more often had a smoking history of >20 pack years, pathological chest X-ray findings, significant pulmonary infections and thus lower PaO_2/FiO_2 ratios. Specifically, DCD donor characteristics such as older age, male predominance, higher BMI and lower PaO_2/FiO_2 ratios have also been described in studies from other countries [6, 9, 17].

Regarding the causes of brain injury, anoxic brain injury was more frequent among DCD donors, which is consistent with the results of earlier studies in the US and Spain [6, 9, 18]. DCD donors also underwent more often preclinical resuscitation, compared to DBD donors (50.6% of DCD donors vs. 34.7% of DBD donors). Furthermore, the resuscitation rate among Swiss organ donors increased from 24.1% (2007-2014) to 39.7% in our study population, possibly contributing to an increase in donors with irreversible hypoxic brain damage [19]. The higher resuscitation rate among DCD donors may increase the risk of aspiration, leading to a higher incidence of pulmonary infections

TABLE 2 | Formation of the aOto Score (aOto) with distribution of accepted and refused DBD and DCD lung offers.

Score parameters	Score points	DBD (n = 1035)		DCD (n = 480)	
		Accepted lung offer; n (%)	Refused lung offer; n (%)	Accepted lung offer; n (%)	Refused lung offer; n (%)
Total		335 (32.4%)	700 (67.6%)	105 (21.9%)	375 (78.1%)
Age (years)					
<45	0	125 (37.3%)	141 (20.1%)	19 (18.1%)	55 (14.7%)
45–54	1	82 (24.5%)	115 (16.4%)	20 (19.0%)	65 (17.3%)
55–59	2	37 (11.0%)	80 (11.4%)	22 (21.0%)	35 (9.3%)
>59	3	91 (27.2%)	364 (52.0%)	44 (41.9%)	220 (58.7%)
Smoking history (PY)					
<20	0	249 (74.3%)	330 (47.1%)	73 (69.5%)	177 (47.2%)
20–39	1	37 (11.0%)	114 (16.3%)	18 (17.1%)	47 (12.5%)
40–59	2	9 (2.7%)	94 (13.4%)	4 (3.8%)	58 (15.5%)
>59	3	6 (1.8%)	53 (7.6%)	1 (1.0%)	37 (9.9%)
Missing	0	34 (10.1%)	109 (15.6%)	9 (8.6%)	56 (14.9%)
Chest X-ray					
Clear, edema or atelectasis	0.5	213 (63.6%)	302 (43.1%)	54 (51.4%)	118 (31.5%)
Shadow or consolidation	2.5	122 (36.4%)	382 (54.6%)	51 (48.6%)	220 (58.7%)
Missing	0	0 (0.0%)	16 (2.3%)	0 (0.0%)	37 (9.9%)
Secretions in bronchoscopy					
No	0.5	11 (3.3%)	12 (1.7%)	4 (3.8%)	7 (1.9%)
Yes	2.5	49 (14.6%)	105 (15.0%)	17 (16.2%)	34 (9.1%)
Missing	0	275 (82.1%)	583 (83.3%)	84 (80.0%)	334 (89.1%)
PaO_2/FiO_2 (mmHg)					
>450	0	71 (21.2%)	41 (5.9%)	17 (16.2%)	31 (8.3%)
351–450	2	129 (38.5%)	140 (20.0%)	39 (37.1%)	76 (20.3%)
301–350	4	63 (18.8%)	103 (14.7%)	16 (15.2%)	64 (17.1%)
<301	6	72 (21.5%)	411 (58.7%)	33 (31.4%)	190 (50.7%)
Missing	3	0 (0.0%)	5 (0.7%)	0 (0.0%)	14 (3.7%)

TABLE 3 | Formation of the aET Score (aET) with distribution of accepted and refused DBD and DCD lung offers.

Score parameters	Score points	DBD (n = 1035)		DCD (n = 480)	
		Accepted lung offer; n (%)	Refused lung offer; n (%)	Accepted lung offer; n (%)	Refused lung offer; n (%)
Total		335 (32.4%)	700 (67.6%)	105 (21.9%)	375 (78.1%)
Age (years)					
<55	1	207 (61.8%)	256 (36.6%)	39 (37.1%)	120 (32.0%)
55–59	2	37 (11.0%)	80 (11.4%)	22 (21.0%)	35 (9.3%)
>59	3	91 (27.2%)	364 (52.0%)	44 (41.9%)	220 (58.7%)
Smoking history					
No	1	171 (51.0%)	240 (34.3%)	52 (49.5%)	126 (33.6%)
Yes	2	130 (38.8%)	351 (50.1%)	44 (41.9%)	193 (51.5%)
Missing	1	34 (10.1%)	109 (15.6%)	9 (8.6%)	56 (14.9%)
Chest X-ray					
Clear, edema or atelectasis	1	213 (63.6%)	302 (43.1%)	54 (51.4%)	118 (31.5%)
Shadow or consolidation	2	122 (36.4%)	382 (54.6%)	51 (48.6%)	220 (58.7%)
Missing	1	0 (0.0%)	16 (2.3%)	0 (0.0%)	37 (9.9%)
Secretions in bronchoscopy					
Clear or nonpurulent	1	27 (8.1%)	29 (4.1%)	4 (3.8%)	15 (4.0%)
Purulent	2	15 (4.5%)	56 (8.0%)	5 (4.8%)	8 (2.1%)
Inflammatory	3	18 (5.4%)	32 (4.6%)	12 (11.4%)	18 (4.8%)
Missing	1	275 (82.1%)	583 (83.3%)	84 (80.0%)	334 (89.1%)
PaO_2/FiO_2 (mmHg)					
>350	1	200 (59.7%)	181 (25.9%)	56 (53.3%)	107 (28.5%)
301–350	2	63 (18.8%)	103 (14.7%)	16 (15.2%)	64 (17.1%)
≤300	3	72 (21.5%)	411 (58.7%)	33 (31.4%)	190 (50.7%)
Missing	2	0 (0.0%)	5 (0.7%)	0 (0.0%)	14 (3.7%)
Donor history					
Compromised	4	58 (17.3%)	165 (23.6%)	26 (24.8%)	69 (18.4%)
Uncompromised	1	277 (82.7%)	532 (76.0%)	79 (75.2%)	305 (81.3%)
Missing	1	0 (0.0%)	3 (0.4%)	0 (0.0%)	1 (0.3%)

TABLE 4 | Formation of the Zurich Donor Score (ZDS) with distribution of accepted and refused DBD and DCD lung offers.

Score parameters	Score points	DBD (n = 1035)		DCD (n = 480)	
		Accepted lung offer; n (%)	Refused lung offer; n (%)	Accepted lung offer; n (%)	Refused lung offer; n (%)
Total		335 (32.4%)	700 (67.6%)	105 (21.9%)	375 (78.1%)
Age (years)					
<50	0	159 (47.5%)	183 (26.1%)	30 (28.6%)	78 (20.8%)
50–69	2	145 (43.3%)	307 (43.9%)	62 (59.0%)	186 (49.6%)
>69	5	31 (9.3%)	210 (30.0%)	13 (12.4%)	111 (29.6%)
Smoking history (PY)					
<20	0	249 (74.3%)	330 (47.1%)	73 (69.5%)	177 (47.2%)
20–49	3	43 (12.8%)	172 (24.6%)	20 (19.0%)	87 (23.2%)
>49	4	9 (2.7%)	89 (12.7%)	3 (2.9%)	55 (14.7%)
Missing	0	34 (10.1%)	109 (15.6%)	9 (8.6%)	56 (14.9%)
Diabetes mellitus					
No	0	317 (94.6%)	602 (86.0%)	95 (90.5%)	330 (88.0%)
Yes	2	15 (4.5%)	84 (12.0%)	10 (9.5%)	43 (11.5%)
Missing	0	3 (0.8%)	14 (2.0%)	0 (0.0%)	2 (0.5%)
PaO_2/FiO_2 (mmHg)					
>300	0	263 (78.5%)	284 (40.6%)	72 (68.6%)	171 (45.6%)
151–300	2	63 (18.8%)	285 (40.7%)	30 (28.6%)	138 (36.8%)
≤150	3	9 (2.7%)	126 (18.0%)	3 (2.9%)	52 (13.9%)
Missing	1.5	0 (0.0%)	5 (0.7%)	0 (0.0%)	14 (3.7%)
Significant pulmonary infection					
No	0	158 (47.2%)	183 (26.1%)	29 (27.6%)	70 (18.7%)
Yes	3	177 (52.8%)	500 (71.4%)	76 (72.4%)	274 (73.1%)
Missing	0	0 (0.0%)	17 (2.4%)	0 (0.0%)	31 (8.3%)

TABLE 5 | Logistic regression model assessing the chance of lung acceptance based on donor type (DBD vs. DCD) and the corresponding score (aOto, aET, ZDS).

Scores	Interqartile difference	Odds ratio (95%-CI)	Chi-square	p-value[a]
aOto score				
Cadaveric donor type	–	–	11.5	<0.001
Cadaveric donor type DCD	–	0.62 (0.47–0.82)	–	–
aOto score	5.00 (5.50–10.50)	0.23 (0.18–0.28)	198	<0.001
Total	–	–	209	<0.001
aET score				
Cadaveric donor type	–	–	10.3	0.001
Cadaveric donor type DCD	–	0.65 (0.50–0.84)	–	–
aET score	3.00 (8.00–11.00)	0.29 (0.24–0.35)	151	<0.001
Total	–	–	164	<0.001
ZDS				
Cadaveric donor type	–	–	7.52	0.006
Cadaveric donor type DCD	–	0.68 (0.52–0.90)	–	–
ZDS	3.50 (5.00–8.50)	0.31 (0.26–0.37)	224	<0.001
Total	–	–	233	<0.001

Abbreviations: 95%-CI, 95% Confidence Interval.
[a]*Pearson's Chi-squared test.*

and, consequently, lower PaO_2/FiO_2 ratios, as observed in the DCD donor characteristics.

Association Between Scores and Lung Acceptance

All three scores showed acceptable to moderate discriminative ability in assessing lung acceptance with respect to AUC. An Austrian study reported similar results, with AUC values of 0.80 (95% CI 0.78–0.82) for the Oto and 0.71 (95% CI 0.68–0.73) for the ET Scores in a retrospective evaluation of 2201 donor lungs [20]. Likewise, a previous Swiss study analyzing 635 donors between 2007 and 2014 found a comparable AUC of 0.719 for their adapted ET Score [19]. This shows that our modifications to the ET and Oto Scores maintained comparable discriminatory power. Compared with the earlier Swiss studies by Elmer et al. [19] and Ehrsam et al. [13], our analysis is based on a more contemporary and comprehensive national donor cohort and evaluates all three established lung donor scores in parallel. Importantly, this study is also the first in Switzerland to separately analyze DBD and DCD donors, providing a more granular understanding of current lung acceptance practices

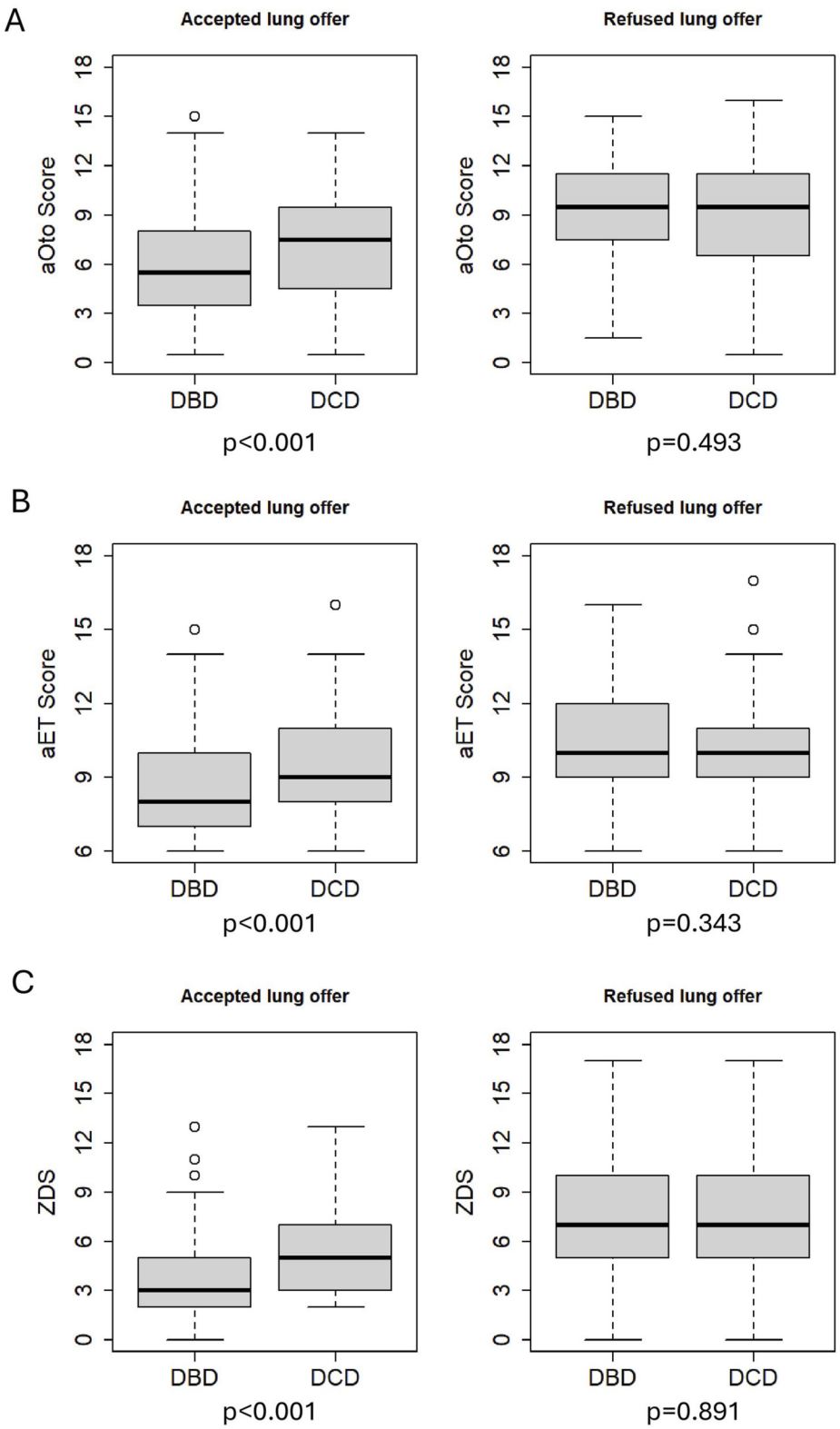


FIGURE 2 | Comparison of total scores between accepted DBD and DCD as well as refused DBD and DCD lung offers. p-values (Bonferroni-adjusted for multiple testing) <0.001 for accepted lung offers. p = 0.493 for refused lung offers of aOto **(A)**, p = 0.343 for refused lung offers of aET **(B)** and p = 0.891 for refused lung offers of ZDS **(C)**.

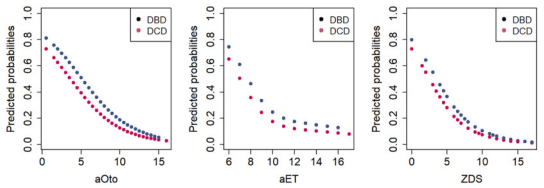


FIGURE 3 | Predicted probabilities of lung acceptance as a function of total scores for DBD and DCD donors.

across donor types. Among the analyzed lung donor scores, the ZDS showed the strongest association with the outcome. This may be due to regional differences in donor characteristics and organ quality assessment criteria, which could influence the applicability of different scores. Swiss transplant centers may prefer a nationally validated score over those developed on Australian or pan-European donor cohorts, like the Oto and ET Scores. Parameters such as diabetes and significant pulmonary infections, included in the ZDS but not in the aOto and aET, may therefore play a crucial role in assessing donor lung quality by Swiss transplant experts. However, it is not well established whether and to what extent the three lung donor scores are actually applied in clinical routine at the two Swiss transplant centers. This highlights the value of the present study, as it demonstrates that the scores align well with actual acceptance practices, even without confirmed clinical use.

Impact of Donor Type on Scores

The regression model showed that DCD donors were less likely to be accepted for lung transplantation at each score value compared to DBD donors, likely because they met ISHLT's ideal lung donor criteria less consistently, as reflected in the donor characteristics [10]. This is consistent with earlier studies reporting that DCD donors more often exhibit ECD characteristics [6]. However, a 2020 systematic review found no significant differences in 1-year survival or primary graft dysfunction between DBD and DCD lung recipients [21]. A 2025 meta-analysis even reported higher 5-year survival among DCD lung recipients in their study cohort, though differing donor characteristics may have influenced the result [22]. This discrepancy between the lower probability of being accepted for transplantation and comparable or superior recipient outcomes in international studies suggests potential for broader use of DCD lung donors [23]. It also questions the impact of ECD criteria on recipient outcomes. A recent European study found no significant difference in 1- and 5-year survival of recipients, regardless of whether the transplanted lungs came from deceased donors aged ≤30, 30-60, or ≥60 years [24]. Similar results were reported in a meta-analysis including several European and one American donor cohort [25]. Age – a key parameter in aET, aOto and ZDS – was significantly higher in DCD donors whose lungs were accepted, suggesting that, with careful and age-appropriate donor-recipient matching, more lungs from older DBD donors could potentially be utilized. Moreover, DCD donors whose lungs were accepted reached significantly higher score values than DBD donors (median 1–2 points higher; $p < 0.001$; see **Figure 2**). This may be an effect of the higher age of DCD donors which adds points to their score values.

Limitations of the Scores

In our study, some DCD and DBD lungs were refused despite low scores, while others were accepted despite high scores. Such cases do not surprise, as factors that are not accounted for in the scores may influence lung quality and thus the chance of transplantation [26, 27]. Furthermore, in the publication by Smits and colleagues, the point distribution for the original ET Score involved statistically inappropriate handling of odds ratios, as they were added rather than multiplied [12]. Rounding of the derived score points may have further compromised the accuracy of the ET Score. Additionally, both the Oto and ET Scores are based on studies and consensus criteria from 1995 to 2008 [10, 11, 28], whereas advances in transplantation medicine have since led to improved outcomes for ECD lung grafts. For instance, a 2020 study showed that the ISHLT's PaO_2/FiO_2 cutoff of 300 mmHg might be too restrictive, as recipients with ≤300 mmHg had similar short-term outcomes to those with >300 mmHg [29]. However, such findings highlight the value of lung donor scores, as they combine multiple donor criteria into a single tool to support more informed decisions on lung acceptance, rather than basing the decision on a single criterion.

Nevertheless, transplant decisions are influenced not only by donor characteristics but also by recipient and perioperative factors [30, 31] – none of which are accounted for in the Oto, ET and ZDS. A retrospective analysis from 2024 even showed that recipient characteristics might have a greater impact on post-transplant survival than donor characteristics [3].

Given these limitations, developing a novel, nationally applicable prediction tool for lung acceptance in Switzerland may be beneficial. A Swiss model could incorporate parameters that reflect up-to-date lung acceptance criteria as well as relevant recipient characteristics to enable more precise donor–recipient matching [3, 32].

Limitations of the Study

There are some methodological limitations to our study. Adaptations were necessary to calculate the Oto and ET Scores, as certain parameters are not routinely recorded in the SOAS. Since bronchoscopy is optional before organ retrieval in Switzerland, this led to frequent missing data, potentially affecting aOto and aET results. Also, the interpretation of certain diagnostic tests, such as CT-scans and bronchoscopy, is somewhat subjective, which may also reduce score accuracy. Among the donors included in this study, the recorded reason for lung refusal may not always have been strictly donor-related, as it is often difficult to determine whether other factors – such as the lack of a compatible recipient – also influenced the transplant decision. Finally, this study confirmed that the three scores are associated solely with lung acceptance. To fully assess the suitability of the respective lung grafts, however, the scores would need to be validated based on short- and long-term recipient outcomes of the corresponding donor lungs.

Despite these limitations, this study offers novel insights into the assessment of lung acceptance practice in Switzerland. To the

authors' knowledge, it is the first to separately analyze lung acceptance for DBD and DCD donors using the three scores.

Conclusion

Our analysis demonstrated that the aOto, aET, and ZDS reliably reflected Swiss lung donor acceptance practice with acceptable to moderate discriminative ability. DCD donors were less likely to be accepted for lung transplantation at each score value, as they less frequently met ISHLT's ideal lung donor criteria compared to DBD donors. However, recent studies suggest that outcomes of lung transplants from DCD donors are comparable to DBD donors, highlighting the potential for a broader use of DCD donors. Furthermore, the impact of *ex-vivo* lung perfusion in DCD donors has not been assessed in our study as this information was not available. Recent European Society for Organ Transplantation (ESOT) recommendations emphasize the importance of perfusion techniques, including *ex vivo* lung perfusion and normothermic regional perfusion, for donor lung assessment and optimization [33]. In addition, emerging evidence demonstrates that these technologies may expand donor suitability and improve graft evaluation, particularly in DCD donation pathways [34]. Future research should study the impact of *ex-vivo* perfusion on lung acceptance as well as on transplant outcomes.

Given the limitations of the scores, a novel prediction tool might be of practical use for lung transplantation in Switzerland. Such a tool should incorporate up-to-date lung acceptance criteria as well as relevant recipient characteristics. This could increase organ utilization, allowing more patients to benefit from transplantation. A prediction tool, however, should only serve as a complementary aid that cannot replace the decision-making of transplant experts. Further research on transplant outcomes from the donors in our cohort would be essential to fully evaluate the potential of DCD donors and to guide future allocation strategies.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Access to Swiss Organ Allocation System (SOAS) data requires permission from the Federal Office of Public Health. The website https://www.gate.bag.admin.ch/artx/ui/home contains information on research data access to SOAS. Requests to access these datasets should be directed to https://www.gate.bag.admin.ch/artx/ui/home.

ETHICS STATEMENT

This analysis of SOAS data does not fall under the Swiss Human Research Act; legal regulation in Switzerland distinguishes between research (which is subject to approval) and quality assurance (not subject to approval). The Ethics Committee of the Canton of Bern determined the study to be of the quality assurance type and therefore exempt from review and the requirement to obtain informed consent (BASEC-ID: Req-2025- 00515).

AUTHOR CONTRIBUTIONS

FaI wrote the manuscript draft, analyzed the data, researched literature. JW advised on the writing of the manuscript, researched literature, reviewed the manuscript. SS advised on and contributed to the statistical analysis, reviewed the manuscript. FB advised on the interpretation of the data, reviewed the manuscript. TK, AK, MS, IO, and GL participated in the interpretation of the data, reviewed the manuscript. FrI Conceived of the study and its design, advised on the interpretation of the data, reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

IO discloses associations with the following institutions or companies: Roche (Institutional Grant), AstraZeneca (Advisory Board and Steering Committee), MSD (Advisory Board), BMS (Advisory Board), Medtronic (Institutional Grant and Advisory Board), Intuitive (Proctorship and Speakers Fee), Sanofi (Speakers Fee), Regeneron (Advisory Board), XVIVO (Institutional Grant), Siemens (Speakers Fee), Astellas (Speakers Fee). IO is IASLC Board Director, Member of the Thoracic Clinical Practice Standards Committee and the Thoracic Education Committee of AATS, iMig Board Member and JTCVS Associate Editor. She is in the Stiftungsrat Schulthessklinik and an Advisory Board Member at Med Uni Wien for Comprehensive Center for Chest Diseases (CCCD).

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

GENERATIVE AI STATEMENT

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

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ORIGINAL RESEARCH
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Incidental Combined Hepatocellular-Cholangiocarcinoma in Liver Transplant Recipients: A Matched Cohort Study

Sudha Kodali[1,2,3,4], *Ashton A. Connor*[1,2,5,6], *David W. Victor III*[1,2,3,4], *Maen Abdelrahim*[2,3,4,7], *Ahmed Elaileh*[5], *Khush Patel*[5], *Elizabeth W. Brombosz*[5], *Edward A. Graviss*[5,6,8], *Duc T. Nguyen*[9], *Susan Xu*[4,10], *Linda W. Moore*[5,6], *Mary R. Schwartz*[8], *Sadhna Dhingra*[8], *Tamneet Basra*[1,2,3], *Michelle R. Jones-Pauley*[1,2,3], *Mazen Noureddin*[1,2,3,11], *Constance M. Mobley*[1,2,5,6], *Mark J. Hobeika*[1,2,5,6], *Caroline J. Simon*[1,2,5,6], *Yee Lee Cheah*[1,2,5,6], *Kirk Heyne*[2,3,4,7], *Ahmed O. Kaseb*[12], *Ashish Saharia*[1,2,5,6], *A. Osama Gaber*[1,2,5,6] and *R. Mark Ghobrial*[1,2,5,6]*

[1]Sherrie and Alan Conover Center for Liver Disease and Transplantation, Houston Methodist Hospital, Houston, TX, United States, [2]JC Walter Jr Transplant Center, Houston Methodist Hospital, Houston, TX, United States, [3]Department of Medicine, Houston Methodist Hospital, Houston, TX, United States, [4]Department of Medicine, Weill Cornell Medical College, New York, NY, United States, [5]Department of Surgery, Houston Methodist Hospital, Houston, TX, United States, [6]Department of Surgery, Weill Cornell Medical College, New York, NY, United States, [7]Department of Oncology, Neal Cancer Center, Houston Methodist Hospital, Houston, TX, United States, [8]Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, TX, United States, [9]Department of Pediatrics, Baylor College of Medicine, Houston, TX, United States, [10]Center for Health Data Science and Analytics, Houston Methodist Hospital, Houston, TX, United States, [11]Houston Research Institute, Houston, TX, United States, [12]Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, United States

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***Correspondence**
R. Mark Ghobrial,
rmghobrial@houstonmethodist.org

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Mixed hepatocellular carcinoma (HCC) with cholangiocarcinoma (HCC-CCA) is an aggressive primary liver cancer and difficult to distinguish from HCC using non-invasive methods. Outcomes of patients incidentally diagnosed with HCC-CCA after LT relative to pure HCC with similar tumor burden were investigated. Medical records of patients undergoing LT (n = 1,898) for HCC (n = 493) from 6/2008–9/2023 were reviewed. Patients incidentally diagnosed with HCC-CCA were propensity matched to HCC patients undergoing LT. Independent analyses were performed using pre-LT (Match1; identifiable pre-LT) and explant pathology (Match2, more prognostic) characteristics. Incidental HCC-CCA occurred in 19 (3.9%) patients; all assumed to have HCC pre-LT and received HCC-directed neoadjuvant treatment. When matched on pre-LT characteristics (Match1, n = 57), more patients with HCC-CCA were outside Milan or University of California, San Francisco criteria on explant (p = 0.01). More patients with HCC-CCA underwent neoadjuvant microwave ablation (p = 0.02) compared to HCC Match2 (n = 45) but were otherwise similar demographically and clinically. Overall and recurrence-free survival were lower for HCC-CCA in Match1 (p = 0.003 and p < 0.001, respectively) and Match2 (p < 0.001 and p = 0.001, respectively). HCC-CCA has an

Abbreviations: AFP, alpha-fetoprotein; CCA, cholangiocarcinoma; HCC, hepatocellular carcinoma; HCC-CCA, mixed hepatocellular-cholangiocarcinoma; LT, liver transplantation.

aggressive phenotype with high recurrence after LT. Better screening tools and biomarkers are needed to distinguish HCC-CCA from HCC to ensure patients receive appropriate treatment and maximize post-LT outcomes.

Keywords: hepatocellular carcinoma, cholangiocarcinoma, liver transplantation, transplant oncology, liver neoplasms

INTRODUCTION

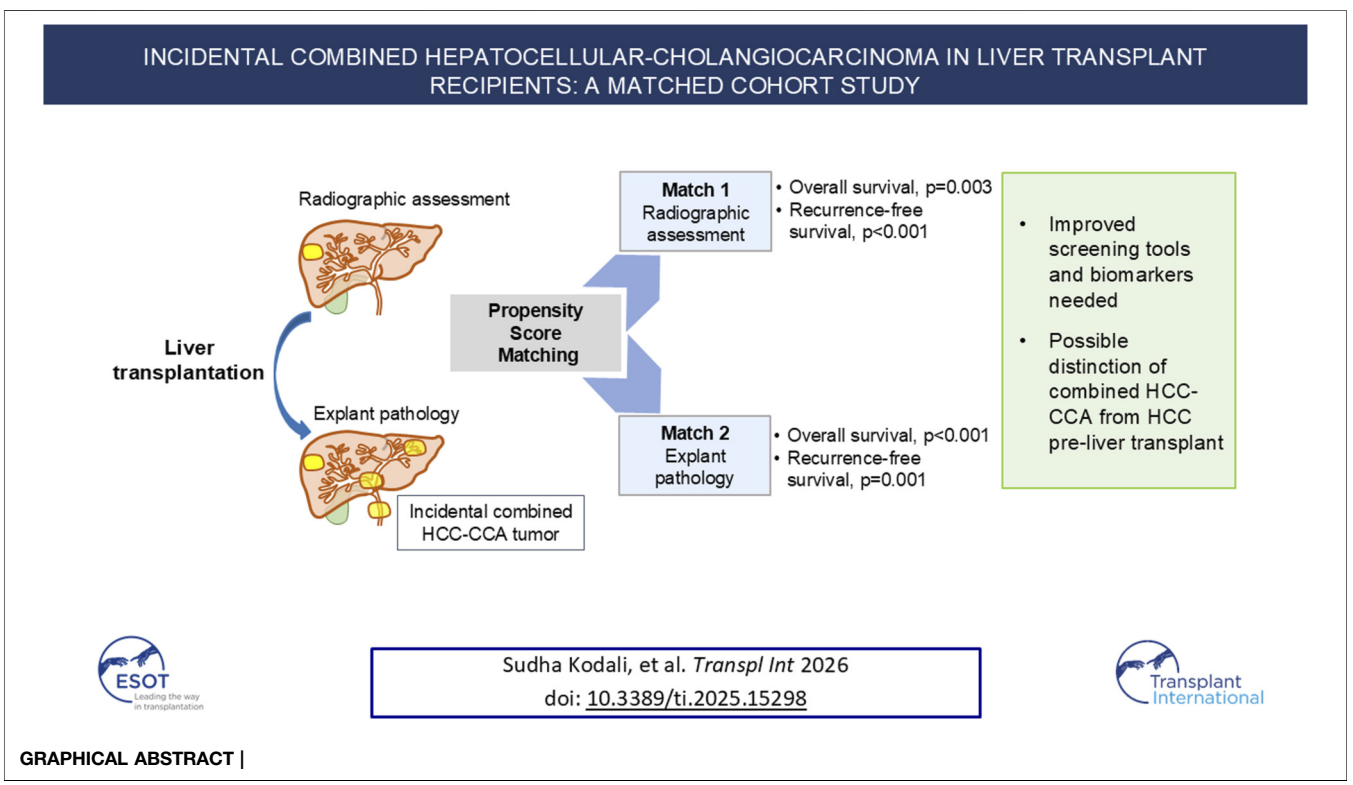
Primary hepatic malignancies are increasing in incidence and are now the third leading cause of cancer-related deaths worldwide [1]. Combined or mixed hepatocellular carcinoma-cholangiocarcinoma (HCC-CCA), accounting for around 0.4%–14.2% of primary liver cancers, is rare and often misclassified as HCC pre-transplant with worse outcomes [2]. Studies indicate that HCC-CCA tumors are more aggressive than HCC tumors and are associated with poorer prognosis than either HCC and or CCA alone [2–5].

Unlike HCC, HCC-CCA has largely been considered a contraindication for liver transplantation (LT) due to the increased risk of post-transplant recurrence and poor outcomes [6]. LT does provide a survival benefit over resection in patients with mixed tumors [7–9], but that benefit has traditionally been outweighed by the need to pursue utility in deceased donor grafts allocation. Importantly, most HCC-CCA cases in LT recipients were considered to be HCC alone prior to transplantation due to the difficulty in distinguishing HCC-CCA from HCC radiologically [10–13]. Thus, incidental diagnosis seems to be the norm for patients with HCC-CCA undergoing LT.

Some reports indicate an increasing incidence of incidental HCC-CCA in LT recipients in recent years [8, 10]. It is important to determine optimal treatment regimens to provide the best medical care possible to patients with HCC-CCA. Given the rarity of this type of tumor and that LT is not standard-of-care, a detailed description of the trajectory of patients with HCC-CCA provides important information on clinical outcomes. The primary aim of this paper is to describe the outcomes of LT recipients presumed to have HCC alone pre-LT and received neoadjuvant treatment for HCC but found to have HCC-CCA on explant. The secondary aims were to compare pre-LT (representing clinical decision making) versus explant predictors and to examine the patterns of recurrence and treatment.

MATERIALS AND METHODS

Medical records of 1,898 adult patients undergoing LT at a single, quaternary care institution between June 2008 and September 2023 were reviewed. Patients diagnosed with mixed HCC-CCA on explant were included in the primary analysis. All work was carried out with approval from the Houston Methodist Research Institute Institutional Review Board under protocol number



GRAPHICAL ABSTRACT |

Pro00000587 with a waiver of authorization. The center follows the guidance of the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

A multidisciplinary tumor board reviewed the medical records of patients referred for LT who had a diagnosis of liver cancer and made clinical care recommendations, including systemic therapy and locoregional therapy (LRT). Patients with large, single tumors (>5 cm in diameter), multifocal lesions, or poorly differentiated tumors received combined neoadjuvant systemic therapy and LRT. Neoadjuvant treatment was HCC-directed, as all patients with HCC-CCA were believed to have HCC prior to undergoing LT. All patients in the study were appropriately treated and down staged with LRT. Microwave ablation, TACE, and TARE were the LRT modalities utilized. Decisions to place patients on the LT waitlist were made by a multidisciplinary transplant medical review board. While on the LT waitlist, patients underwent close monitoring, including cross-sectional imaging every 3 months to rule out disease progression.

Statistical Analysis

HCC-CCA recipients were matched with HCC alone recipients using a propensity score method of 1:3 (as 1 HCC-CCA case to 3 HCC cases), using a non-replacement, caliper width 0.2 approach. Propensity score matching allowed comparisons between patients with similar disease burden. Since the patients with HCC-CCA were determined at the time of liver explant, it was decided to perform 2 independent propensity score matches. Variables were chosen based on established prognostic factors in HCC. The first match utilized characteristics measurable pre-transplant that could inform clinical decision making and transplant candidate selection ("pre-LT match"): pre-transplant alpha-fetoprotein (AFP) levels and total radiologic tumor diameter. No imputation of missing variables was planned.

The second, independently performed propensity score match used features from explant pathology ("explant match"), which are frequently more prognostic than pre-transplant variables in HCC [14–16]. This match more reflects the actual pathologic risk of the lesions on explant. The propensity match was performed using a 1:3 ratio of 1 HCC-CCA to 3 HCC alone cases, again using the non-replacement, 0.2 caliper width approach. The scoring was based on pathologic total tumor diameter, tumor differentiation, and presence or absence of vascular invasion. No imputation of missing variables was planned.

Demographic and clinical data are reported as frequencies and proportions for categorical variables and as median and interquartile range (IQR) for continuous variables. Differences between patients with HCC-CCA and matched patients with HCC were compared using the chi-square or Fisher's exact tests for categorical variables and Kruskal-Wallis test for continuous variables. Balance of the covariates used as the matching criteria was evaluated by the percent standardized bias. Overall all-cause patient and recurrence-free survival are presented by Kaplan-Meier curves. Differences in survival across groups were compared using the log-rank test. All analyses were performed on Stata version 17.0 (StataCorp LLC, College Station, TX). A $P < 0.05$ was considered statistically significant.

RESULTS

Patients With Mixed Hepatocellular Carcinoma and Cholangiocarcinoma

Of 493 patients having LT for HCC, 19 (3.9%) patients with incidentally diagnosed HCC-CCA underwent LT for HCC during the study period (**Table 1**). Recipients were predominantly male (15, 78.9%) and white (14, 73.7%). Most had viral disease etiology (Hepatitis C: 8 [42.1%]; Hepatitis B: 2 [10.5%]). All received a deceased donor LT. Median laboratory Model for End-Stage Liver Disease (MELD) score at transplant was 17 (IQR, 9–29). These patients generally had low serum tumor markers: median alpha fetoprotein (AFP) was 7.1 (2.7–22.2) ng/mL at listing and was 5.2 (2.6–20.9) ng/mL at transplant. Median carbohydrate antigen 19–9 (CA19-9) level measured soonest prior to LT was 34.0 (19.3–54.0) U/mL, and 11 (57.9%) patients had "normal" CA19-9 values (<37 U/mL). Only one patient (5.3%) had CA19-9 >100 U/mL.

Because the patients were thought to have HCC prior to LT based on imaging characteristics, they received neoadjuvant therapies directed at HCC. Most (n = 16, 84.2%) received some type of neoadjuvant therapy (**Table 1**). TACE was most frequently used (n = 11, 57.9%), followed by sorafenib (n = 5, 26.3%), and radiofrequency ablation (RFA, n = 4, 21.1%, including 1 patient who received both RFA and TACE). Three patients (15.8%) received microwave ablation and two (10.5%) received yttrium-90 (Y90) as neoadjuvant treatment. The 5 patients who received neoadjuvant sorafenib underwent treatment in 2015 or earlier and are included in the count of those who received TACE. Based on pre-LT radiographic measurements, most (n = 16, 84.2%) were within Milan criteria. Two patients (10.5%) were outside Milan but within University of California, San Francisco (USCF) criteria, and one patient (5.3%) was outside UCSF criteria (**Table 1**).

The median largest tumor size in the HCC-CCA cases was ~3.0 (IQR, 2.0–3.8); most patients had multifocal disease. Based on pathology results, 7 (36.8%) patients were within Milan, 6 (31.6%) were outside Milan and within UCSF, and 6 (31.6%) were outside USCF criteria. Of the patients who were outside UCSF criteria on explant, 5 patients responded to LRT with tumor size stabilization or reduction. One patient was transplanted urgently and had only hepatic ultrasound pre-LT; thus, this case did not receive neoadjuvant chemotherapy or LRT.

Most patients had T2 tumors (9, 47.4%), based on pathologic findings in the explants (**Table 1**). One patient (5.3%) had nodal metastases. None of the patients had macrovascular invasion, and 2 (10.5%) patients were found to have microvascular invasion (**Supplementary Table S2**). Most patients had moderately (n = 9, 47.4%) or poorly (n = 9, 47.4%) differentiated tumors; only one (1.8%) patient had well-differentiated HCC-CCA.

Data on post-LT adjuvant therapy was available for 18 of 19 patients. Of those 18 patients, 13 received adjuvant therapy with most patients receiving gemcitabine- or capecitabine-based therapy (**Supplementary Table S3**). None of the patients had metastatic disease at transplant.

At a median post-transplant follow-up of 1.95 years, 13 (68.4%) of the 19 patients with HCC-CCA were deceased (**Table 1**). Nine

TABLE 1 | Clinical characteristics of liver transplant recipients with mixed hepatocellular carcinoma-cholangiocarcinoma and propensity-matched patients with hepatocellular carcinoma only based on pre-transplant variables ("pre-LT match").

Recipient Characteristics	Mixed tumor	HCC Pre-LT match	p-value
	N = 19	N = 57	
Age (years), median (IQR)	65.2 (61.1, 69.5)	62.0 (57.0, 67.0)	0.12
Sex, n (%)			0.77
Male	4 (21.1)	15 (26.3)	
Female	15 (78.9)	42 (73.7)	
Race/ethnicity, n (%)			0.76
White	14 (73.7)	39 (68.4)	
Black	0 (0.0)	4 (7.0)	
Hispanic	3 (15.8)	10 (17.5)	
Asian	2 (10.5)	4 (7.0)	
BMI at LT (kg/m^2), median (IQR)	29.6 (24.8, 33.9)	27.3 (23.9, 32.7)	0.64
Laboratory MELD at transplant, median (IQR)	17.0 (9.0, 29.0)	13.0 (10.0, 19.0)	0.57
Underlying etiology of liver disease, n (%)			0.19
Hepatitis C	8 (42.1)	39 (68.4)	
Hepatitis B	2 (10.5)	3 (5.3)	
Alcohol-associated liver disease	3 (15.8)	7 (12.3)	
MASLD or cryptogenic cirrhosis	5 (26.3)	7 (12.3)	
Other	1 (5.3)	1 (1.8)	
Waiting time from listing (days), median (IQR)	332.0 (148.0, 806.0)	346.0 (190.0, 525.0)	0.67
Pre-transplant tumor markers			
Last AFP prior to transplant (ng/mL), median (IQR)	5.2 (2.6, 20.9)	6.6 (3.6, 27.3)	0.63
Neutrophil/lymphocyte ratio pre-LT, median (IQR)	3.5 (2.0, 7.2)	5.8 (2.7, 17.9)	0.15
Neoadjuvant therapy			
Neoadjuvant therapy, n (%)			
TACE	11 (57.9)	43 (75.4)	0.16
Radiofrequency ablation	4 (21.1)	13 (22.8)	1.00
Resection	0 (0.0)	2 (3.5)	1.00
Sorafenib	5 (26.3)	14 (24.6)	1.00
Yttrium-90	2 (10.5)	3 (5.3)	0.59
Microwave ablation	3 (15.8)	0 (0.0)	**0.01**
Total number of LRT, median (IQR)	2.0 (1.0, 3.0)	1.0 (1.0, 2.0)	0.09
Pre-transplant radiographic tumor characteristics			
Tumor burden classification, n (%)			0.54
Within Milan	16 (84.2)	45 (78.9)	
Outside Milan, within UCSF	2 (10.5)	4 (7.0)	
Outside UCSF	1 (5.3)	8 (14.0)	
Pathologic tumor characteristics			
Tumor burden classification, n (%)			**0.01**
Within Milan	7 (36.8)	38 (66.7)	
Outside Milan, within UCSF	6 (31.6)	4 (7.0)	
Outside UCSF	6 (31.6)	15 (26.3)	
Tumor T stage, n (%)			0.30
T0	1 (5.3)	1 (2.8)	
T1s	1 (5.3)	0 (0.0)	
T1	4 (21.1)	15 (41.7)	
T2	9 (47.4)	17 (47.2)	
T3a	2 (10.5)	2 (5.6)	
T3b	1 (5.3)	1 (2.8)	
T4	1 (5.3)	0 (0.0)	
Tumor N Stage, n (%)			0.37
N0	8 (42.1)	21 (58.3)	
N1	0 (0.0)	1 (2.8)	
NX	11 (57.9)	14 (38.9)	
Microvascular invasion, n (%)	2 (10.5)	2 (5.6)	0.60
Total number of tumors (pathology), median (IQR)	2.0 (2.0, 4.0)	2.0 (1.0, 3.0)	0.34
Largest tumor diameter (cm), median (IQR)	3.0 (2.0, 3.8)	2.5 (2.0, 3.1)	0.20
Outcomes			
Tumor recurrence, n (%)			**0.001**
No	10 (52.6)	51 (89.5)	
Yes	9 (47.4)	6 (10.5)	
Patient status, n (%)			**0.003**
Deceased	13 (68.4)	16 (28.1)	
Alive	6 (31.6)	41 (71.9)	

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TABLE 1 | (*Continued*) Clinical characteristics of liver transplant recipients with mixed hepatocellular carcinoma-cholangiocarcinoma and propensity-matched patients with hepatocellular carcinoma only based on pre-transplant variables ("pre-LT match").

Recipient Characteristics	Mixed tumor	HCC Pre-LT match	p-value
	N = 19	N = 57	
Propensity score matching criteria			
AFP at listing (ng/mL), median (IQR)	7.1 (2.7, 22.2)	7.9 (4.3, 32.9)	0.22
Total radiographic total tumor diameter at listing (cm), median (IQR)	2.2 (1.3, 4.3)	2.3 (1.2, 5.3)	0.71
Total number of tumors at last scan pre-LT, median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.80

Bold values denote statistical significance (p < 0.05).

AFP, alpha fetoprotein; BMI, body mass index; HCC, hepatocellular carcinoma; IQR, interquartile range; LRT, locoregional therapies; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-Stage Liver Disease, TACE, transarterial chemoembolization; UCSF, University of California, San Francisco.

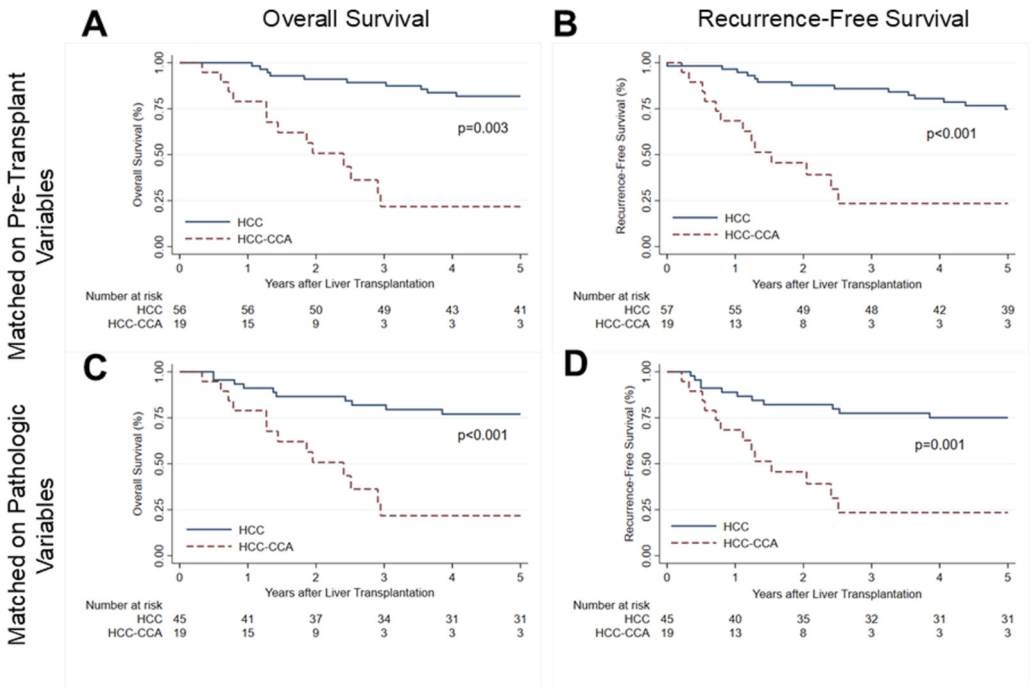

FIGURE 1 | Survival after liver transplantation for patients with mixed hepatocellular carcinoma-cholangiocarcinoma (solid line) and propensity-matched patients with hepatocellular carcinoma (dashed line). **(A)** Overall patient survival and **(B)** recurrence-free survival for mixed tumor patients and patients with HCC matched on pre-transplant characteristics. **(C)** Overall patient survival and **(D)** recurrence-free survival for mixed tumor patients and HCC patients matched on explant pathology characteristics. HCC, hepatocellular carcinoma; HCC-CCA, mixed hepatocellular carcinoma-cholangiocarcinoma.

(47.4%) patients ultimately died from metastatic adenocarcinoma, 2 (10.5%) from cardiac arrest, 1 (5.3%) from multi-system organ failure, and 1 (5.3%) from respiratory failure. Overall survival (OS) rates of patients with mixed tumors were 78.9% at 1 year and 23.8% at 3 and 5 years post-LT (**Figure 1A**). Recurrence-free survival (RFS) was 68.4% at 1 year and 26.8% at 3 and 5 years after transplant (**Figure 1B**).

Pre-Liver Transplantation Matched Hepatocellular Carcinoma Patient Comparison

The pre-LT match included 57 patients with HCC matched to the 19 patients with HCC-CCA based on pre-transplant characteristics. No missing variables occurred in the match. Characteristics of the entire HCC cohort are presented in **Supplementary Table S1**. Demographically, patients with mixed tumor and HCC alone were similar, and they also had similar indications for LT (all $p > 0.05$; **Table 1**; **Supplementary Table S2**). There were also no differences in severity of illness: laboratory MELD ($p = 0.57$), listing MELD ($p = 0.80$), and medical condition at transplant ($p = 1.00$) were all statistically similar.

Serum tumor markers (AFP, neutrophil-to-leukocyte ratio) at the time of listing and prior to LT were also not significantly different between patients with HCC-CCA and matched patients with HCC (all $p > 0.05$) when matched on pre-LT features (**Table 1**). Radiographically, tumor number ($p = 0.86$) and total tumor diameter at listing ($p = 0.71$) were similar. Patients

TABLE 2 | Clinical characteristics of liver transplant recipients with mixed hepatocellular carcinoma-cholangiocarcinoma and propensity-matched patients with hepatocellular carcinoma only based on explant pathology variables ("explant match").

Recipient Characteristics	Mixed Tumor	HCC Explant Match	p-value
	N = 19	N = 45	
Laboratory MELD at transplant, median (IQR)	17.0 (9.0, 29.0)	13.0 (10.0, 25.0)	0.58
List MELD at txp, median (IQR)	29.0 (26.0, 33.0)	29.0 (27.0, 32.0)	0.85
Underlying etiology of liver disease, n (%)			0.62
Hepatitis C	8 (42.1)	27 (60.0)	
Hepatitis B	2 (10.5)	2 (4.4)	
Alcohol-associated liver disease	3 (15.8)	5 (11.1)	
MASLD or cryptogenic cirrhosis	5 (26.3)	8 (17.8)	
Other	1 (5.3)	3 (6.7)	
Waiting time from listing (days), median (IQR)	332.0 (148.0, 806.0)	364.0 (206.0, 571.0)	0.98
Pre-transplant tumor markers			
AFP at listing (ng/mL), median (IQR)	7.1 (2.7, 22.2)	17.2 (4.8, 56.1)	0.07
Last AFP prior to transplant (ng/mL), median (IQR)	5.2 (2.6, 20.9)	7.6 (3.6, 25.1)	0.75
Neutrophil/lymphocyte ratio pre-LT, median (IQR)	3.5 (2.0, 7.2)	4.4 (2.2, 9.2)	0.59
Neoadjuvant therapy			
Neoadjuvant therapy, n (%)			
TACE	11 (57.9)	33 (73.3)	0.25
Radiofrequency ablation	4 (21.1)	13 (28.9)	0.76
Resection	0 (0.0)	3 (6.7)	0.55
Sorafenib	5 (26.3)	17 (37.8)	0.57
Yttrium-90	2 (10.5)	5 (11.1)	1.00
Microwave ablation	3 (15.8)	0 (0.0)	**0.02**
Any neoadjuvant therapy, n (%)	16 (84.2)	41 (91.1)	0.41
Total number of LRT, median (IQR)	2.0 (1.0, 3.0)	2.0 (1.0, 2.0)	0.78
Pre-transplant radiographic tumor characteristics			
Tumor burden classification, n (%)			0.11
Within Milan	16 (84.2)	25 (55.6)	
Outside Milan, within UCSF	2 (10.5)	11 (24.4)	
Outside UCSF	1 (5.3)	9 (20.0)	
Total radiographic total tumor diameter at listing (cm), median (IQR)	2.2 (1.3, 4.3)	3.5 (2.1, 5.3)	0.09
Total number of tumors at listing, median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.84
Pathologic tumor characteristics			
Tumor burden classification, n (%)			0.44
Within Milan	7 (36.8)	17 (37.8)	
Outside Milan, within UCSF	6 (31.6)	8 (17.8)	
Outside UCSF	6 (31.6)	20 (44.4)	
HCC necrosis estimate (%), median (IQR)	35.0 (10.0, 80.0)	65.0 (20.0, 95.0)	0.32
Tumor location, n (%)			0.26
Right lobe	8 (42.1)	27 (60.0)	
Left lobe	3 (15.8)	4 (8.9)	
Bilobar	7 (36.8)	14 (31.1)	
Other	1 (5.3)	0 (0.0)	
Tumor T stage, n (%)			0.49
T0	1 (5.3)	1 (2.2)	
T1s	1 (5.3)	0 (0.0)	
T1	4 (21.1)	14 (31.1)	
T2	9 (47.4)	20 (44.4)	
T3a	2 (10.5)	8 (17.8)	
T3b	1 (5.3)	1 (2.2)	
T4	1 (5.3)	1 (2.2)	
Tumor N Stage, n (%)			0.36
N0	8 (42.1)	27 (60.0)	
N1	0 (0.0)	1 (2.2)	
NX	11 (57.9)	17 (37.8)	
Microvascular invasion, n (%)	2 (10.5)	1 (2.2)	0.21
Total number of tumors (pathology), median (IQR)	2.0 (2.0, 4.0)	2.0 (1.0, 4.0)	0.87
Largest tumor diameter (cm), median (IQR)	3.0 (2.0, 3.8)	3.5 (2.7, 4.7)	0.08
Outcomes			
Tumor recurrence, n (%)			**0.01**
No	10 (52.6)	38 (84.4)	
Yes	9 (47.4)	7 (15.6)	
Patient status, n (%)			**0.005**

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TABLE 2 | (*Continued*) Clinical characteristics of liver transplant recipients with mixed hepatocellular carcinoma-cholangiocarcinoma and propensity-matched patients with hepatocellular carcinoma only based on explant pathology variables ("explant match").

Recipient Characteristics	Mixed Tumor	HCC Explant Match	p-value
	N = 19	N = 45	
Deceased	13 (68.4)	13 (28.9)	
Alive	6 (31.6)	32 (71.1)	
Total intraoperative PRBC (units), median (IQR)	4.0 (2.0, 10.0)	5.0 (2.0, 6.0)	0.99
Propensity score matching criteria			
Pathologic total tumor diameter (cm), median (IQR)	5.6 (3.5, 7.3)	6.0 (4.1, 11.0)	0.83
Pathologic differentiation, n (%)			0.68
Well	1 (5.3)	3 (6.7)	
Moderate	9 (47.4)	27 (60.0)	
Poor	9 (47.4)	15 (33.3)	
Any vascular invasion, n (%)			0.21
No	17 (89.5)	44 (97.8)	
Yes	2 (10.5)	1 (2.2)	

Bold values denote statistical significance (p < 0.05).

AFP, alpha fetoprotein; BMI, body mass index; HCC, hepatocellular carcinoma; IQR, interquartile range; LRT, locoregional therapies; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, Model for End-Stage Liver Disease, TACE, transarterial chemoembolization; UCSF, University of California, San Francisco.

with HCC-CCA also received similar types of neoadjuvant therapy (all p > 0.05) apart from microwave ablation (MWA), which occurred more often in HCC-CCA (p = 0.01; **Table 1**). The number of locoregional therapy treatments were similar between groups (p = 0.70; **Table 1**). HCC T and N staging based on explant pathology was also similar between patients with HCC-CCA and pre-LT matched HCC alone (T stage, p = 0.30; N stage, p = 0.37; **Table 1**). Both groups also had similar pathologic estimated tumor necrosis (p = 0.40). Importantly, although pre-LT tumor burden was similar between groups, a significantly greater proportion of patients with HCC-CCA were found to be outside Milan and UCSF criteria on explant, indicative of the true biological disease burden (p = 0.01; **Table 1**).

Relative to matched patients with HCC, patients with HCC-CCA had significantly lower OS (log-rank: p = 0.003; **Figure 1A**) and RFS (log-rank: p < 0.001; **Figure 1B**). By Cox proportional hazards analysis, OS for patients with HCC-CCA had a hazard ratio (HR) of 6.47 (95% CI, 2.87–14.55; p < 0.001) relative to patients with HCC only matched on pre-LT features. Similarly, RFS rates were significantly inferior for patients with HCC-CCA (HR, 5.55; 95% CI, 2.58–11.97; p < 0.001).

Explant Pathology Matched Hepatocellular Carcinoma Patient Comparison

The second, independent propensity match using explant pathology features ("explant match") included 45 patients with HCC matched to the core cohort of 19 patients with HCC-CCA. No missing variables occurred in the match. The patients with HCC-CCA had similar demographics as the patients with explant-matched HCC (all p > 0.05; **Supplementary Table S4**). Etiology of liver disease was not significantly different between the two groups (p = 0.62; **Table 2**), and they also had similar laboratory MELD scores at transplant (p = 0.58). AFP levels at listing and immediately prior to transplant were not statistically different between patients with HCC-CCA and patients with HCC (p = 0.07 and p = 0.75, respectively; **Table 2**). Patients with HCC-CCA were more likely to have received neoadjuvant MWA than patients with HCC matched on explant pathology features (15.8% vs. 0%; p = 0.02; **Table 2**).

Disease burden was similar between HCC-CCA and HCC alone in the "explant match" group. The proportion of patients within or outside Milan or USCF criteria were similar between groups (p = 0.44). Pre-transplant radiographic lesion number (p = 0.84) and total tumor diameter (p = 0.09) were not statistically different. Total tumor number (p = 0.87) and tumor diameter (p = 0.08) on explant were also statistically comparable. T (p = 0.49) and N (p = 0.36) staging were similar between groups (**Table 2**). Microvascular invasion rates were similar among HCC-CCA (10.5%) and HCC alone in the "explant match" group (2.2%; p = 0.21).

Mixed tumor cases had significantly lower OS (log-rank: p < 0.001; **Figure 1C**) and RFS (log-rank: p = 0.001; **Figure 1D**) rates than those with HCC alone matched on explant features. In univariable Cox proportional hazards analysis, both OS (HR, 4.67; 95% CI, 2.07–10.53; p = 0.0003) and RFS (HR, 3.65; 95% CI, 1.70–7.82; p = 0.001) were significantly inferior for patients with HCC-CCA.

DISCUSSION

Patients with HCC-CCA had significantly worse OS and RFS than HCC, despite similar clinical features. This reflects the aggressive biology and challenges of pre-LT diagnosis. These comparisons identified patients with HCC with similar features that inform pre-LT clinical decision making and that approximate actual pathologic risk, respectively. Unfortunately, the mixed tumor patients had low AFP and CA19-9 levels and were radiographically similar to patients with HCC alone, making correct pre-LT diagnosis difficult. Like many other studies, the patients with mixed tumor in this cohort were originally diagnosed with HCC and thus received HCC-directed neoadjuvant therapy. It is likely that the CCA component of the mixed HCC-CCA lesions did not receive appropriate neoadjuvant systemic treatment, such as standard chemotherapy regimens for CCA. All patients with intrahepatic CCA considered for LT at our institution receive neoadjuvant

TABLE 3 | Summary of survival outcomes of literature reports of patients undergoing liver transplantation for combined hepatocellular-cholangiocarcinoma.

Paper	Year	n	Data source	Dates	1y OS (%)	3y OS (%)	5y OS (%)
Present study		19	Texas, US (single center)	2008–2022	78.9	23.8	23.8
Panjala et al.	2010	12	Florida, US (single center)	1998–2008	79	66	16
Groeschl et al.	2013	19	SEER database (US)	1973–2008	89	48	
Sapisochin et al.	2014	15	Spain (multicenter)	2000–2010	93	78	78
Vilchez et al.	2016	94	UNOS database	1994–2013	82	47	40
Jung et al.	2017	32	Seoul, South Korea (single center)	2005–2014	84.4	73.1	65.8
Antwi et al.	2018	19	Florida, US (single center)	2001–2016	84	74	
Lunsford et al.	2018	12	California, US (single center)	1984–2015	75	54	42
Li et al.	2019	301	Meta-analysis	2000–2018			41
Spolverato et al.	2019	220	National cancer database	2004–2015			52.6
Dageforde et al.	2021	99	US consortium (12 centers)	2009–2017	89.1[a]	77.1[a]	70.1[a]
Jaradat et al.	2021	19	Germany, Turkey, Jordan (multi-center)	2001–2018	57.1	38.1	
Brandão et al.	2022	7	Brazil (single center)	1997–2019	85.7		54.1
Chen et al.	2022	60	SEER database (US)	2004–2015	86.7	68.3	56.6
Anilir et al.	2023	17	Turkey (single center)	2004–2019	80.2	57.3	66.7
Garcia-Moreno et al.	2023	6	Spain (single center)	2006–2019	83.3	66.7	66.7
Mi et al.	2023	49	SEER database (US)	2000–2018	86.2	72.4	60.3
Penzkofer et al.	2023	6	Germany (single center)	2008–2020	100	100	80
Kim et al.	2023	111	Korea (multicenter)	2000–2018	84.4	63.8	

[a]*Patients within Milan criteria.*

gemcitabine and cisplatin as bridging and downstaging therapy, which is also used to inform patient selection [17]. It was not possible to follow the standard protocol in patients who were determined to have HCC-CCA only at the time of examination of the liver explant. These patients did receive CCA-focused adjuvant therapy. Due to the small sample size, we are unable to make conclusions regarding the efficacy of one adjuvant therapy over another, and the adjuvant regimens remain hypothesis-generating only.

The propensity match analysis provides insight into the clinical presentation and biology of HCC-CCA compared to HCC with similar pre-LT (Match 1) and post-LT (Match 2) characteristics. Matching on a small subset of prognostic variables allows us to better understand differences in mixed tumors and HCC when controlling for tumor burden. In both analyses, patients with HCC-CCA were more likely to have received neoadjuvant MWA. MWA has been shown to be an effective treatment in both HCC [18] and iCCA [19], and single-center studies have demonstrated its efficacy as a bridging [20, 21] and downstaging therapy [22]. Thus, it is unlikely that the use of MWA significantly affected outcomes. Patients matched on pre-LT characteristics (Match 1) were more likely to be outside Milan criteria on explant, highlighting the difficulty of radiologic staging in biologically aggressive tumors. This result highlights the difficulty of estimating tumor burden pre-LT in patients whose tumors have aggressive biology, such as HCC-CCA. It is interesting that 9 of the HCC-CCA patients with tumors inside Milan criteria radiologically pre-LT were outside Milan on explant pathology. Only 2 patients were outside Milan criteria due to lymphovascular invasion, which is very difficult to detect radiologically.

The 3- and 5-year OS rates for the cohort of 19 patients with HCC-CCA described here were much lower than other papers have reported (**Table 3**). Most patients with mixed tumors were thought to be within Milan criteria pre-LT (16, 84.2%), demonstrating that poor outcomes can occur even with a small tumor burden. Other papers have also shown that patients with HCC-CCA have worse outcomes than matched patients with HCC alone [13, 23–25], although some centers have reported similar survival rates [8, 9, 26, 27]. The OS rates reported here are also much lower than what our own center has demonstrated for patients with large HCC tumor burden (beyond UCSF criteria) [28], and for patients with intrahepatic CCA [17]. Penzkofer and colleagues noted that outcomes seemed to be more strongly associated with the CCA component of the mixed tumors [11]; our data also support this conclusion.

This study highlights the need for unique biomarkers, whether blood, tissue, or imaging, to distinguish HCC from HCC-CCA. Other studies of LT recipients have shown that CCA-specific biomarkers like CA19-9 were similar between patients with pure HCC and patients with mixed tumors [13]. Given that patients with mixed tumors have reduced expected post-LT survival, better methods for diagnosing HCC-CCA pre-LT are needed, particularly as the number of patients undergoing LT for oncologic indications increases. Patients whose lesions are identified as liver imaging reporting and data system (LIRADS)-M, presumed to have likely or definite malignancy, or imaging characteristics not typical of HCC, should undergo image-guided biopsy for definitive diagnosis. If a patient is confirmed to have HCC-CCA, centers should obtain genetic profiling/next-generation sequencing data to optimize tailoring treatment. Such genomic data can help guide physicians in selecting neoadjuvant systemic options that will treat both components (hepatocellular and adenocarcinoma) of the cancer. Given poor outcomes and high rates of recurrence, institution-based protocols are necessary for treating these aggressive cancers, considering the dearth of data in post-transplant outcomes in patients with HCC-CCA.

This study is limited by its retrospective nature and because it only incorporates patients from a single center. Additionally, very few patients underwent LT for HCC-CCA during the study period, limiting the sample size of this cohort, particularly at longer follow-

up (>3 years post-LT) when many patients had died. Thus, the small number of patients could reduce the confidence in long-term follow up outcomes. Although our institution is in a region with high racial and ethnic diversity, the results presented here may not accurately reflect the experiences at other centers. There might be residual confounding arising from unmeasured patients' attributes. Despite these limitations, this study has several strengths. To our knowledge, this manuscript presents the largest propensity score matching analysis of patients undergoing LT for HCC-CCA vs. HCC using multiple variables to select patients with similar disease burden. Thus, the conclusions drawn here provide important insight into the surgical treatment of patients with HCC-CCA. Another major strength of this cohort is the diverse patient population at our center. Although most patients with HCC-CCA were non-Hispanic White, this work still provides an accurate representation of the incidence of HCC-CCA in a diverse transplant population.

This manuscript provides a propensity-score matched comparison utilizing granular center medical records of patients receiving LT from deceased donors for HCC where incidental HCC-CCA occurred. Although LT can offer superior OS relative to resection [7, 9, 11], the study showed that survival is still much lower for patients with HCC-CCA than for HCC, the most common oncologic indication for LT. Given that most patients with HCC-CCA are diagnosed incidentally after transplant and are associated with inferior outcomes, allocation policy may need to weigh whether LT for HCC-CCA is justified without better selection tools and treatment options. Accurate pre-LT diagnosis may have allowed patients with HCC-CCA to receive adequate neoadjuvant treatment for the CCA component of the tumor, potentially improving outcomes. Better screening techniques are needed to identify patients with these rare tumors pre-transplant to ensure they receive the most appropriate treatment possible. Liquid biopsy and next-generation sequencing show promise in helping to accurately distinguish HCC-CCA from HCC [29]. Given the improved survival after LT for HCC-CCA relative to resection, increasing utilization of machine perfusion [30] and extended criteria donor grafts [31–34] may allow greater expansion of LT to well-selected patients.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Individual privacy is a concern when reporting on rare conditions. Therefore, the data are not available to be released. Requests to access these datasets should be directed to rmghobrial@houstonmethodist.org.

ETHICS STATEMENT

The studies involving humans were approved by Houston Methodist Research Institute Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the study was minimal risk. Informed consent was not practicable because some of the patients had died. The study uses only secondary data analysis.

AUTHOR CONTRIBUTIONS

SK – conception or design of the work; acquisition and interpretation of data; preparation of the manuscript; review and final approval of the manuscript. AC and AE – acquisition of data; interpretation of data; review and final approval of the manuscript. DV and MA interpretation of data; review and final approval of the manuscript. KP – conception or design of the work; acquisition and analysis of data; interpretation of data; review and final approval of the manuscript. EB – conception or design of the work; acquisition, analysis, and interpretation of data; preparation of the manuscript; review and final approval of the manuscript. EG, DN, and SX – analysis and interpretation of data; review and final approval of the manuscript. LM – acquisition and interpretation of data; preparation of the manuscript; review and final approval of the manuscript. MS, SD, TB, M-JP, MH, CS, YL, KH, AK, AS, and AG – interpretation of data; review and final approval of the manuscript. RG – conception or design of the work; interpretation of data; review and final approval of the manuscript. 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.2025.15298/full#supplementary-material

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ORIGINAL RESEARCH
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Donor-Derived Cell-Free DNA in Pancreas-Kidney, Heart-Kidney, and Liver-Kidney Multiorgan Transplant Recipients (MOTR)

Gaurav Gupta[1], David Wojciechowski[2], Alp Sener[3], Timothy Gong[4], Ty B. Dunn[5†], Nadiesda Costa[6], Jon S. Odorico[7], Reem Daloul[8†], Vinayak S. Rohan[9], D. Giovanni Biagini[10], David Barnes[10], Navchetan Kaur[10], Geethanjali Gude[10], Ebad Ahmed[10], Jing Xie[10], Catherine J. Spellicy[10], Nour Al Haj Baddar[10], Michelle S. Bloom[10], Zachary Demko[10], Adam Prewett[10], Phil Gauthier[10], Sangeeta Bhorade[10], Hossein Tabriziani[10] and Sanjeev K. Akkina[11] on behalf of the MOTR study investigators*

[1]Virginia Commonwealth University, Richmond, VA, United States, [2]UT Southwestern Medical Center, Dallas, TX, United States, [3]Western University, Schulich School of Medicine and Dentistry, London, ON, Canada, [4]Baylor University Medical Center, Dallas, TX, United States, [5]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States, [6]MedStar Georgetown University Hospital, Washington, DC, United States, [7]Medical College of Wisconsin, Milwaukee, WI, United States, [8]The Ohio State University, Columbus, OH, United States, [9]Northwestern University Feinberg School of Medicine, Chicago, IL, United States, [10]Natera, Inc., Austin, TX, United States, [11]Loyola University Medical Center, Maywood, IL, United States

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***Correspondence**
Gaurav Gupta,
gaurav.gupta@vcuhealth.org

†Present address:
Ty B. Dunn,
Medical College of Wisconsin,
Milwaukee, WI, United States
Reem Daloul,
Allegheny General Hospital, Pittsburgh,
PA, United States

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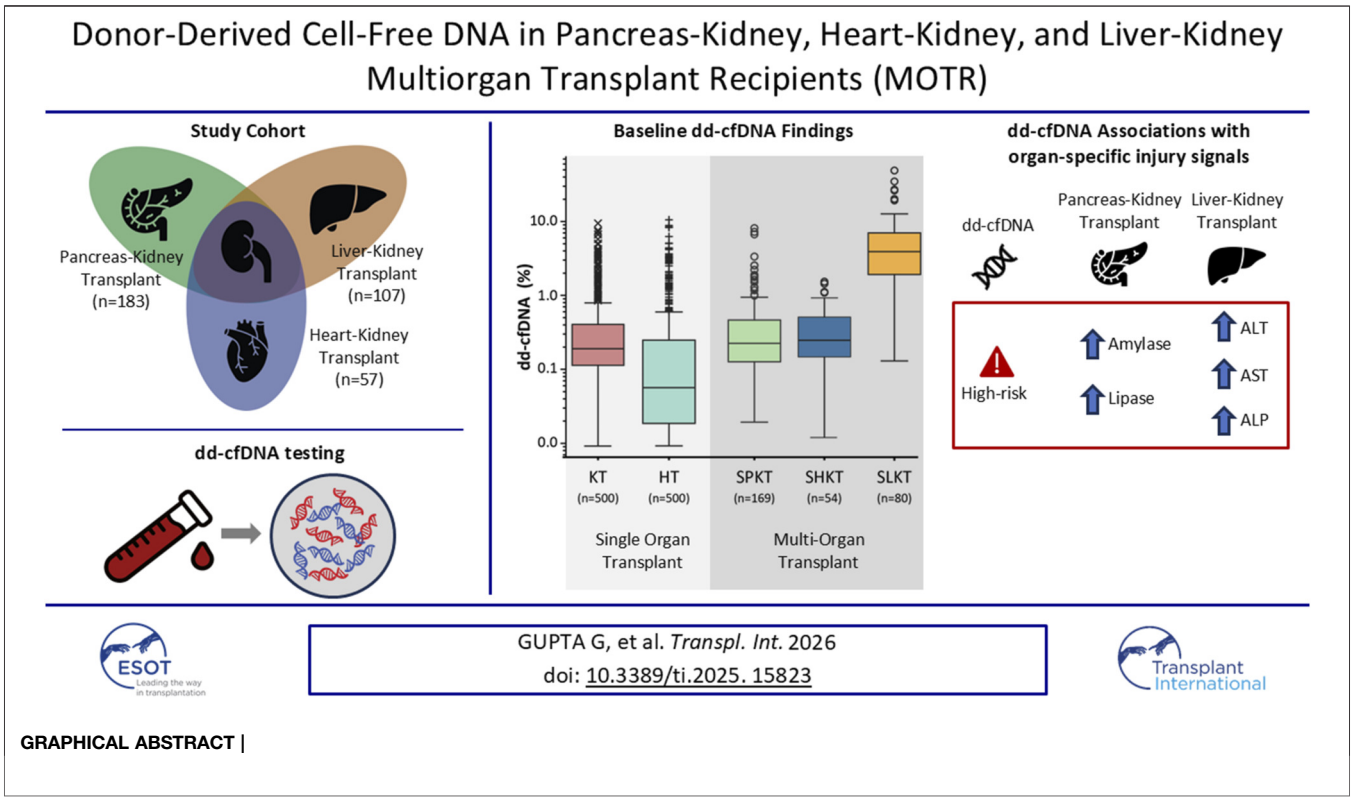
Donor-derived cell free DNA (dd-cfDNA) is an established biomarker for detection of rejection in single organ transplants; data is limited in multi-organ transplant (MOT) recipients. "Use of dd-cfDNA in Multi-Organ Transplant Recipients" (MOTR) was a multicenter, prospective, cross-sectional study that assessed dd-cfDNA fraction (%) and donor quantity score (DQS, cp/mL) in pancreas-kidney (PKT), heart-kidney (HKT), and liver-kidney (LKT) recipients. We explored dd-cfDNA baseline levels across the different organ combinations, and compared them to kidney-only (KT) and heart-only (HT) transplant recipients. Among 347 MOT recipients from 18 sites (PKT = 183, HKT = 57, LKT = 107), most (88.2%) had simultaneous transplants. Median dd-cfDNA levels in PKT and HKT recipients were not significantly different from KT; median dd-cfDNA levels among HKT recipients were significantly higher than in HT recipients ($p < 0.001$). In LKT recipients, median dd-cfDNA was significantly higher compared to KT ($p < 0.001$). dd-cfDNA showed associations with organ impairment indicated by abnormal values of pancreatic and liver enzymes in PKT and LKT. As the largest multi-center study to date evaluating dd-cfDNA levels in MOT recipients, MOTR showed that organ-specific physiology affects dd-cfDNA levels across organ transplant combinations, laying the foundation for future efforts to use dd-cfDNA to assess organ-specific signatures of allograft injury in MOT recipients.

Keywords: allograft rejection, dd-cfDNA, heart transplant, kidney translant, multi-organ transplant



GRAPHICAL ABSTRACT |

INTRODUCTION

Multi-organ transplantation (MOT) is an increasingly important therapeutic strategy driven by the rising burden of chronic disease, aging patient population, and the complex interplay of multi-organ dysfunction. As more patients present with concurrent multiple organ failure, MOT is the optimal treatment, providing life-saving intervention [1, 2]. The number of patients undergoing MOT between 2011 and 2021 with a kidney and additional solid organ has grown 23.4% [3]. Clinical management of MOT recipients is significantly more complex than single organ transplant, requiring more resources for monitoring and coordination between multiple clinical teams. Thus, there is a growing need to understand the applicability of emerging non-invasive biomarkers in this expanding high-risk population.

The physiological rationale for MOT is well-established across different clinical scenarios. Simultaneous pancreas-kidney transplant (SPKT) improves outcomes in patients with diabetes and end-stage renal disease (ESRD) [4]. Heart-kidney transplantation (HKT) benefits patients with coexisting cardiac and renal failure, a common clinical scenario resulting from the inter-independence of both organs [5], reducing the risk of calcineurin inhibitor (CNI)-induced nephrotoxicity during heart transplantation which has contributed to a six-fold rise in US transplants since 2010 [6]. Simultaneous liver-kidney transplantation (SLKT) treats end-stage liver disease with concomitant kidney impairment or ESRD [7, 8], a common complication in this population [9]. Also, patients who may not qualify for a kidney transplant alone due to significant cardiac or hepatic dysfunction may qualify through the addition of the heart or liver allograft.

Traditional biomarkers for monitoring acute rejection (AR) in MOT are limited in their prognostic utility. For example, serum creatinine (sCr), proteinuria, amylase, lipase, and liver enzymes (like alanine aminotransferase (ALT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST)) are non-specific and can be confounded by unrelated factors [10–12]. Heart transplant biomarkers like B-type natriuretic (BNP) and N-terminal pro-BNP (NT-proBNP) are weakly-associated with heart transplant rejection [13]. Although biopsy remains the gold standard, its invasive nature and susceptibility to sampling error highlight the need for non-invasive biomarkers with improved sensitivity and specificity for organ injury in patients with MOT.

Donor-derived cell-free DNA (dd-cfDNA) is a validated biomarker for detecting AR in kidney [14, 15], lung [16], and heart single-organ transplant recipients [17]. Numerous studies have consistently demonstrated the high negative predictive value and strong correlation of dd-cfDNA with molecular and histologic rejection phenotypes across single-organ transplant types [18–22]. While dd-cfDNA was historically reported as a fraction of total circulating cf-DNA, studies have demonstrated that quantification of the plasma concentration of dd-cfDNA improves discrimination of rejection and reduces confounding from fluctuations in total cfDNA [23, 24]. Moreover, the combination of dd-cfDNA fraction and a donor quantity score (DQS), which estimates the quantity of dd-cfDNA in copies per mL of patient's plasma, has also been shown to

TABLE 1 | Demographics and clinical characteristics of MOTR study patients.

Recipient characteristics	All patients (N = 347)	Pancreas-kidney Cohort (N = 183)	Heart-kidney cohort (N = 57)	Liver-kidney (N = 107)	P value[a]	Pairwise p-values[b] PKT-HKT PKT-LKT HKT-LKT
Age (years)	57.1 (48.7–65.9)	51.1 (45.4–57.3)	62.1 (54.6–68.9)	64.8 (59.3–71.1)	<0.0001	<0.0001 <0.0001 0.2901
Sex ratio					0.0398	0.1094
Male	224 (64.6%)	115 (62.8%)	45 (78.9%)	64 (59.8%)		1.0000
Female	123 (35.4%)	68 (37.2%)	12 (21.1%)	43 (40.2%)		0.0647
BMI (kg/m^2)	28.2 (24.9–32.7)	27.2 (24.1–31.8)	28.9 (26.0–32.9)	29.0 (26.0–33.4)	0.0404	0.1958 0.0828 1.0000
Time from most recent transplant to dd-cfDNA testing (months)	23.5 (8.4–52.7)	33.8 (9.2–73.9)	13.1 (6.4–33.2)	19.0 (8.2–41.8)	0.0001	0.0003 0.0220 0.2001
Race					<0.0001	<0.0001
White	179 (51.6%)	82 (44.8%)	18 (31.6%)	79 (73.8%)		<0.0001
African American	96 (27.7%)	44 (24.0%)	32 (56.1%)	20 (18.7%)		<0.0001
Other	6 (1.7%)	4 (2.2%)	0 (0.0%)	2 (1.9%)		
Asian	11 (3.2%)	3 (1.6%)	5 (8.8%)	3 (2.8%)		
Unknown	55 (15.9%)	50 (27.3%)	2 (3.5%)	3 (2.8%)		
Ethnicity					<0.0001	0.0002
Not hispanic or latino	263 (75.8%)	116 (63.4%)	53 (93.0%)	94 (87.9%)		<0.0001
Hispanic or latino	28 (8.1%)	16 (8.7%)	3 (5.3%)	9 (8.4%)		1.000
Unknown	56 (16.1%)	51 (27.9%)	1 (1.8%)	4 (3.7%)		
Contemporaneous DSA status to dd-cfDNA testing					0.1115	0.7925 1.0000
Yes	23	12	7	4		0.2379
No	324	171	50	103		
Transplant sequence					<0.0001	0.8934
Non-simultaneous	36 (10.4%)	7 (3.8%)	3 (5.3%)	26 (24.3%)		<0.0001
Simultaneous	303 (87.3%)	169 (92.3%)	52 (91.2%)	80 (74.8%)		0.00181
Repeat	8 (2.3%)	7 (3.8%)	2 (3.5%)	1 (0.9%)		
Biopsies					<0.0001	<0.0001
For-cause	49 (14.1%)	34 (18.6%)	7 (12.3%)	8 (7.5%)		0.0008
For-protocol	48 (13.8%)	6 (3.3%)	27 (47.4%)	15 (14.0%)		<0.0001
Not reported	250 (72.0%)	143 (78.1%)	23 (40.4%)	84 (78.5%)		
Mortality status					0.7509	1.0000
Alive	345 (99.4%)	182 (99.5%)	57 (100.0%)	106 (99.1%)		1.0000
Died	2 (0.6%)	1 (0.5%)	0 (0.0%)	1 (0.9%)		1.0000
Kidney donor characteristics						
Donor age (years)	32.0 (22.0–41.0)	27.0 (20.0–35.0)	33.0 (27.0–45.0)	40.0 (30.2–49.0)	<0.0001	0.0009 <0.0001 0.0768
Donor relationship to recipient					0.1030	1.0000
Not related	342 (98.6%)	178 (97.3%)	57 (100.0%)	107 (100.0%)		0.6259
Biologically related	5 (1.4%)	5 (2.7%)	0 (0.0%)	0 (0.0%)		1.0000
Donor type					0.1190	0.7209
Living	11 (3.2%)	7 (3.8%)	3 (5.3%)	1 (0.9%)		0.7031
DCD	43 (12.4%)	22 (12.0%)	2 (3.5%)	19 (17.8%)		0.0805
DBD	270 (77.8%)	144 (78.7%)	47 (82.5%)	79 (73.8%)		
Not reported	23 (6.6%)	10 (5.5%)	5 (8.7%)	8 (7.5%)		
KDPI	23.0 (6.0–41.0)	11.0 (0.0–26.0)	28.0 (15.2–46.5)	39.0 (24.0–64.0)	<0.0001	<0.0001 <0.0001 0.0424
Pancreas/Heart/Liver donor characteristics (non-simultaneous)						
Donor age (years)	28.0 (20.5–39.5)	20.0 (17.5–24.5)	29.0 (24.8–32.5)	33.0 (25.5–45.0)	0.0090	0.6017 0.0088 1.0000

(Continued on following page)

TABLE 1 | (*Continued*) Demographics and clinical characteristics of MOTR study patients.

Recipient characteristics	All patients (N = 347)	Pancreas-kidney Cohort (N = 183)	Heart-kidney cohort (N = 57)	Liver-kidney (N = 107)	P value[a]	Pairwise p-values[b] PKT-HKT PKT-LKT HKT-LKT
Donor type					0.0132	
DCD	3 (6.5%)	1 (7.1%)	0 (0.0%)	2 (7.4%)		
DBD	36 (78.3%)	7 (50.0%)	5 (100.0%)	24 (88.9%)		
Not reported	7 (15.2%)	6 (42.9%)	0 (0.0%)	1 (3.7%)		

Categorical variables are shown as median (IQR). BMI: body mass index, dd-cfDNA: Donor-derived cell-free DNA, DSA: donor specific antibodies, CPRA: calculated panel reactive antibody, DCD: donation after cardiac death, DBD: donation after brain death, KDPI: kidney donor profile index, CMV: cytomegalovirus, EBV: Epstein-Barr virus, HIV: Human immunodeficiency virus.

[a]*Kruskal-Wallis test comparing PKT, HKT, and LKT, cohorts.*

[b]*Post-hoc Mann-Whitney U or Chi-Square test comparing PKT-HKT, PKT-LKT, and HKT-LKT, with Bonferroni correction for significant Kruskal-Wallis values.*

improve accuracy in the detection of AR with rejection thresholds of ≥1.0% and/or ≥78 cp/mL in kidney [25, 26], and ≥0.26% and/or ≥18 cp/mL in heart transplants [27]. While dd-cfDNA has been studied and characterized in SPKT recipients in a single-center study [28], its behavior in other MOT combinations remains largely unexplored, highlighting the need for additional research.

Here we introduce the "Use of dd-cfDNA in Multi-Organ Transplant Recipients" (MOTR) study; a multicenter, prospective, cross-sectional study designed to evaluate the dd-cfDNA baseline levels in real-world cohort of MOT recipients who were either clinically stable or who underwent a scheduled biopsy of at least one transplanted organ. This study analyzed dd-cfDNA levels, as a fraction (%), and donor quantity score (DQS; copies/mL) in pancreas-kidney (PK), heart-kidney (HK), and liver-kidney (LK) transplant recipients, and compared them to matched, real-world single-organ KT and HT recipients.

MATERIALS AND METHODS

Study Design

The MOTR study was an international, prospective, cross-sectional, multicenter study that evaluated dd-cfDNA baseline levels in patients with MOT. The studies involving human participants were reviewed and approved by local or central institutional review boards (IRBs, **Supplementary Table S1**). All PK, HK and LK transplant recipients who met the eligibility criteria were consented according to the IRB-approved protocol. The study has been performed in full adherence to the Declaration of Helsinki.

Patients were considered eligible for enrollment into the study if they met the following inclusion criteria: (1) age ≥18 years at the time of signing informed consent, (2) history of pancreas-kidney, kidney-heart, or liver-kidney transplant, (3) either considered clinically stable (defined as no history of rejection or no clinical indication of rejection within 3 months prior to enrollment in the study), or scheduled to undergo a biopsy of at least one of the transplanted organs, (4) able to read, understand, and provide written informed consent, and (5) willing and able to comply with the study-related procedures. Patients were excluded from this study if, at the time of enrollment they (1) were pregnant, (2) were on dialysis, (3) had received an allograft from an identical twin, and/or (4) had more than 2 unique organ transplant types (i.e.: pancreas, liver, heart).

Clinical and biological data related to recipient characteristics, donor characteristics, transplant procedure, and contemporaneous laboratory tests including SCr, lipase, amylase, ALP, AST, ALT, DSA, and viral loads, were collected for patients in both the stable arm and the biopsy-matched arm (**Table 1**).

dd-cfDNA Testing

dd-cfDNA samples were analyzed using the methodology previously described (the Prospera™ test; Natera, Inc., Austin, TX) [29]. Blood samples for dd-cfDNA testing were collected in two 10 mL Streck Cell-Free DNA BCT tubes and shipped at room temperature to Natera's Clinical Laboratory Improvement Amendments-certified and College of American Pathologists-accredited laboratory. Samples were processed within 8 days of collection, or according to previously validated standard operating protocol [30]. The algorithm was designed to provide a single composite value by combining non-recipient cfDNA for both dd-cfDNA % and DQS, which is an estimate of the concentration of dd-cfDNA in plasma reported as genomic copies per mL (cp/mL). Blood draws for dd-cfDNA testing were performed within 0–7 days before biopsy in the biopsy-matched arm, or according to clinical standard in the stable arm. Results of the investigational test (dd-cfDNA) were not shared with the patients or the attending physicians, and thus not used in patient management.

Biopsy Classification

Allograft biopsies of kidney, pancreas, heart, and liver transplants were graded as previously reported [31–34]. Biopsy reports were centrally reviewed by pathologists for data accuracy.

Statistical Analysis

dd-cfDNA levels in PKT, HKT, LKT recipients were compared to real-world cohorts of KT and HT recipients matched for time post-transplant.

Statistical analyses were performed in Python (3.8.10). Normally distributed variables were reported as mean and standard deviation; non-normally distributed variables were reported as median and interquartile range (IQR). Categorical variables were represented as counts and percentages and evaluated using Chi-square test as appropriate. Kruskal-Wallis

tests were performed for groupwise comparisons. For significant p-values, post-hoc tests of chi-square or Mann Whitney U tests were performed, as appropriate, with Bonferroni corrections for multiple testing.

Random forest classifiers were applied to identify the relationship between known clinical variables and positivity of dd-cfDNA (i.e., high risk by dd-cfDNA) testing. dd-cfDNA positivity was defined using the clinical thresholds established for kidney-alone transplant rejection (dd-cfDNA%≥1.0% OR DQS≥78.0 cp/mL) for the PKT and HKT cohorts, and an investigational, unvalidated threshold for liver-alone transplant rejection (dd-cfDNA%≥10.0%) based on prior studies [35–37] for the LKT cohort. Modeling was not feasible in the HKT cohort due to the limited number of dd-cfDNA-positive cases. Modeling included PKT cases with complete known matched eGFR (estimated glomerular filtration rate), amylase and lipase values, and LKT cases with complete known matched eGFR, ALP, AST, and ALT values, and was trained on these values along with time from transplant, Kidney Donor Profile Index (KDPI), and body mass index (BMI) and optimized for F1 score. The Shapley values of these features were assessed on a holdout random set of 20% of the complete cases.

Spearman correlation analyses were performed between dd-cfDNA (%, cp/mL) and the clinical biomarkers relevant to each transplanted organ, as described above. For each variable pair, correlation was calculated using cases with complete data.

SRTR Database

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

The data reported here have been supplied by the Hennepin Healthcare Research Institute (HHRI) as the contractor for SRTR. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

Contemporaneous data from SRTR were queried to compare the MOTR study cohorts (PKT, HKT, and LKT) to the corresponding national cohorts for each MOT type, to assess representativeness and generalizability. Variables included MOT recipient age, sex, BMI, race/Ethnicity, and repeat transplant status as indicated in **Supplementary Table S2**.

RESULTS

Study Cohort

Between October 2020 and June 2022, 385 subjects from 18 sites were enrolled in the MOTR Study (**Supplementary Table S1**). Of these, 38 subjects were excluded due to ineligibility or lack of valid dd-cfDNA testing (e.g., insufficient plasma volume). Of the remaining 347 transplant recipients, 183 had PKT, including 169 with a simultaneous pancreas-kidney transplant (SPKT; 92.4%), 7 with a pancreas-after-kidney transplant (PAKT; 3.8%). 7 patients (3.8%) underwent repeat transplant following a kidney-pancreas transplant: Four received kidney re-transplant after SPK, and three received a pancreas retransplant (one after PAK, two after SPK). 57 subjects had HKT, including 54 with a simultaneous heart-kidney transplant (SHKT; 94.7%) and 3 with a kidney-after-heart transplant (KAHT; 5.3%). 107 subjects had LKT including 80 with a simultaneous kidney-liver transplant (SLKT; 74.8%), 24 with a kidney-after-liver transplant (KALT; 22.4%), two with a liver-after-kidney transplant (LAKT; 1.9%), and one (0.9%) with a liver re-transplant following a kidney-after-liver transplant (**Figures 1**, **2**).

The MOTR cohort was 64.6% male (n = 224), had a median age of 57.1 y (IQR: 48.7–65.9), and a median BMI of 28.2 kg/m^2 (IQR: 24.9–32.7). Patients were 51.6% White, 27.7% African American, and 8.1% Hispanic and/or Latino. In the PKT, HKT, and LKT cohorts, 3.8% (7/183), 5.3% (3/57), and 0.9% (1/107) of the transplanted kidneys were donated by living donors, respectively. The median KDPI across all deceased donor's kidney transplants was 23.0 (IQR: 6.0–41.0). The majority (72%) of MOTR participants were considered clinically stable at enrollment, and the remaining 28% underwent biopsy; (*for-cause:* n = 49, 50.5%; *for-protocol:* n = 48, 49.5%) (**Table 1**). *For-cause* and *for-protocol* biopsies were observed in 18.6% and 3.3% of PKT, 12.3% and 47.4% of HKT, and 7.5% and 14.0% of LKT recipients, respectively; 70% of all biopsies were performed on the transplanted kidney.

The covariates of the PKT, HKT, and LKT subcohorts, such as MOT recipient demographics including age, sex, and ethnicity, were also compared to a contemporaneous national cohort's covariates as represented in data requested from the SRTR (https://www.srtr.org/) (**Supplementary Table S2**).

dd-cfDNA Fraction and DQS Estimates

In this analysis, a single dd-cfDNA test from each patient was used, along with a matched biopsy, when available. The median time from most recent transplant to dd-cfDNA testing was 23.5 months (IQR: 8.4–52.7) and was significantly longer in the PKT cohort (33.8 months) compared to the HKT (13.1 months) and LKT (19.0 months) cohorts ($p < 0.05$).

Among the PKT recipients, there were no significant differences in the median (IQR) dd-cfDNA % or DQS between the SPKT (dd-cfDNA%: 0.23% (0.13–0.47); DQS: 9 (4–17) cp/mL), PAKT (dd-cfDNA%: 0.13% (0.11–0.23); DQS: 4 (3–7) cp/mL) or those who underwent kidney or pancreas retransplant after PKT (dd-cfDNA%: 0.29% (0.21–0.44); DQS: 16 (6–22) cp/mL) cohorts and the KT cohort (dd-cfDNA%: 0.23% (0.12–0.48); DQS: 9 (5–20) cp/mL) ($p = 0.38$, 0.31, and 0.55, respectively) (**Figure 3A**). The distribution of total cfDNA paralleled that of both dd-cfDNA (%) and DQS (cp/mL) among these groups (**Supplementary Figure S1A**).

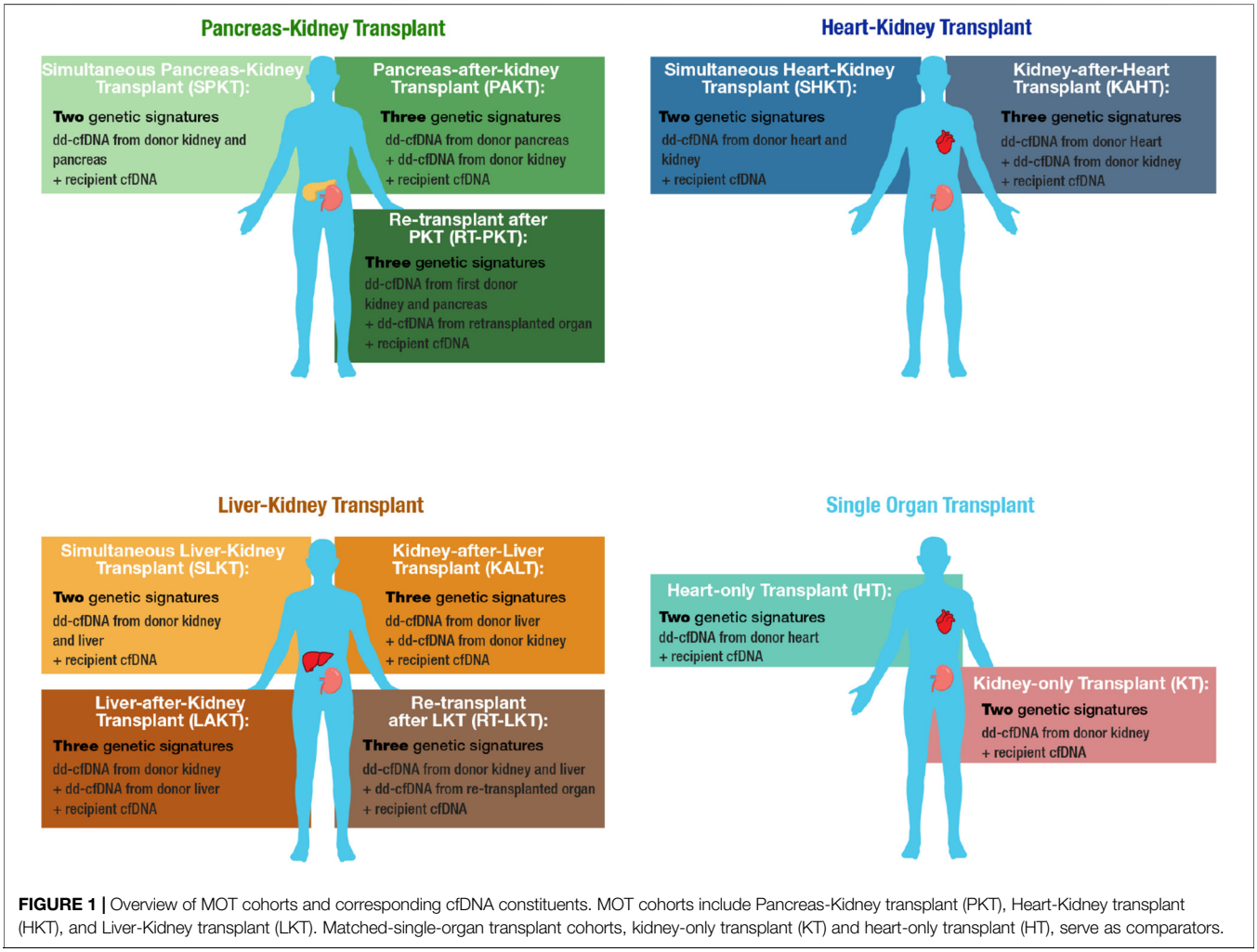


FIGURE 1 | Overview of MOT cohorts and corresponding cfDNA constituents. MOT cohorts include Pancreas-Kidney transplant (PKT), Heart-Kidney transplant (HKT), and Liver-Kidney transplant (LKT). Matched-single-organ transplant cohorts, kidney-only transplant (KT) and heart-only transplant (HT), serve as comparators.

Similarly, among the HKT recipients, there were no significant differences in the median (IQR) dd-cfDNA % or DQS (cp/mL) between the SHKT (dd-cfDNA%: 0.21% (0.12–0.42); DQS: 10 (7–18) cp/mL) or the KAHT cohorts (dd-cfDNA%: 0.32% (0.30–0.39; DQS: 22 (15–23) cp/mL) and the KT cohort (dd-cfDNA%: 0.24% (0.12–0.51); DQS: 10 (5–22) cp/mL ($p = 0.36$, 0.47, respectively) (**Figure 3B**). Both the median dd-cfDNA % and DQS (cp/mL) were significantly higher among the SHKT cohort when compared to the HT cohort (dd-cfDNA%: 0.21% (0.12–0.42); DQS: 10 (7–18) cp/mL) vs. (dd-cfDNA%: 0.06 (0.02–0.21), DQS: 2 (1–11) cp/mL, $p < 0.001$) (**Figure 3B**). There were no differences in total cfDNA when comparing SHKT and KAHT to KT and SHKT and KAHT to HT cohorts (**Supplementary Figure S1B**).

Among the LKT recipients, both the median (IQR) dd-cfDNA % and DQS for the SLKT (dd-cfDNA%: 3.92% (1.92–6.99); DQS: 147 (75–258) cp/mL) and KALT cohorts (dd-cfDNA%: 3.35% (1.59–5.14); DQS: 35 (73–284) cp/mL) were significantly higher than the KT (dd-cfDNA%: 0.23% (0.12–0.49); DQS: 9 (5–22) cp/mL; $p < 0.001$ for both) (**Figure 3C**). Lower total cfDNA levels in the SLKT compared to the KALT cohort may contribute to differences between dd-cfDNA% and DQS (cp/mL) observed between them (**Supplementary Figure S1C**).

Patients With Biopsy-Proven Acute Rejection (BPAR)

While this study did not contain sufficient patients with BPAR to assess appropriate dd-cfDNA cutoffs for rejection risk in MOT, we felt it was still illustrative to interpret the data in the context of the validated kidney-only threshold, as we would expect the dd-cfDNA values for kidney-only transplant patients to approximate a lower-bound for the appropriate MOT rejection risk threshold. A total of three patients in the SPKT cohort had kidney BPAR, two of which had dd-cfDNA above the 1.0% threshold used to define increased rejection risk in KT recipients (**Supplementary Figure S2A**): one recipient with T-cell-mediated rejection (TCMR) had dd-cfDNA levels of 3.11% and 63 cp/mL, while two patients with chronic active antibody-mediated rejection (AMBR) had dd-cfDNA% of 0.51% and 1.59% and DQS of 21 and 55 cp/mL. Three patients among the LKT cohort had BPAR in the kidneys (**Supplementary Figure S2B**), including

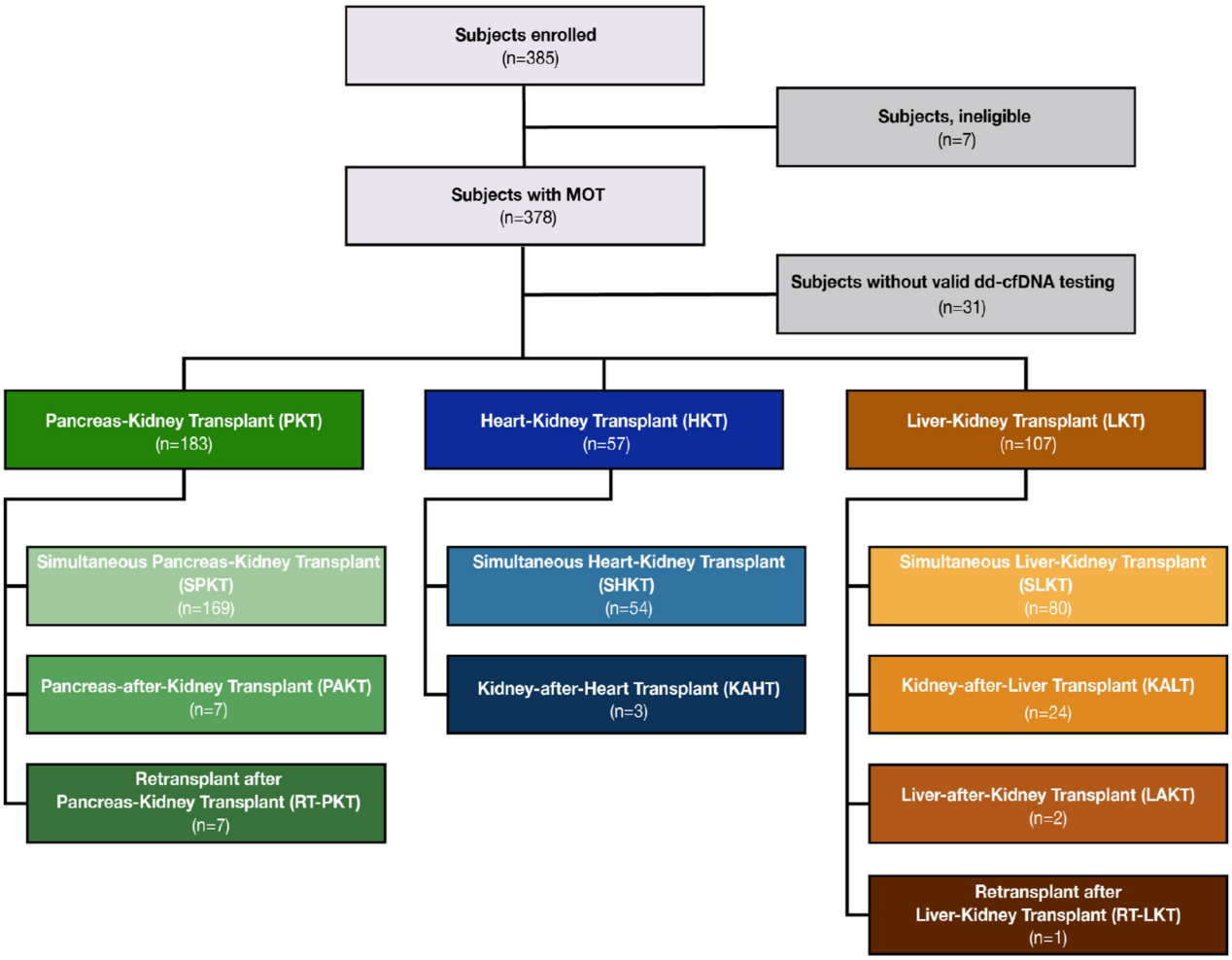


FIGURE 2 | CONSORT diagram of study enrollment and breakdown of organ groups by transplant sequence.

TCMR 1A with dd-cfDNA of 1.32%, 86 cp/mL, chronic active ABMR (2.31%, 114 cp/mL), and ABMR (6.98%, 698 cp/mL). No patients in the HKT cohort showed acute rejection on biopsy (**Supplementary Figure S2B**). Of the remaining 91 biopsies, 68 showed no rejection, 18 showed other findings not representing rejection, and 5 consisted of limited sample tissue and were thus unable to be diagnosed.

Patients With dd-cfDNA Values Above Thresholds for Kidney-Only Transplant Rejection

Of the 240 non-rejecting PKT and HKT recipients, 21 (19 PKT and 2 HKT) exceeded KT dd-cfDNA thresholds (≥1.0% and/or ≥78 copies/mL). All but one of these transplants were simultaneous; the remaining one was a kidney re-transplant after SPK. Seven patients (33.%) underwent biopsies (6 kidney, 1 heart), all without significant findings. The remaining 14 patients (13 PKT, 1 HKT) were considered clinically stable and did not undergo biopsy; one of these had substantially elevated amylase levels, while the other 13 were clinically stable by all parameters apart from dd-cfDNA. Of the 219 patients with dd-cfDNA below KT threshold, only one experienced BPAR (chronic-active ABMR).

Of the 107 subjects in the LKT cohort, 12 (11.2%; 11 SLKT, 1 KALT) had dd-cfDNA above 10%, which prior studies have posited as an appropriate threshold for rejection in liver-only transplants [35–37]. Two of these subjects received surveillance biopsies of the kidney, both demonstrating no rejection; no patients received biopsies of the liver.

Variables Associated With Elevated dd-cfDNA Levels in MOT Recipients

We sought to identify the clinical variables in MOT recipients that were associated with elevated dd-cfDNA levels using a random forest classifier with the PKT (**Figure 4A**) and LKT (**Figure 4B**) cohorts. The traditional markers for respective organ function were chosen as variables. In the PKT cohort, the most influential variables included amylase, time since transplant, and

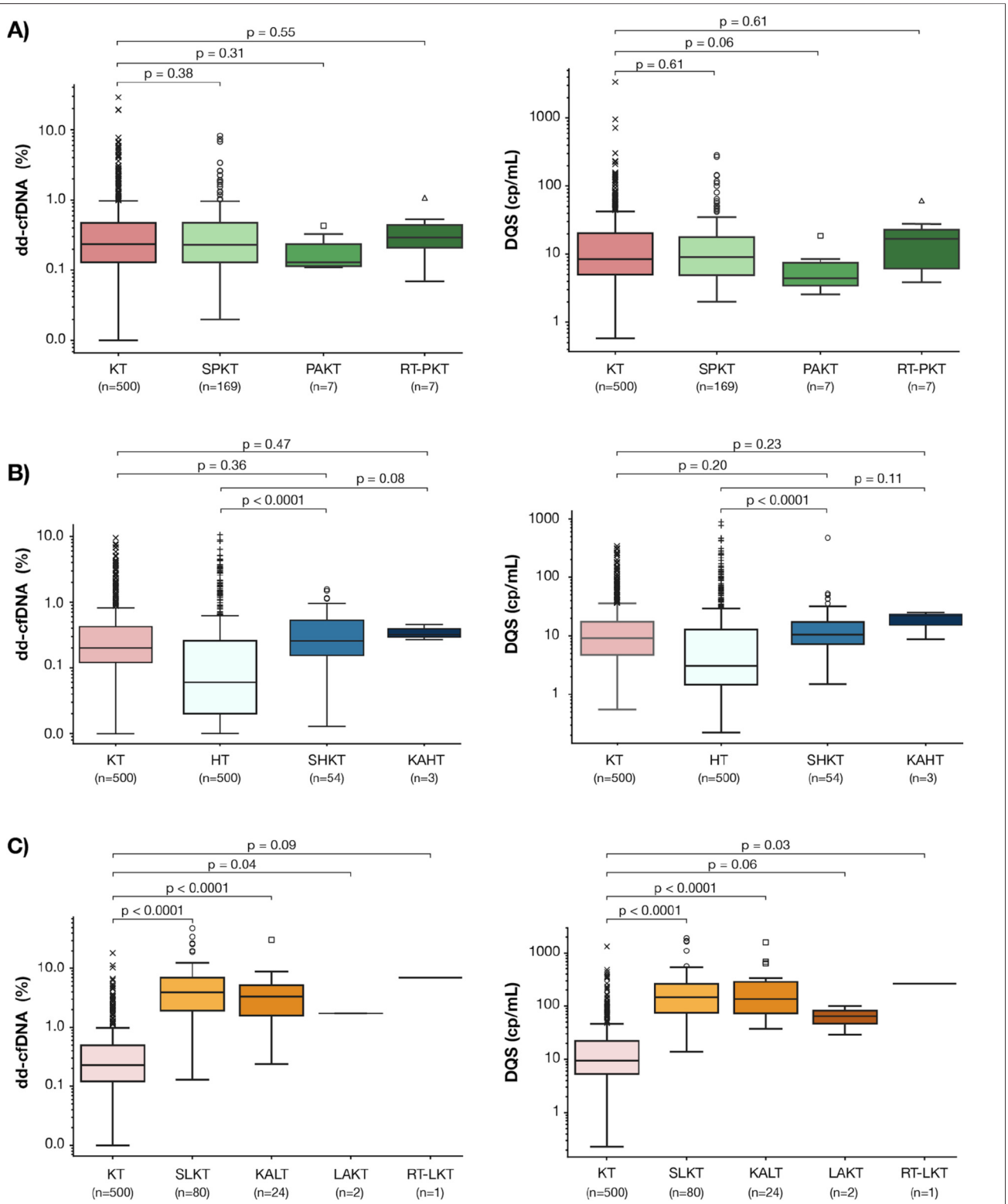


FIGURE 3 | Baseline dd-cfDNA fraction (%) and DQS (cp/mL) levels in the PKT **(A)**, HKT **(B)**, and LKT **(C)** sub-cohorts. Box-and-whisker plots display the median and interquartile range (IQR); whiskers extend to 1.5x IQR representing the expected data range; outliers beyond this range are shown as individual points. P values denote pairwise comparisons in dd-cfDNA levels between: **(A)** SPKT, PAKT, and PK-RT and KT cohorts, **(B)** SHKT, KAHT and KT, HT cohorts, **(C)** SLKT, KALT, LAKT,

(*Continued*)

FIGURE 3 | KL-RT and KT cohorts. PKT: Kidney-Pancreas transplant, SPKT: Simultaneous Kidney-Pancreas transplant, PAKT: Pancreas-after-Kidney transplant, PK-RT: Pancreas-Kidney Repeat transplant, KT: Kidney transplant, HT: Heart transplant, HKT: Kidney-Heart transplant, KAHT: Kidney-after-Heart transplant, SLKT: Simultaneous kidney-liver transplant, KALT: Kidney-after-liver transplant, LAKT: Liver-after-kidney transplant, KL-RT: Kidney-liver Repeat transplant.

lipase. Shorter time post-transplant, higher amylase values, and higher lipase values were associated with higher likelihood of elevated dd-cfDNA (**Figure 4A**). Looking at the continuous relationship between dd-cfDNA and the laboratory markers in the PKT cohort, significant positive correlations were observed in the PKT cohort between dd-cfDNA% and amylase and lipase ($p < 0.001$, 0.006, respectively), as well as between DQS and amylase and lipase ($p = 0.006$, 0.027, respectively). eGFR did not show a significant association with dd-cfDNA in either the random forest model or using Spearman correlations (**Supplementary Figure S3**).

In the LKT cohort, the most influential variables in the random forest classifier were ALT, AST, and ALP. Higher liver enzyme profiles were associated with higher likelihood of elevated dd-cfDNA (**Figure 4B**). Across all dd-cfDNA levels in this cohort, significant positive correlations were observed between dd-cfDNA% and ALT and AST ($p < 0.001$ for both), and between DQS and ALT and AST ($p < 0.001$ for both). No significant correlations were found between dd-cfDNA levels and eGFR (**Supplementary Figure S4**).

As the model indicated a significant association between time post-transplant and the likelihood of elevated dd-cfDNA levels, we further assessed the relationship between dd-cfDNA and time post-transplant in the different MOT cohorts (**Supplementary Figure S5**). In the PKT and HKT cohorts, dd-cfDNA% and DQS (cp/mL) both decreased over time. Total cfDNA remained steady in the PKT cohort while the HKT cohort showed a dramatic decrease in the first 40 months post-transplant before stabilizing. Despite these fluctuations, dd-cfDNA levels in both cohorts remained below the validated thresholds for KT rejection. In the LKT cohort, dd-cfDNA % and DQS increased slightly over time, whereas the total cfDNA decreased slightly, before stabilizing.

DISCUSSION

This study represents the largest comprehensive characterization of dd-cfDNA (fraction and quantity) baseline levels in MOT recipients, addressing a gap in transplant biomarker research in this growing high-risk population. With characteristics comparable to the national SRTR registry, this cohort reflects real-world diversity and provides reference data for these populations. Key findings show that dd-cfDNA baselines vary by MOT combination and were generally aligned with known dd-cfDNA patterns from the major contributing organ: PKT and HKT had values comparable to KT recipients, while the higher dd-cfDNA levels in LKT recipients likely reflected the larger dd-cfDNA contribution from the liver transplants. Further, our data show associations between elevated dd-cfDNA and abnormal levels of traditional biomarkers used to test allograft functions indicating that dd-cfDNA levels reflect functional impairment of the respective transplanted organ (kidney, liver). Collectively, these data may help establish dd-cfDNA baseline levels for different MOT combinations, underscoring the potential for dd-cfDNA to serve as a non-invasive biomarker for rejection risk assessment in MOT recipients.

The release of dd-cfDNA from transplanted organs is influenced by several factors, including order of organ transplantation, organ size, organ vascularization, and cellular turnover rate [38]. The broad inclusion criteria include patients with both simultaneous and sequential transplants, allowing us to explore the impact of the order of organ transplant on dd-cfDNA levels. Our data suggests that the pancreas is the minor dd-cfDNA contributor in PKT recipients as the levels in SPKT were comparable to those of KT recipients. Similarly, the baseline dd-cfDNA levels in the HKT recipient's cohort, including SHKT and KAHT, were comparable to those of KT recipients and significantly higher in SHKT than those of HT recipients, suggesting heart is the minor dd-cfDNA contributor relative to kidney. In contrast, dd-cfDNA levels were higher among the LKT cohort compared to KT recipients which is consistent with previous reports that LT recipients exhibit significantly higher dd-cfDNA levels than other solid organ transplants [35–37]. Given these data, it is not surprising that in this cohort, 2/3 PKT patients with kidney BPAR had dd-cfDNA above the 1.0% threshold established for KT rejection, as were 3/3 of the LKT patients with BPAR in the kidney. Of note, none of the three LKT patients with BPAR in the kidney had dd-cfDNA% above the exploratory 10% threshold proposed for liver transplant (LT) rejection; likely due to the lack of evidence of rejection in the liver of these patients. Taken together, these data suggest that the dd-cfDNA levels from the organ with the higher baseline may obscure rejections in the organ with the lower dd-cfDNA baseline, as seen in LKT and HKT (**Supplementary Figure S2C**). These findings underscore the importance of considering organ-specific dd-cfDNA levels when interpreting combined dd-cfDNA results in MOT populations and how it can be extrapolated from those established in single organ transplant recipients.

The clinical value of dd-cfDNA in MOT is further supported by its associations with abnormal levels in traditional biomarkers. In the PKT cohort, dd-cfDNA positivity was associated with increased serum amylase and lipase levels, suggesting that pancreas-derived injury signals correlate with higher dd-cfDNA release associated with rejection. Similarly, in the LKT cohort, strong associations between dd-cfDNA positivity and elevated liver enzymes (ALT, AST) are consistent with prior data suggesting that elevated dd-cfDNA levels in LT patients are associated with impaired liver function. These findings suggest that elevations in dd-cfDNA may serve as a sensitive indicator of allograft dysfunction across different transplanted organ types in MOT recipients.

In our study, the incidence of AR in our cohort (6.2%) was lower than that reported in similar MOT studies (24%) [39, 40] and (43%) [28]. This may reflect the large proportion of clinically stable patients enrolled in the study, which could be due to the relatively long post-transplant timeframe observed in this cohort. An added effect could be the immunoprotective role

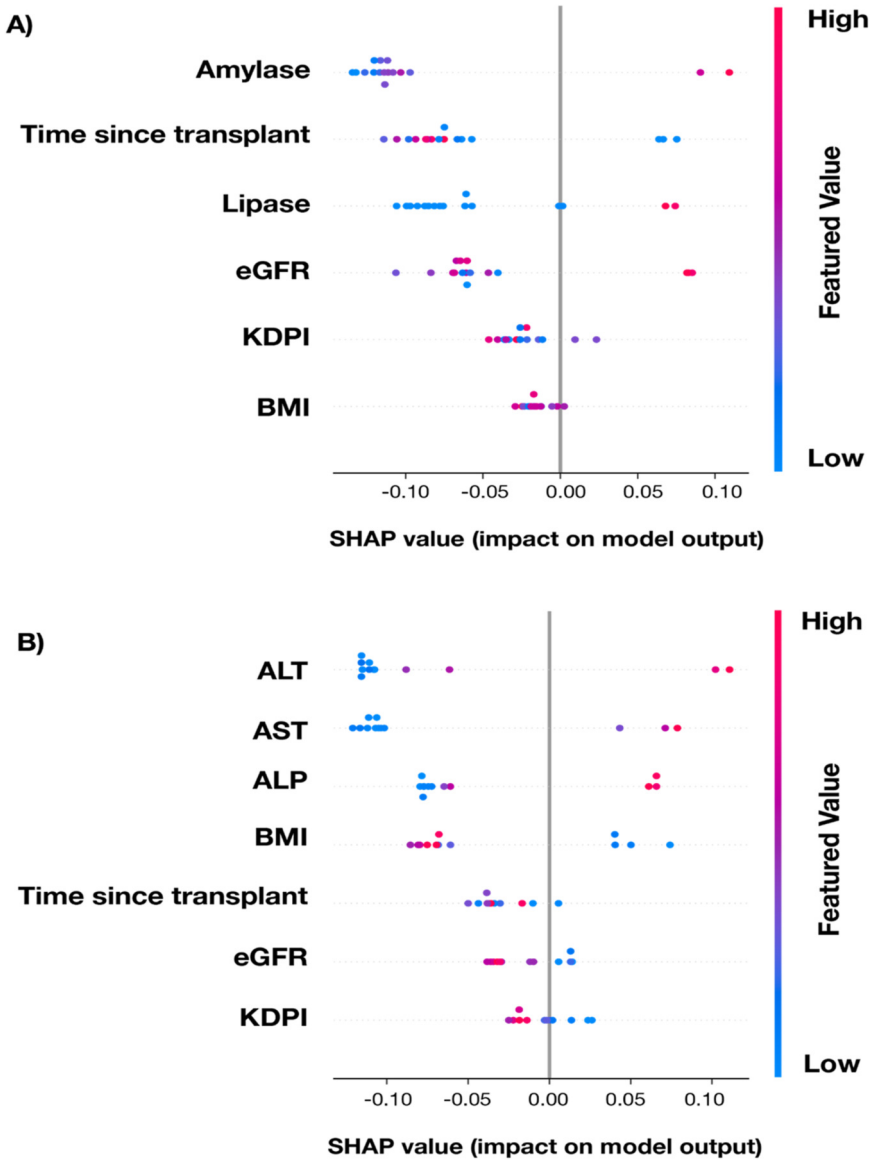


FIGURE 4 | SHAP (SHapely Additive exPlanations) summary plot for a randomly-selected holdout testing subset of cases with complete data from the PKT **(A)** and LKT **(B)** transplant cohorts displaying the contribution of key variables to the random forest model's prediction of increased-risk dd-cfDNA results. Each dot represents an individual patient. SHAP values on the x-axis indicate the variable's impact on the model output (positive values increase likelihood of positive result, negative values decrease it). Features are ranked by overall importance from top to bottom. Color represents the variable value, with blue indicating low values and red indicating high values.

hypothesized in MOT recipients, which could explain the seemingly counterintuitive finding that rejection rates are lower in MOT than in single organ transplant. Previous studies have shown that patients with dual organ transplants involving the heart and/or liver, tend to exhibit greater graft stability compared to single transplants alone [41, 42]. While it was previously thought that only MOT patients with a liver allograft experienced this immunoprotective effect, data has now shown that other simultaneously-transplanted organs also have this immunologic benefit [8, 43, 44]. This effect was not observed in sequential transplants, indicating that shared antigenicity in simultaneous MOT may be required for immunoprotection to manifest [44]. In this study, the majority of participants were simultaneous MOT, which could have contributed to the lower incidence of AR via this 'immunoprotective' MOT mechanism.

A key challenge in MOT is identifying the graft undergoing rejection while managing immunosuppression to avoid toxicity. This becomes more complex when the transplanted organs are from different donors. The ability to discern the rejecting graft in these cases could be augmented by distinguishing between donor-specific cfDNA signatures, an approach proven feasible

in a recent study of pregnant kidney recipients where fetal- and graft-derived cfDNA were successfully differentiated [45]. Analogous advances in noninvasive prenatal testing (NIPT), such as SNP-based assays that enable precise attribution of cfDNA to individual fetuses in twin pregnancies, demonstrate that identifying the tissue origin of circulating cfDNA is feasible [46]. While this approach would not allow for differentiation of organ-specific dd-cfDNA in simultaneous MOT where the two transplanted organs are from the same donor, other studies have revealed that the cfDNA methylation patterns can be used to identify the tissue-of-origin, independent of donor number or type [47].

This study has several limitations. First, biopsy data were not available for 72% of patients, with the designation of "non-rejecting" made based on clinical characteristics, and of those patients with a biopsy, very few patients had a biopsy from both organs. Second, the overall number of BPAR cases was insufficient to allow determination of a dd-cfDNA threshold for the clinical detection rejection in MOT recipients. Third, the study did not differentiate between dd-cfDNA contributions from multiple donors in MOT recipients, limiting the ability to precisely attribute dd-cfDNA elevations to a specific organ. Fourth, this analysis was cross-sectional in nature, limiting the assessment of the dynamic changes of dd-cfDNA over time.

In conclusion, this study is the largest of its kind, in which dd-cfDNA% and DQS baselines were characterized in pancreas-kidney, heart-kidney, and liver-kidney transplant recipients. This study provides foundational insights into how dd-cfDNA levels differ among and between different combinations of MOT, how dd-cfDNA levels relate to more traditional rejection biomarkers, and how these levels may be interpreted relative to each other. Future longitudinal studies focusing on MOT cohorts are needed to develop clinically valid assays to detect and define thresholds of organ-specific dd-cfDNA and improve rejections detection in these complex transplant scenarios.

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

This study involved human subjects. All patients who met the eligibility criteria were consented according to local or central institutional review-board approved protocol, in accordance with local legislation and institutional requirements. A list of all IRB is provided in **Supplementary Table S1**.

AUTHOR CONTRIBUTIONS

GaG contributed to conceptualization, investigation, methodology, resources, and writing (original draft, review and editing); DW, AS, TG, TD, NC, JO, RD, VR, and SA contributed to investigation, resources, and writing (original draft, review and editing); DGB contributed to data curation, formal analysis, investigation, methodology, project administration, software, visualization, and writing (original draft, review and editing); DaB. contributed to formal analysis, investigation, software, visualization, and writing (review and editing); NK contributed to conceptualization, data curation, methodology, project administration, supervision, and writing (original draft, review and editing); GeG contributed to data curation, formal analysis, investigation, and writing (review and editing); EA contributed to methodology, validation, and writing (review and editing); JX and CS contributed to data curation, validation, and writing (review and editing); NA and MB contributed to visualization and writing (original draft, review and editing); ZD contributed to conceptualization, visualization, and writing (original draft, review and editing); AP contributed to conceptualization, project administration, supervision, and writing (review and editing); PG contributed to conceptualization, methodology, project administration, supervision, and writing (review and editing); SB contributed to conceptualization, project administration, supervision, and writing (original draft, review and editing); and HT contributed to conceptualization, methodology, project administration, supervision, validation, and writing (original draft, review and editing). All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

GaG reports institutional research support from Merck and Veloxis (through Virginia Commonwealth University); consulting or advisory roles with Appellis, CareDx, Eurofins-Viracor, Natera, Novartis, and Specialist Direct; and honoraria from CareDx. He serves as Chair of the Kidney Pancreas Community of Practice of the American Society of Transplantation. DW received grants and/or contracts and consulting fees from Natera. AS reports institutional research support from the Canadian Institutes of Health Research (CIHR). TG reports research support from a grant funded by the American Society of Transplantation. JO reports support from Veloxis, received royalties for content contributed to UpToDate, and reports grant support from Breakthrough T1D. RD serves on the Data and Safety Monitoring Board (DSMB) of an NIH-sponsored clinical trial. SA reports consulting or advisory roles with Natera and Transplant Genomics and has received honoraria from Verici and Natera. DGB, DaB, NK, GeG, EA, JX, CS, NA, MB, AP, PG, SB, and HT are employees of Natera, Inc., and receive salary and may own stock and/or stock options. ZD is a

named inventor on several patents and is an employee of Natera, Inc., and receives salary and may own stock and/or stock options.

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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.2025.15823/full#supplementary-material

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GLOSSARY

ABMR antibody-mediated rejection
ALT alanine aminotransferase
ALP alkaline phosphatase
AMBR antibody-mediated rejection
AR acute rejection
AST aspartate aminotransferase
BMI body mass index
BNP B-type natriuretic peptide
BPAR biopsy-proven acute rejection
cfDNA cell-free DNA
CNI calcineurin inhibitor
cp/mL copies per milliliter
dd-cfDNA donor-derived cell-free DNA
DQS donor quantity score
DSA donor-specific antibodies
eGFR estimated glomerular filtration rate
HK heart–kidney
HKT heart–kidney transplant
HT heart transplant
IQR interquartile range
KAHT kidney-after-heart transplant
KALT kidney-after-liver transplant
KDPI Kidney Donor Profile Index
KT kidney transplant
LAKT liver-after-kidney transplant
LK liver–kidney
LKT liver–kidney transplant
LT liver transplant
MOT multi-organ transplantation
MOTR Multi-Organ Transplant Recipients study
NIPT noninvasive prenatal testing
NT-proBNP N-terminal pro–B-type natriuretic peptide
OPTN Organ Procurement and Transplantation Network
PAK pancreas-after-kidney transplant
PAKT pancreas-after-kidney transplant
PKT pancreas–kidney transplant
sCr serum creatinine
SHKT simultaneous heart–kidney transplant
SPKT simultaneous pancreas–kidney transplant
SLKT simultaneous liver–kidney transplant
SNP single-nucleotide polymorphism
SRTR Scientific Registry of Transplant Recipients
TCMR T-cell–mediated rejection

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ORIGINAL RESEARCH
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A Prospective Multicenter Luminex-Based Clinical Algorithm to Define Unacceptable HLA Mismatches Before Kidney Transplantation. Consequences on Outcome, Waiting Time, and Wait List Composition

*Fabian Köppen[1], Martina Koch[2], Kai Lopau[3], Katharina Heller[4], Markus Luber[5], Bernd Spriewald[5], Kerstin Amann[6], Achim Jung[7], Julia Weinmann-Menke[8], Thomas Drasch[1], Jens Werner[9], Bernhard Banas[1] and Daniel Zecher[1]**

[1]Department of Nephrology, Regensburg University Hospital, Regensburg, Germany, [2]Department of General, Visceral and Transplantation Surgery, University Medical Center, Mainz, Germany, [3]Department of Internal Medicine, University of Würzburg, Würzburg, Germany, [4]Department of Nephrology and Hypertension, University Hospital Erlangen, Erlangen, Germany, [5]Department of Internal Medicine 5-Hematology and Oncology, University Hospital Erlangen, Erlangen, Germany, [6]Department of Nephropathology, Institute of Pathology, University of Erlangen-Nürnberg, Erlangen, Germany, [7]Institute of Transfusion Medicine -Transfusion Centre, Johannes Gutenberg University Medical Centre, Mainz, Germany, [8]1st Department of Medicine, Division of Nephrology, Mainz University Hospital, Mainz, Germany, [9]Department of Surgery, Regensburg University Hospital, Regensburg, Germany

Determination of unacceptable human leukocyte antigen (HLA) mismatches (UAM) before kidney transplantation (KT) aims at minimizing immunological risk and routinely involves Luminex single antigen bead (SAB) testing. SAB-UAM criteria, however, often lack standardization. We implemented standardized mean fluorescence intensity (MFI)-based SAB-UAM criteria in four German transplant centers and prospectively studied the consequences on waitlist composition as well as waiting time, early antibody-mediated rejection (AMR) and graft loss in 267 patients. HLA were deemed unacceptable in case of CDC-reactivity or antibodies against known HLA from previous transplants irrespective of MFI. For all other antibodies, the MFI cut-off was 5.000 with the exception of 10.000 for anti-HLA DQ. We observed significant accumulation of highly sensitized patients (virtual panel-reactivity >95%) on the waiting list during the study period. Median time to KT was longer in patients with UAM, but differences were not statistically significant. Patients with preformed donor-specific anti-

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***Correspondence**
Daniel Zecher,
daniel.zecher@ukr.de

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Abbreviations: AM, acceptable mismatch; AMR, antibody-mediated rejection; CDC, complement-dependent cytotoxicity; DSA, donor-specific anti-HLA antibodies; ESP, Eurotransplant Senior Program; ETKAS, Eurotransplant Kidney Allocation System; ETRL, Eurotransplant Reference Laboratory; eGFR, estimated glomerular filtration rate; GMZTP, Mainz Transplant Center; GNBTP, Erlangen Transplant Center; GRBTP, Regensburg Transplant Center; GWZTP, Würzburg Transplant Center; HLA, human leukocyte antigen; KT, kidney transplantation; MFI, mean fluorescence intensity; MVI, microvascular inflammation; SAB, single antigen bead; SAB-DSA, DSA detected by the SAB test prior to KT; TCMR, T cell-mediated rejection; UAM, unacceptable HLA antigen mismatches; vPRA, virtual panel reactivity.

HLA antibodies (DSA) below the UAM cut-off criteria (39/267) experienced more AMR episodes compared to DSA-negative patients (10.3% vs. 1.3%, $p < 0.001$). Graft survival, however, was not statistically different over a median follow-up of four years. Standardized SAB-UAM criteria associated with good short-term outcomes but resulted in accumulation of highly sensitized patients on the waiting list.

Keywords: highly sensitized, kidney transplantation (KT), outcome, unacceptable HLA antigen mismatches, waiting time

INTRODUCTION

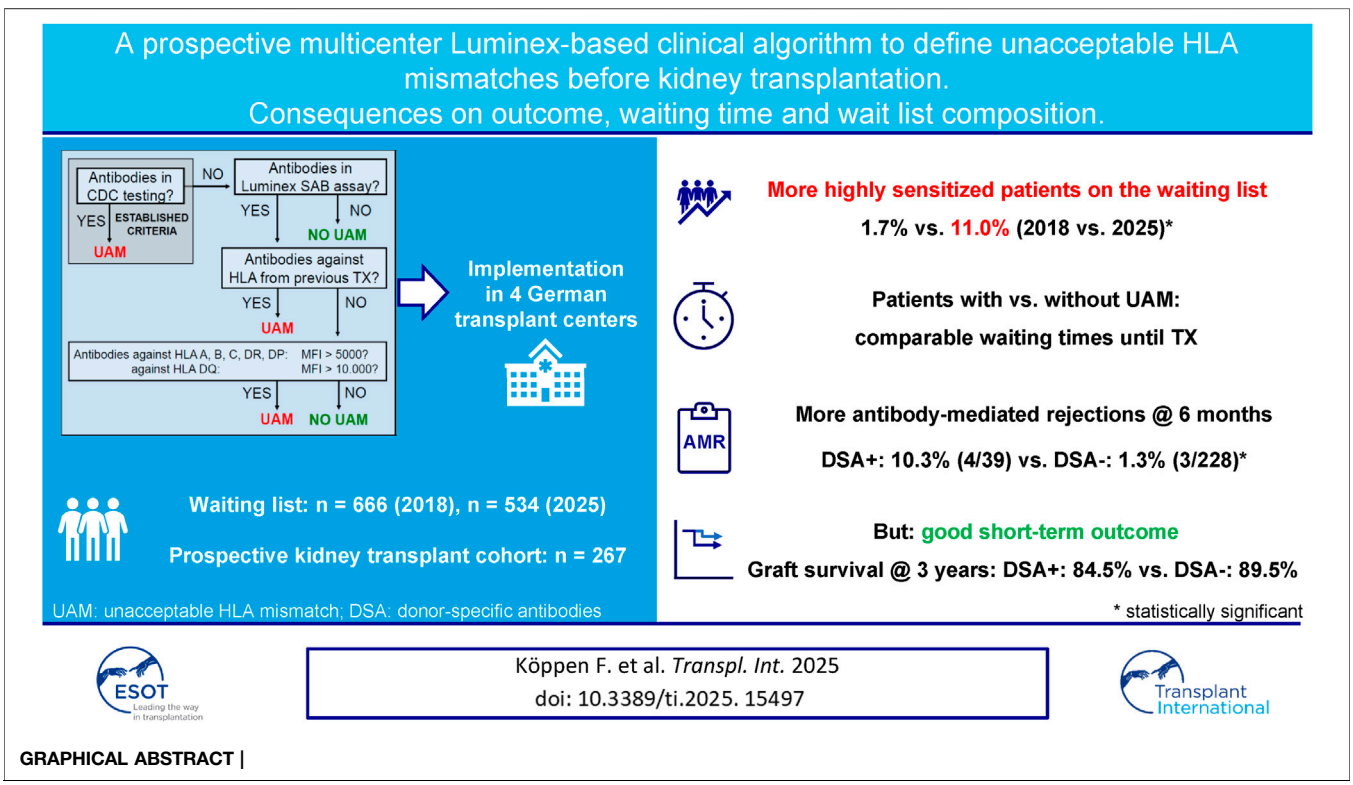
Successful kidney transplantation (KT) remains a cornerstone in the treatment of end-stage renal disease [1], significantly improving patient survival and quality of life [2, 3]. Overcoming the immunological barriers between donor and recipient, however, remains a critical challenge.

To avoid transplantation of human leukocyte antigen (HLA)-incompatible grafts with a high risk of early antibody-mediated rejection (AMR) and premature graft loss, transplant physicians and tissue typing laboratories have for long defined unacceptable HLA antigen mismatches (UAM) prior to KT. When a patient has anti-HLA antibodies that are considered high-risk, organs carrying these HLA will be excluded for a patient and the respective HLA will be declared unacceptable. The stricter UAM are defined, the lower is the risk of early rejection at the cost of prolonging waiting times due to an increasing donor pool restriction [4–6].

In the last 20 years, the Luminex single antigen bead (SAB) test has revolutionized anti-HLA antibody detection, providing a highly sensitive and specific semiquantitative measurement of antibody strength expressed as mean fluorescence intensity (MFI). Many studies have demonstrated that the presence of donor-specific anti-HLA antibodies (DSA) detected by the SAB test prior to KT correlates with an increased risk of early AMR and graft loss, even in the absence of cytotoxicity in CDC assays [7–12].

The relationship between the MFI and clinical outcomes in DSA-positive patients is less clear [13]. Whereas some studies have demonstrated a positive association between MFI levels and the incidence of early AMR and premature graft loss [7, 8, 10, 14–16], other studies have reported poorer graft survival in DSA-positive patients regardless of MFI levels [10, 12, 17].

The SAB test has some well-described technical limitations that can result in false-positive results [17, 18]. Moreover, the lack of a truly quantitative measure and potential differences in pathogenicity do not allow for a precise prediction of the immunological risk of a given antibody based on its MFI alone, resulting in a low predictive value of DSA in an individual patient [19]. Consequently, UAM algorithms are



GRAPHICAL ABSTRACT |

almost always individualized, lack standardization, and are highly variable between transplant centers.

In an attempt to standardize UAM criteria and balance the risk between early immunological complications and prolonged waiting times, we implemented CDC- and MFI-based SAB-UAM criteria at four German transplant centers. We used MFI thresholds that had previously been shown to result in excellent short-term clinical outcomes [20]. A retrospective analysis applying the same SAB-UAM criteria to a cohort transplanted at our own center in the pre-Luminex era further suggested that patients transplanted against DSA that fulfilled these SAB-UAM criteria had a high risk of premature graft loss, whereas patients with preformed DSA below the thresholds of our algorithm had excellent outcomes [19]. To further minimize risk, all known HLA from previous transplants were deemed unacceptable if antibodies against these HLA were detected in the SAB test [21, 22]. In this manuscript, we give a comprehensive overview of the consequences of this SAB-UAM algorithm, namely changes in waitlist composition over time as well as the impact on waiting time prior to KT, the incidence of early AMR, and graft loss, in a prospective cohort of KT patients.

PATIENTS AND METHODS

HLA Typing

Serological HLA typing of both donors and recipients was performed according to standards of the European Federation for Immunogenetics. During patient recruitment (01.01.2019 until 31.12.2021), donor and recipient HLA typing was only mandatory for HLA-A, -B, and -DR in the Eurotransplant region but was most often extended by the local tissue typing laboratories. Completeness of 11-loci donor and recipient HLA typing is shown in **Supplementary Table S1**.

HLA Antibody Testing

For three transplant centers (Regensburg, GRBTP; Würzburg, GWZTP; and Erlangen, GNBTP), HLA antibody testing was done at quarterly intervals in the tissue typing laboratory at Erlangen University Hospital. Screening was done using a commercial solid-phase microsphere-based assay (LSM12; One Lambda Inc., Los Angeles, CA). Sera were analyzed on a LABScan 200 Luminex (Luminex Corp., Austin, TX) flow analyzer, applying a threshold ratio for positive results of 2.5. In positive sera, HLA specificity was determined by a single-antigen assay for HLA class I and/or HLA class II antigens (LABScreen Single Antigen, Class I or II, respectively, both One Lambda Inc.). The tests were performed according to the manufacturers' instructions and analyzed on a LABScan 200 Luminex flow analyzer, applying a baseline-adjusted MFI cutoff for positive reactions of 500.

In Mainz (GMZTP), screening and specification of HLA antibodies was performed using a commercial solid-phase microsphere-based assay (LSA Class I and Class II; Immucor GTI Diagnostics Inc., Waukesha, WI, USA). Sera were analyzed on a LABScan 200 Luminex flow analyzer (Luminex Corp., Austin, TX). All assays were conducted according to the manufacturers' instructions. Sera were considered positive for specific HLA antibodies when the raw MFI was above 750 and the MFI/LRA (lowest ranked antigen) ratio was greater than the bead/lot-specific cut-off provided by the manufacturer.

Definition of Luminex-Based Unacceptable HLA Antigen Mismatches (SAB-UAM)

HLA were classified as UAM prior to KT if at least one of the predefined criteria (**Figure 1**) were met at any time. Once an HLA was classified as unacceptable, it remained listed as such, irrespective of subsequent reductions in antibody MFI, lack of antibody detection, or a negative result in CDC-testing. During patient recruitment, UAM could only be reported to ET on the serological level.

Impact of SAB-UAM Assignment on Wait List Composition and Waiting Time

The impact of UAM on waiting time in adult (≥18 years) patients listed for KT via the standard Eurotransplant Kidney Allocation System (ETKAS) or the Eurotransplant Senior Program (ESP) was studied in a cross-sectional approach at five time points. The first was in September 2018, prior to implementation of the current SAB-UAM algorithm. Until then, UAM assignment was not systematically performed but rather done on an individual patient's basis, considering mostly CDC-specificities and HLA against which antibodies directed against HLA from previous transplants were detected in Luminex SAB testing. The remaining time points were after implementation of the current SAB-UAM algorithm at the three transplant centers (GRBTP, GWZTP, and GNBTP) in June 2019, and three (March 2022), four (May 2023) and six (June 2025) years later. As in GMZTP, the SAB-UAM criteria were only implemented in February 2020, the GMZTP June 2019 waitlist data were omitted from analysis. Highly immunized patients listed in the acceptable mismatch (AM)-program were excluded, as were patients listed for multi-organ transplantation, with kidney-after-other-organ status, or with a high urgency status. Waiting time was defined as the time between the date of first dialysis and the respective reference date. Virtual panel reactivity (vPRA) levels were calculated based on UAM by ET using the Eurotransplant Reference Laboratory (ETRL) donor frequency calculator at https://www.etrl.org (last accessed on June 25, 2025).

Clinical Study Protocol and Patients

The SAB-UAM algorithm was prospectively implemented for all adult (≥18 years) patients on the kidney and kidney-pancreas waiting lists of the participating transplant centers (GRBTP starting 01.01.2019, GWZTP on 21.02.2019, GNBTP on 01.05.2019, and GMZTP on 01.02.2020) and was maintained

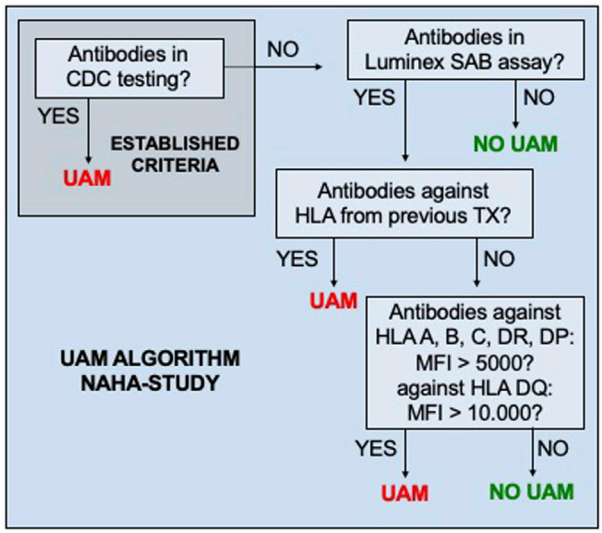


FIGURE 1 | Standardized criteria of unacceptable HLA mismatches (UAM). CDC, complement-dependent cytotoxicity; MFI, mean fluorescence intensity of anti-HLA antibodies detected in the Luminex single-antigen bead (SAB) test.

unchanged until the end of the recruitment phase on 31.12.2021. Patient recruitment into the study, however, varied considerably between the four centers, mostly because of the constraints of the COVID pandemic in GNBTP and GWZTP (**Supplementary Figure S1**).

Patients that were transplanted against UAM for any reason but included in the study were excluded from analyses (n = 4). Study data were collected using REDCap electronic data capture tools hosted at Regensburg University Hospital [23] at baseline (day of KT) as well as at 14 days, 3 months, 6 months, 12 months, and then yearly thereafter.

All patients gave their written informed consent. The study was approved by the local institutional review boards of the participating centers (GRBTP 18-1153_1-101, GNBTP 410_19 Bc, GWUTP 9/19_awbz, and GMZTP 2019-14663_1-NIS).

Assignment of DSA

Patients were categorized as DSA-positive if they had HLA antibodies against donor HLA in the most recent Luminex SAB assay prior to transplantation. Assignment of donor-specificity was performed on the serological level based on the available donor HLA typing. In cases of DSA against self-HLA, high-resolution typing of both donor and recipient was performed retrospectively (n = 4). This approach revealed true donor-specificity in 1/4 cases. All other cases were counted as DSA-negative. Missing HLA typing was retrospectively performed in case of potential DSA. With this approach, patient categorization into DSA-positive or DSA-negative was possible in all patients with detectable anti-HLA antibodies. DSA were considered positive with MFI ≥1000 in the most recent SAB assay prior to KT.

Diagnosis of Rejection

All rejection episodes were biopsy-proven. Biopsies were obtained either as protocol biopsies on days 14, 90, and at 1 year (GRBTP) or when clinically indicated (all centers). Specimens were evaluated on light microscopy and immunohistochemistry for C4d and SV40 staining and were graded according to the BANFF 2019 classification [24].

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 28.0.0.0 (SPSS Inc., Chicago, IL, USA). Data are presented as median (interquartile range, IQR) or median (range). For categorial data, comparisons were based on the chi-square test or Fisher's exact test. Mann-Whitney-U- and Kruskal-Wallis-tests were used to compare interval scaled or metric data. The Kaplan-Meier method was used to conduct survival analyses and group differences were evaluated by the log-rank test. All tests performed were two-sided. $P < 0.05$ was considered statistically significant.

RESULTS

Consequences of SAB-UAM on Wait List Composition and Waiting Time

We first analyzed the consequences of the new SAB-UAM algorithm on the waiting list composition of the four participating transplant centers after exclusion of all highly sensitized patients listed in the AM program. Cross-sectional analysis of the active kidney waiting list at various time points over a period of 7 years revealed a continuous decrease from 666 patients in 2018 to 534 patients in 2025 (**Table 1**), following a general trend in Germany [25]. Implementation of SAB-UAM in early 2019 in three of the participating centers resulted in a fourfold increase in patients with vPRA > 95% (1.7% vs. 7.3%, $p < 0.001$). Median vPRA in sensitized patients also increased significantly from 60.4% to 81.5% ($p < 0.001$) (**Table 1**). Ever since, the proportion of sensitized patients (vPRA >0%) continuously increased from 19.8% in 2018 to 39.3% in 2025, with the most dramatic effect on the proportion of patients with vPRA >95% (1.7% vs. 11.0%, $p < 0.001$) (**Table 1**). Whereas overall waiting time did not change significantly over time (**Supplementary Table S2**), we noticed accumulation of highly sensitized patients (vPRA >95%) who waited 3 years longer in 2025 as compared to non-sensitized patients (7.3 vs. 4.2 years, $p < 0.001$, **Table 2**).

Characteristics of Transplanted Patients

267 patients were included in the study, of which 39 (14.6%) had pretransplant DSA with MFI levels below the UAM-SAB criteria. As expected, more DSA-positive patients were sensitized and had higher vPRA levels as compared to DSA-negative patients, with a higher rate of patients with previous transplantations in the former group as compared to the latter. Median MFI^{max} was 2009 (IQR 1373–2988) in DSA-positive patients. The rate of living donations was comparable between the groups (23.1% vs. 21.1%). Thymoglobulin induction was used significantly more

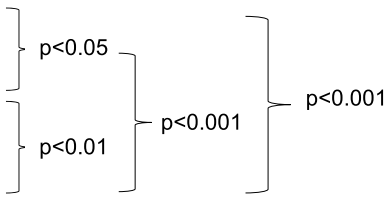
TABLE 1 | vPRA over time in patients on the waiting list.

vPRA category	Time of analysis					
	09/2018 n = 666	06/2019[a] n = 590	03/2022 n = 622	05/2023 n = 563	06/2025 n = 534	*p*
vPRA = 0%	534 (80.2)	442 (74.9)	424 (68.2)	369 (65.5)	324 (60.7)	<0.001
0% < vPRA ≤50%	47 (7.1)	39 (6.6)	61 (9.8)	62 (11.0)	84 (15.7)	<0.001
50% < vPRA ≤85%	61 (9.2)	40 (6.8)	53 (8.5)	52 (9.2)	51 (9.6)	0.457
85% < vPRA ≤95%	13 (2.0)	26 (4.4)	27 (4.3)	20 (3.6)	16 (3.0)	0.092
vPRA >95%	11 (1.7)	43 (7.3)	57 (9.2)	60 (10.7)	59 (11.0)	<0.001
vPRA [%], median (IQR)[b]	60.4 (34.1–82.3)	81.5 (46.5–97.6)	73.5 (27.9–96.3)	72.7 (32.1–96.7)	64.6 (23.9–97.1)	0.009

Data are shown as n (% of total) unless indicated otherwise.
[a]*Data from GMZTP excluded.*
[b]*Only patients with vPRA >0%. vPRA, virtual panel reactivity based on unacceptable antigen mismatches.*

TABLE 2 | Waiting time in years according to vPRA on 01.06.2025 (n = 534).

vPRA category	Waiting time
vPRA = 0%	4.2 (2.7–6.3)
0% < vPRA ≤50%	4.8 (3.1–7.3)
50% < vPRA ≤85%	5.9 (3.2–8.4)
85% < vPRA ≤95%	5.9 (3.3–8.6)
vPRA >95%	7.3 (5.1–10.1)



Data are shown as median (IQR).

often in DSA-positive as compared to DSA-negative patients (61.5% vs. 13.6%). Maintenance immunosuppression consisted of tacrolimus, mycophenolate, and prednisolone in the vast majority of patients. Three patients were lost to follow-up; all other patients were followed for a minimum of 3 years. Median follow-up was 4 years in DSA-positive and 3 years in DSA-negative patients (p = 0.09) (**Table 3**).

Waiting Time

Median waiting time prior to deceased donor KT was longer in UAM-positive as compared to UAM-negative patients in both the standard kidney allocation system ETKAS (8.6 vs. 7.7 years) and the senior program ESP (5.6 vs. 4.8 years) [26]. However, these differences were not statistically significant (**Supplementary Table S3**). Of note, in ETKAS, the difference in median waiting time between UAM-positive and UAM-negative patients decreased to 5 months after exclusion of patients prioritized during allocation because of a full-house (serological match in HLA A, B, and DR) organ (**Table 4**).

Incidence of AMR

We observed a significantly higher incidence of early AMR in patients with preformed DSA as compared to DSA-negative patients. 4/39 DSA-positive patients experienced AMR within the first 6 months after KT as compared to 3/228 DSA-negative patients (10.3% vs. 1.3%, p = 0.01). 2/4 vs. 2/3 of the respective index biopsies were C4d-positive. 2/4 of the AMR episodes in DSA-positive patients were found in protocol biopsies at 3 months in patients with stable graft function. Of note, six additional DSA-negative patient biopsies fulfilled the criteria of DSA-negative C4d-negative microvascular inflammation (MVI), as proposed by the recent Banff 2022 update [27]. Protocol biopsies were only performed in one (GRBTP) out of the four participating centers. However, the incidence of early AMR and MVI episodes was not statistically different between GRBTP and the other centers (**Supplementary Table S4**). One of the DSA-positive patients with early AMR lost his graft during follow-up due to a combination of AMR and BK nephropathy following ABO-incompatible living KT. The incidence of early T cell-mediated rejection (TCMR) was comparable between the groups (7.7% vs. 11.4%, p = 0.78).

Incidence of *De Novo* DSA

Post-transplant DSA screening was performed in approximately 80% of patients (**Supplementary Table S8**). During follow-up, 4/39 (10.9%) of patients with preformed DSA developed additional *de novo* DSA, whereas *de novo* DSA were detected in 16/228 (7%) of patients without DSA at the time of KT (p = 0.51, **Supplementary Table S9**).

Graft Function

Graft function (eGFR) remained stable in both patient groups during follow-up but was significantly higher in DSA-positive patients at early time points (**Supplementary Table S5**). Albuminuria was generally low but highly variable with no

TABLE 3 | Baseline characteristics of the study cohort.

Characteristic	DSA-positive (n = 39)	DSA-negative (n = 228)	*p*
Transplant center			0.13
Mainz	15 (38.5)	54 (23.7)	
Würzburg	2 (5.1)	35 (15.4)	
Regensburg	18 (46.2)	107 (46.9)	
Erlangen	4 (10.3)	32 (14.0)	
Donor			
Female	23 (59.0)	124 (54.4)	0.73
Age [years]	54 (44–59)	56 (47–66)	0.09
Living donor	9 (23.1)	48 (21.1)	
ETKAS	22 (56.4)	124 (54.4)	
Full-house allocation	3 (7.7)	22 (9.6)	1.00
ESP	6 (15.4)	50 (21.9)	
AM	1 (2.6)	1 (0.4)	
KPTX	1 (2.6)	4 (1.8)	
HU	0 (0.0)	1 (0.4)	
HLA-A/B/DR mismatches	4 (3–4)	3 (2–4)	0.14
Transplantation			
Cold ischemia time (h:min)	7:23 (4:27–11:54)	8:05 (4:54–12:18)	0.30
Warm ischemia time (h:min)	0:36 (0:29–0:48)	0:37 (0:30–0:48)[a]	0.49
Recipient			
Female	19 (48.7)	79 (34.6)	0.11
Age [years]	51 (40–62)	57 (47–65)	0.11
HLA antibodies before KT	39 (100.0)	114 (50.0)	<0.001
vPRA >0%	20 (51.3)	27 (11.8)	<0.001
vPRA[b]	71.7 (37.8–89.3)	47.0 (22.0–84.0)	0.16
Retransplantation	12 (30.8)	17 (7.5)	<0.001
Time on dialysis (years)[c]	7.0 (2.8–9.6)	6.4 (3.6–8.7)	0.92
Preemptive	2 (5.1)	16 (7.0)	1.00
AB0-incompatible	2 (5.1)	16 (7.0)	1.00
HLA-DSA			
No. Of HLA-DSA[d]	1 (1–5)	-	-
Class I only	18 (46.2)	-	-
Class II only	19 (48.7)	-	-
Class I + II	2 (5.1)	-	-
MFI^{max}	2009 (1373–2988)	-	-
Induction therapy			<0.001
Basiliximab	15 (38.5)	197 (86.4)	
Thymoglobulin	24 (61.5)	31 (13.6)	
Initial immunosuppression			0.29
TAC-MMF	0 (0.0)	14 (6.1)	
TAC-MMF-Pred	38 (97.4)	204 (89.5)	
Other	1 (2.6)	10 (4.4)	
Follow-up (years)	4.0 (3.0–4.3)	3.0 (3.0–4.0)	0.09

Data are shown as median (IQR) or n (% of total) unless indicated otherwise.
[a]*2 missing.*
[b]*Only vPRA >0%.*
[c]*Without preemptive KTX.*
[d]*Data are shown as median (range). MFI^{max}, highest mean fluorescence intensity of all DSA in cases of more than one DSA.*
ETKAS, Eurotransplant Kidney allocation system; ESP, Eurotransplant Senior Program; AM, Acceptable Mismatch program; KPTX, kidney-pancreas transplantation; HU, high urgency; vPRA, virtual panel reactivity; TAC, tacrolimus; MMF, mycophenolate; Pred, prednisolone.

TABLE 4 | Waiting time (years) prior to KTX.

Allocation program	UAM-positive	UAM-negative	*p*
ETKAS	8.7 (7.6–10.0) [n = 33]	8.2 (6.1–10.3) [n = 91]	0.14
ESP	5.6 (4.6–9.6) [n = 6]	4.8 (3.2–7.0) [n = 49]	0.18

Data are shown as median (IQR). Patients in the acceptable mismatch (AM)-program, with high urgency status and after full house *allocation, were excluded from analysis.*
UAM, unacceptable HLA mismatches; ETKAS, Eurotransplant Kidney Allocation System; ESP, Eurotransplant Senior Program.

significant differences between DSA-positive and DSA-negative patients (**Supplementary Table S6**).

Graft Loss and Patient Death

6/39 (15.4%) DSA-positive patients lost their graft during follow-up as compared to 16/228 (7.0%) DSA-negative patients (p = 0.11). Graft survival at one, two, and three years in DSA-positive as compared to DSA-negative patients

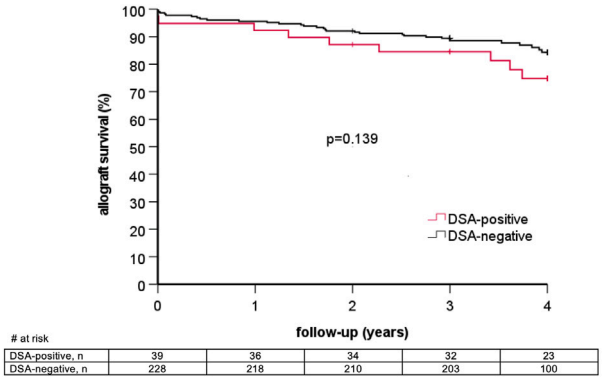


FIGURE 2 | Overall graft survival stratified by the presence of pretransplant donor-specific anti-HLA antibodies (DSA).

was 92.3% vs. 95.6%, 87.2% vs. 92.1%, and 84.5% vs. 89.5%, respectively (log rank p = 0.14, **Figure 2**). Two graft losses in the DSA-positive group occurred in patients with previous biopsy-proven AMR. There was no graft loss in patients with previous AMR in the DSA-negative group (**Table 5**). Graft survival censored for death at one, two, and three years was 94.9% vs. 96.5%, 92.2% vs. 94.7%, and 89.4% vs. 93.3% in DSA-positive vs. DSA-negative patients, respectively (log rank 0.10, **Figure 3**). Multivariable Cox regression analysis identified thymoglobulin-induction treatment and donor age as independent predictors for graft loss, whereas the presence of preformed DSA and sensitization (vPRA >0%) prior to KT, TCMR, and AMR were not (**Table 6**).

During follow-up, 5/39 (12.8%) DSA-positive patients died, whereas death occurred in 22/229 (9.6%) DSA-negative patients (p = 0.57, **Table 5**). Patient survival at one, two, and three years post KT was comparable between the groups (94.8% vs. 98.2%, 92.2% vs. 94.7% and 92.2% vs. 94.3%, log rank p = 0.70, **Supplementary Figure S2**). Of note, significantly more DSA-positive patients died from infection as compared to patients without DSA (80.0% vs. 18.2%, p < 0.05, **Supplementary Table S7**).

TABLE 5 | Graft loss and patient death.

Outcome parameter	DSA-positive (n = 39)	DSA-negative (n = 228)	*p*
Graft loss	6 (15.4)	16 (7.0)	0.11
Graft loss after previous AMR	2 (5.1)	0 (0.0)	0.02
Death	5 (12.8)	22 (9.6)	0.57
Death with functioning allograft	4 (10.3)	16 (7.0)	0.51
Death and/or graft loss	10 (25.6)	32 (14.0)	0.09

Data are shown as n (% of total). DSA, donor specific anti-HLA antibody; AMR, antibody-mediated rejection.

DISCUSSION

A standardized UAM algorithm integrating CDC reactivity, MFI-based SAB test results, and HLA typing information from previous transplants was associated with good short-term outcomes in our cohort. Graft survival of patients with preformed DSA defined as acceptable by the SAB-UAM criteria was superior at 3 years compared to previous studies comprising comparable patient populations and DSA characteristics [8, 10, 12]. At the same time, waiting times between patients with and patients without UAM were not statistically different in both ETKAS and the ESP, underscoring the clinical utility of the chosen UAM criteria.

Given the small sample size of the DSA-positive cohort and the associated low event numbers, we acknowledge that our study is underpowered to demonstrate equivalence in outcome and waiting times between DSA-positive and DSA-negative patients. Likewise, in the Cox model, the number of events relative to the number of covariates was limited, which is why the risk estimates, especially for DSA and UAM, should be interpreted with caution. As protocol biopsies were performed only in one center (GRBTP), and two of the four early AMR episodes in DSA-positive patients were detected on protocol biopsies in patients with stable graft function, there is a potential detection bias in our study (**Supplementary Table S4**). Again, the low number of events does not justify any final conclusion. Systematic protocol biopsies might be a valuable tool to detect early subclinical rejection in patients with preformed or *de novo* DSA [28, 29], especially as new treatment options for AMR have recently emerged [30].

For the definition of UAM, plausibility testing of SAB test results was restricted to known HLA from previous transplants. To reflect clinical reality, we did not include other sensitizing events such as blood transfusions or previous pregnancies, for which detailed HLA typing information is often not available. Prior transplantations have the strongest impact on allosensitization, likely due to the long-term persistence of alloantigens following KT [31]. However, there is no clinical evidence that antibodies elicited during pregnancies or blood transfusions or even antibodies of unknown etiology are clinically less relevant [32]. In our cohort, the outcome of DSA-positive women with previous pregnancies was not different from all other DSA-positive patients (not shown). Larger studies must be undertaken to find out whether meticulous plausibility testing considering all previous sensitization events can further improve risk stratification.

In case of HLA antibodies not clearly related to a previous KT, we applied MFI cutoffs of 5.000 (10.000 for anti-HLA DQ due to the higher antigen density on anti-DQ beads) for the definition of UAM, as these boundaries were shown to retrospectively identify the majority of DSA-positive KT patients with poor renal outcome [19]. However, it is well established that the MFI only incompletely reflects the immunological risk of a given antibody. Despite a positive correlation of the MFI with early AMR episodes in many studies [7, 8, 10, 14–16], the impact of the MFI on long-term graft survival in DSA-positive patients is less clear [7, 8, 10, 12, 14, 17]. It remains to be shown whether incorporation of dilution/titration studies to address the technical limitations of the SAB assay

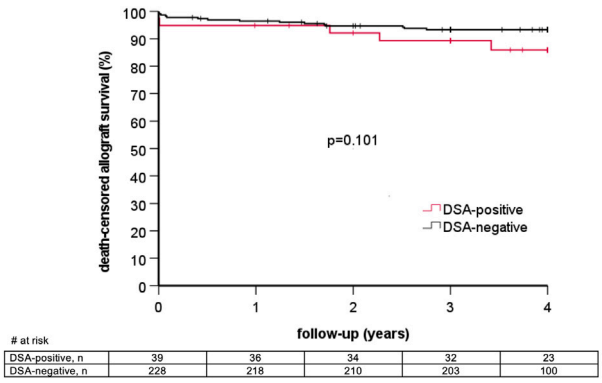


FIGURE 3 | Death-censored allograft survival stratified by the presence of pretransplant donor-specific anti-HLA antibodies (DSA).

TABLE 6 | Multivariate Cox regression analysis of graft loss.

Variable	Hazard ratio	95% confidence interval	*p*
Retransplantation	0.260	0.045–1.484	0.13
DSA	2.209	0.673–7.252	0.19
UAM	0.754	0.184–3.091	0.70
Thymoglobulin	4.220	1.560–11.414	0.01
Living donation	0.273	0.060–1.241	0.09
Age of donor	1.047	1.005–1.091	0.03
Age of recipient	0.997	0.959–1.037	0.90
AMR	1.867	0.290–12.038	0.51
TCMR	1.810	0.603–5.438	0.29

DSA, donor specific anti-HLA antibody; UAM, unacceptable HLA mismatches; AMR, antibody-mediated rejection.

[33] or incorporation of other test systems, such as B cell memory [34, 35] or C1q [36] assays, will further improve UAM algorithms.

In our study, SAB assays from two different manufacturers were used for risk stratification at the participating tissue typing laboratories. It was previously shown that both assays detect most antibodies with MFI levels above 4000 [37]. However, methodological differences in MFI levels might have consequences on both outcome and waiting times as well when strict MFI thresholds are used for classification of DSA and UAM.

One of the major limitations of our study is the assignment of both SAB-UAM and DSA based on serological HLA typing data. Recently, Senev and colleagues showed that DSA assignment based on second-field high-resolution HLA typing revealed misclassification of donor-specificity in over 20% of patients. This approach was clinically relevant as graft survival in these patients was comparable to DSA-negative patients [38]. High-resolution typing, however, is still not routinely performed at the time of organ allocation in deceased-donor transplantation due to both time and financial constraints but might become available soon [39]. As noted in a recent review by Bezstarosti et al., clinical evidence for a clear benefit for prospective epitope/eplet matching both in terms of waiting time and clinical outcome is still lacking [40]. Nevertheless, allel-specific and molecular assignment of UAM based on epitope/eplet analysis has the potential to further improve individual risk stratification and help enlarge the donor pool, especially in highly sensitized patients. Comparing epitope/eplet patterns of antibody profiles with previous sensitizing events could help establish plausibility when defining UAM [41] and allowed for the delisting of irrelevant UAM in a recent study [42].

Irrespective of how UAM are defined, it is well established that an increasing donor pool restriction results in longer waiting times, with the most dramatic effect in highly sensitized patients [4, 6, 43]. What has not been reported in detail previously is the significant and continuous accumulation of highly sensitized patients on the waiting list following implementation of SAB-UAM. Due to the stringent entry criteria, these patients were not accepted in the ET AM program despite high vPRA levels and a highly restricted donor pool. We have previously shown that the transplant rate of highly sensitized patients not listed in the AM program is less than half than that of AM patients, with this population being numerically twice that of the AM population in Germany [4]. From an equal opportunity perspective, these findings illustrate the urgent need to implement better compensation mechanisms for highly sensitized patients during allocation. Besides potential new therapeutic strategies such as imlifidase induction treatment [44], novel delisting strategies will have to be developed to enable timely transplantation of highly sensitized patients at acceptable immunological risks [36, 45].

Ultimately, sensitization is only one of many factors that influence waiting time prior to KT [4]. Finding the sweet spot between an acceptable immunological risk and increased waiting times remains a critical challenge when defining UAM algorithms. A satisfactory answer to what acceptable waiting times are is highly complex and beyond the scope of this manuscript. Besides the medical aspects that are often discussed in isolation, i.e. the clinical condition of an individual patient and the well-known survival benefit and better quality of life after KT as compared to remaining on dialysis, other aspects such as equity have to be considered as well.

DATA AVAILABILITY STATEMENT

Publicly available clinical datasets were analyzed for this study and entered into and retrieved from a RedCap-based study database.

ETHICS STATEMENT

All patients gave their written informed consent. The study was approved by the local institutional review boards of the participating centers (GRBTP 18-1153_1-101, GNBTP 410_19 Bc, GWUTP 9/ 19_awbz, and GMZTP 2019-14663_1-NIS).

AUTHOR CONTRIBUTIONS

FK participated in research design and data analysis and wrote the paper. KH, KL, MK, JW-M, JW, TD, and BB participated in the performance of the research, KA, ML, BS, and AJ participated

in data analysis, and DZ designed the study, analyzed data, and wrote the paper. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

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SUPPLEMENTARY MATERIAL

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ORIGINAL RESEARCH
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Multicentre Collaborative Prospective Cohort Study Investigating the Impact of Enhanced Recovery After Surgery on Kidney Transplant Outcomes: The CRAFT Study

Ruth Owen[1,2], Georgios Kourounis[1,2], Bishow Karki[1,3], Katie Connor[1,4], Charlotte Brown[1,5], Kayani Kayani[1,6], Mohamed Elzawahry[1,7†], Ruth Blanco[1,8], Davide Schilirò[1,9], Paul Smith[10], Jenny Mehew[10], Miriam Manook[11], Carrie Scuffell[2], Aimen Amer[2], Samuel Tingle[1,2], Emily R. Thompson[1,2] and CRAFT Study Collaborators*

[1]Herrick Society CRAFT Study Committee, Newcastle Upon Tyne, England, [2]Institute of Transplantation, Freeman Hospital, Newcastle Upon Tyne, United Kingdom, [3]Department of Surgery, Royal Hallamshire Hospital, Sheffield, United Kingdom, [4]Department of Surgery, Edinburgh Royal Infirmary, Edinburgh, United Kingdom, [5]Department of Surgery, University Hospital of Wales, Cardiff, United Kingdom, [6]Department of Surgery, Queen Elizabeth Hospitals NHS Foundation Trust, Birmingham, United Kingdom, [7]Nuffield Department of Surgical Sciences, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom, [8]Department of Surgery, Leeds Teaching Hospitals, Leeds, United Kingdom, [9]Department of Surgery, Duke University, Durham, NC, United States, [10]Statistics and Clinical Research, NHS Blood and Transplant, Bristol, United Kingdom, [11]Addenbrookes Hospital, Cambridge, United Kingdom

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***Correspondence**
Emily R. Thompson,
emily.thompson3@newcastle.ac.uk

†ORCID:
Mohamed El Zawahry
orcid.org/0000-0001-5300-912X

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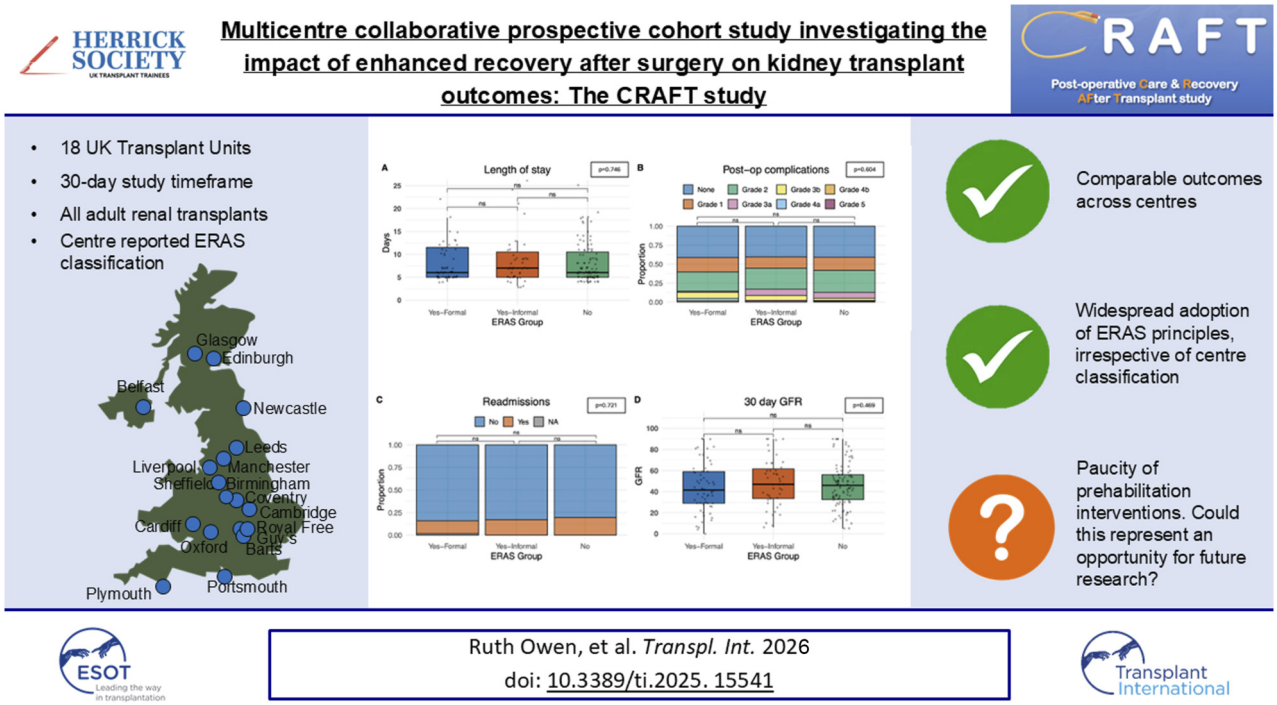
Perioperative complications are common in kidney transplantation. Enhanced recovery after surgery (ERAS) is a well-established multimodal perioperative care pathway designed to improve patient outcomes, however, its efficacy in renal transplant remains poorly described. Participating centres included adult renal transplant recipients and 30-day follow-up data. The primary outcome was LOS. Multivariable hierarchical models compared cohorts. 213 patients were included in the study period. 18/23 UK kidney transplant centres were represented. Analysis of the perioperative care delivery demonstrated similar patterns irrespective of reported protocols, with a tendency towards ERAS-type care. Between cohorts, the incidence of complications were similar; formal ERAS 14.3%, ERAS informal 17.0%, no ERAS 12.6%; p = 0.64. Median LOS was also similar; formal ERAS 6.0 days (5.0–11.5), informal ERAS 7.0 days (5.0–10.5) vs. no ERAS 6.0 days (5.0–10.5); p = 0.75. Readmissions were comparable; p = 0.721. Multivariable models confirmed these findings and demonstrated frailer patients had longer LOS and more readmissions. Currently, most UK renal transplant centres deliver a form of peri-operative ERAS care, indicating broad adoption of ERAS principles. Consequently, a formal ERAS protocol is not associated with decreased complications, LOS or readmissions. Efforts to improve outcomes should focus on prehabilitation of at-risk groups on the waiting list.

Keywords: enhanced recovery after surgery (ERAS), ERAS in kidney transplantation, kidney, perioperative care, prehabilitation



GRAPHICAL ABSTRACT |

INTRODUCTION

Kidney transplantation remains the optimal treatment for patients with end-stage kidney disease (ESKD), offering superior survival and quality of life compared to dialysis [1]. However, despite advancements in surgical techniques and immunosuppression, post-transplant complications, delayed graft function (DGF), and prolonged hospital stays continue to present significant challenges [2].

Enhanced Recovery After Surgery (ERAS) protocols, originally developed in colorectal surgery [3], have been increasingly adopted across multiple other surgical disciplines, demonstrating improvements in post-operative recovery, reduced complications, and shorter hospital stays [4]. The application of ERAS principles to kidney transplantation represents a promising strategy to optimize perioperative care and improve patient outcomes.

Broadly, ERAS protocols offer a suite of pre, intra and post operative goals or interventions, to guide surgical patient management, however local implementation of various aspects may differ. Preoperative measures focus on patient education, prehabilitation exercises, nutritional optimization, annual reviews on the waiting list, blood pressure management, smoking cessation and avoidance of prolonged fasting [5]. Intraoperatively, goal-direct fluid delivery, minimising the use of surgical drains, optimal anaesthetic protocols and opioid-sparing analgesia are emphasized to minimize physiological stress [6, 7]. Postoperative strategies prioritize early mobilization, multimodal pain management, and early oral intake to expedite functional recovery and reduce complications [8]. Evidence from non-transplant surgical specialties suggests that ERAS implementation leads to significant reductions in hospital length of stay, morbidity, and healthcare costs [9], but data on UK kidney transplantation remain limited to single respondent surveys [10], guidelines [11] or reviews.

Recent studies suggest that components of ERAS, such as restrictive fluid management and multimodal analgesia, may positively influence kidney transplant outcomes by reducing the incidence of DGF and improving early graft function [12, 13]. However, the efficacy and safety of a standardized ERAS protocol in this patient population have not been comprehensively evaluated prospectively across multiple centres. The effects of ERAS have been reviewed in a single centre setting, first by the Sheffield group [14] and included patient education and discharge planning (commenced on admission), carbohydrate loading, goal-directed fluid therapy, early oral intake post-operatively, early catheter removal (~day 4), early drain removal and early mobilisation. Their results suggested a shorter length of stay (LOS) of 5 days (range 3–9 days), compared with a median LOS of 7 days (range 5–30 days) prior to the ERAS programme being implemented. A similar study was published by the Belfast group in 2021 which also showed a decreased LOS after implementation of their ERAS

protocol [15]. Given the complexity of the kidney transplant recipient population, incorporating ERAS principles requires careful including consideration of immunosuppression regimens, fluid balance management, and recipient comorbidities [7, 8].

Using prospectively collected, real world data, this study aims to investigate the impact of ERAS implementation on kidney transplant outcomes, including length of hospital stay, postoperative complications, and readmission rates across multiple UK transplant centres. We compare kidney transplant recipients managed with and without an ERAS protocols, in order to determine whether this structured perioperative approach can enhance recovery and optimize transplantation outcomes. Understanding the role of ERAS in kidney transplantation may lead to standardized protocols that improve patient care, reduce healthcare costs, and enhance long-term allograft function.

PATIENTS AND METHODS

The CRAFT study was a multicentre prospective cohort study investigating the impact of ERAS on kidney transplant outcomes in the UK. Consecutive adult recipients undergoing live or deceased donor kidney transplantation at participating centres over a defined recruitment period were included. Paediatric recipients and those receiving multi-organ transplants (e.g., simultaneous pancreas kidney) were excluded.

Patients were categorized into *formal* ERAS, *informal* ERAS and *non*-ERAS centres based on a survey of the centre-reported care pathway collected prior to the data collection period. *Formal* ERAS centres were defined as those where an official ERAS protocol was in place which included preoperative optimization, intraoperative fluid and analgesic management, and postoperative recovery strategies that the department adhered to. Centres were classified as *informal* ERAS centres if they delivered ERAS-type care that was not protocolised but widely implemented and considered to be ERAS-like care by the department, and non-ERAS centres followed their standard surgical protocols. The non-ERAS centres served as the comparator group.

Data were collected prospectively for 30 days post-transplant using the Research Electronic Data Capture (REDCap™) system. The primary outcome was length of hospital stay (LOS). Secondary outcomes included the incidence of Clavien-Dindo grade ≥3 complications, graft function, and 30-day readmission rates.

This study was conducted as a national service evaluation project and local audit and research governance approvals were obtained for all participating centres by the responsible principal investigators. No changes to clinical care nor patient-identifiable data were stored in the REDCap™ system, and all data were anonymized before analysis.

Statistical Analysis

Continuous data were summarized as medians with interquartile ranges, while categorical data were presented as counts and percentages. Differences between groups for continuous outcomes were assessed using the unpaired non-parametric Kruskal-Wallis test. For categorical data, the chi-squared test was used, and Fisher's exact test was applied for groups with small sample sizes. Post hoc pairwise comparisons were conducted to identify which groups differed from one another. Wilcoxon rank-sum tests were used for continuous outcomes, and Chi-squared tests were used for categorical outcomes. To assess the impact of ERAS protocols on length of stay multivariable Cox regression models were used with a frailty term (random effect) for transplant centre. For this analysis each centre was considered a single cluster, even if the use of ERAS protocols varied at the patient-level. This hierarchical strategy accounts for the clustered nature of the data, whilst allowing adjustment for patient-level variables (including recipient, transplant and donor factors). For these analyses, LOS was treated as a time-to-event variable, with discharge being the event (with higher hazard ratios indicating faster discharge). All analyses were performed in R version 4.2.1 (R Project for Statistical Computing).

RESULTS

Centre Reported Protocols

Eighteen adult kidney transplant centres across the United Kingdom participated in the study, of a possible 24. Each hospital submitted a centre-reported perioperative care pathway questionnaire which detailed whether they had a formal ERAS programme and what the standard elements of pre-, intra-, and post-operative care included, **Table 1**. This allowed us to categorise the centres. One hospital had an informal ERAS programme when they began the CRAFT study data collection, however, during the study period initiated a separate trial which brought in a formal ERAS programme. As such this hospital is treated as two separate centres throughout our descriptive analyses (Centre E – *informal* – to represent the patients prior to the trial starting, and Centre E – *formal* to represent the patients after the trial started). Another hospital, Centre K had an *informal* ERAS programme for living donor kidneys but no ERAS programme for deceased donor kidneys recipients. This centre was also treated as two "separate centres" within our descriptive analyses to ensure the difference in ERAS protocoled care was accounted for. Of the 20 separate centres, n = 5 had a *formal* ERAS protocol, n = 7 considered themselves to have *informal* ERAS care and n = 8 had *no specific* ERAS programme.

213 transplants took place across the 20 centres during the 30-day study timeframe (15th January – 15th February 2024). Donor and recipient demographics were compared between centres that defined themselves as a formal ERAS centre, an informal ERAS centre a non-ERAS centre. Data completeness for this study was 99.8% and so a missing value analysis was not undertaken.

Donor and Recipient Demographics

Donor demographics were comparable between groups with regards to donor sex, donor age, donor type (live/DBD/DCD), UK Donor Risk Index [16], HLA mismatch, and hypothermic

TABLE 1 | Site survey results. Centre-reported ERAS implementation.

Centre	ERAS for recipients of:		ERAS Care includes			Routine pre-operative care						Routine intra- and post- operative care				
	LD	DBD/ DCD	Nurse or coordinator	Pre-op counselling	Patient support document	Annual review on waiting list	Rehab exercise programme	Carb loading drinks	Nutrison optimisation	Smoking cessation	Weight and BP optimisation	Itra-op goal directed fluids	Ureteric stenting	Time to removal of stent (weeks)	Method of removal	Placement of surgical drain
Formal ERAS Centre																
A	Yes	Yes				Yes	Yes	Yes		Yes	Yes	Yes	Yes	3	Flexible	
B	Yes	N/A				Yes		Yes	Yes	Yes		Yes	Yes	4	cystoscopy	Yes
C	Yes	Yes				Yes				Yes			Yes	6	with LA	
D	Yes	Yes	Yes	Yes	Yes	Yes	Yes			Yes	Yes	Yes	Yes	2	in OPD	Yes
E-formal	Yes	Yes				Yes						Yes	Yes	3		Yes
Total	100%	100%	20%	20%	20%	100%						80%	100%	$\bar{x}$ = 3.6		60%
Informal ERAS Centre																
E-informal	Yes	Yes				Yes						Yes	Yes	3	Flexible	Yes
F	Yes	Yes				Yes							Yes	6	cystoscopy	Yes
G	Yes	Yes						Yes			Yes	Yes	Yes	2	with LA	
H	Yes	Yes											Yes	6	in OPD	
I	Yes	Yes				Yes			Yes	Yes	Yes	Yes	Yes	6		Yes
J	Yes	Yes											Yes	2		
K-LD	Yes	N/A				Yes	Yes		Yes	Yes	Yes		Yes	6		
Total	100%	100%	0%	0%	0%	57%	14%	14%	29%	29%	43%	43%	100%	$\bar{x}$ = 4.4		43%
Non-ERAS Centre																
K-DBD/ DCD	N/A	No				Yes	Yes		Yes	Yes	Yes		Yes	6	Flexible cystoscopy	
L	No	No				Yes							Yes	6	with LA	
M	No	No				Yes			Yes		Yes		Yes	6	in OPD	
N	No	No											Yes	6		Yes
O	No	No											Yes	2		
P	No	No				Yes							Yes	3		Yes
Q	No	No									Yes		Yes	4		Yes
R	No	No				Yes							Yes	4		Yes
Total	0%	0%	0%	0%	0%	63%	13%	0%	25%	13%	38%	0%	100%	$\bar{x}$ = 4.6		50%

Breakdown of units that considered themselves to have a formal ERAS protocol, and informal protocol or no protocol. Detailed information about the standard of care provided in the pre-operative, intra-operative and post-operative period. Abbreviations: BP – Blood Pressure DBD – Donation after Brainstem Death; DCD – Donation after Circulatory Death; ERAS – Enhanced Recovery After Surgery; LA- Local Anaesthetic; LD – Living Donor; OPD – Outpatient Department $\bar{x}$ - mean.

TABLE 2 | Donor Demographics. *Data shown as number + percentage.*

Donor Demographics	Variable	ERAS – Formal	ERAS – Informal	No ERAS	Total	p
Total	N (%)	63 (29.6)	47 (22.1)	103 (48.4)	213	
Donor age	Median (IQR)	54.0 (36.5 to 63.5)	51.0 (39.0 to 62.5)	53.0 (42.0 to 62.0)	53.0 (39.0 to 63.0)	0.779
Donor sex	F	26 (41.3)	19 (40.4)	42 (40.8)	87 (40.8)	0.996
Donor type	Live	22 (34.9)	22 (46.8)	31 (30.1)	75 (35.2)	0.206
	DBD	22 (34.9)	16 (34.0)	34 (33.0)	72 (33.8)	
	DCD	19 (30.2)	9 (19.1)	38 (36.9)	66 (31.0)	
UKDRI	Median (IQR)	1.4 (0.7 to 1.6)	1.4 (1.1 to 1.7)	1.2 (1.0 to 1.6)	1.3 (0.9 to 1.6)	0.615
Terminal eGFR	Median (IQR)	90.0 (72.0 to 90.0)	83.0 (62.0 to 90.0)	90.0 (78.8 to 90.0)	90.0 (75.0 to 90.0)	0.040
Cold ischaemic time (minutes)	Median (IQR)	649.0 (301.0 to 963.0)	386.0 (234.5 to 834.0)	631.0 (317.5 to 927.0)	615.0 (249.0 to 902.0)	0.213
Warm ischaemic time (minutes)	Median (IQR)	46.0 (34.0 to 87.8)	22.5 (19.0 to 28.2)	38.5 (22.2 to 185.0)	38.5 (23.0 to 178.5)	0.097
HLA mismatch - DR	2	9 (14.3)	8 (17.0)	17 (16.5)	34 (16.0)	0.955
NRP	Yes	6 (9.5)	0 (0.0)	13 (12.6)	19 (8.9)	0.041
Hypothermic Machine perfusion	Yes	0 (0.0)	0 (0.0)	3 (2.9)	3 (1.4)	0.211

DBD – Donation after Brainstem Death, DCD - Donation after Circulatory Death. UKDRI – UK donor risk index. HLA – Human Leucocyte antigen, NRP- Normothermic Regional Perfusion.

TABLE 3 | Recipient Demographics. *Data shown as number + percentage.*

Recipient Demographics	Variable	ERAS – Formal	ERAS – Informal	No ERAS	Total	p
Total	N (%)	63 (29.6)	47 (22.1)	103 (48.4)	213	
Age	Median (IQR)	53.0 (43.5 to 60.0)	51.0 (36.0 to 62.0)	54.0 (40.5 to 61.0)	54.0 (40.0 to 60.0)	0.761
Sex	F	26 (41.3)	11 (23.4)	35 (34.0)	72 (33.8)	0.146
	M	37 (58.7)	36 (76.6)	68 (66.0)	141 (66.2)	
BMI	Median (IQR)	27.9 (23.3 to 31.1)	26.1 (23.3 to 30.3)	27.0 (24.2 to 30.6)	26.7 (24.0 to 30.8)	0.457
WHO performance status	0	41 (65.1)	30 (63.8)	59 (57.3)	130 (61.0)	0.685
Pre-emptive transplants	None	11 (17.5)	10 (21.3)	17 (16.5)	38 (17.8)	0.505
Previous kidney transplants	None	54 (85.7)	40 (85.1)	87 (84.5)	181 (85.0)	0.897
Urological pathology	Yes	3 (4.8)	3 (6.4)	8 (7.8)	14 (6.6)	0.749
Standard anatomy	Yes	42 (66.7)	37 (78.7)	70 (68.0)	149 (70.0)	0.303
Immuno-suppression	Augmented	6 (9.5)	10 (21.3)	6 (5.8)	22 (10.3)	0.015

BMI- Body Mass Index. Urological pathology. Those with augmented immunosuppression relates to any immunosuppression protocol beyond that of standard immunosuppression.

machine perfusion. Warm ischaemic time (WIT) and cold ischaemic time (CIT) were also similar between the two groups.

Live donor transplants accounted for 34.9% (n = 37) or transplants performed in *formal* ERAS centres, 46.8% (n = 22) of transplants performed in an *informal* ERAS centre and 30.1% (n = 31) transplants performed in centres with *no* ERAS programme. The UK donor risk index (UKDRI) was calculated for all donors. There was comparable donor risk grafts utilised by *formal* ERAS centres (Median 1.4, IQR 0.7–1.6), when compared to *informal* centres (Median 1.4, IQR 1.1–1.7) and *non*-ERAS centres (Median 1.2, IQR 1.0–1.6), p = 0.615, **Table 2**. There were also a comparable number of donors having a renal transplant pre-emptively (defined as prior to the start of dialysis) in centres with a *formal* ERAS programme (n = 11, 17.5%), compared with *informal* centres (n = 10, 21.3%) and *non*-ERAS centres (n = 17, 16.5%). CIT was also comparable between those with a formal, informal or no ERAS programme, p = 0.213, **Table 2**.

Donor Terminal eGFR was statistically significantly lower (p = 0.040) in centres with an *informal* ERAS programme when compared to those with a *formal* programme and *no* programme at all, **Table 2**. NRP was also noted to be statistically significantly less likely to be utilised in the *formal* ERAS programme (p = 0.041).

There was no significant difference in any other recipient demographics between comparator groups. This included analysis of age, sex, body mass index (BMI - categorised by the WHO classification) [17], WHO performance status, number of previous transplants, urological pathology, anatomy, and immunosuppression regime, **Table 3**. Indicating that the groups were well matched.

Intraoperative Patient Management

Prospective data was collected on intra- and peri-operative management to better understand how care was actually being delivered, alongside how centres had reported that they delivered care in the site survey.

Volume of intraoperative fluid provided was compared between our groups. Centres with a *formal* ERAS protocol gave statistically significantly (p < 0.001) large fluid volumes (2,800 mL IQR: 2,000–3,900) when compared with *informal* ERAS centres (2,000 mL IQR: 1,500–2,950) and *non*-ERAS centres (2,000 mL IQR: 1,500–2,950), **Figure 1A**. Most patients (55.9%, n = 116) received TAP block analgesia with or without continuous infusion, intraoperatively. Patients in a

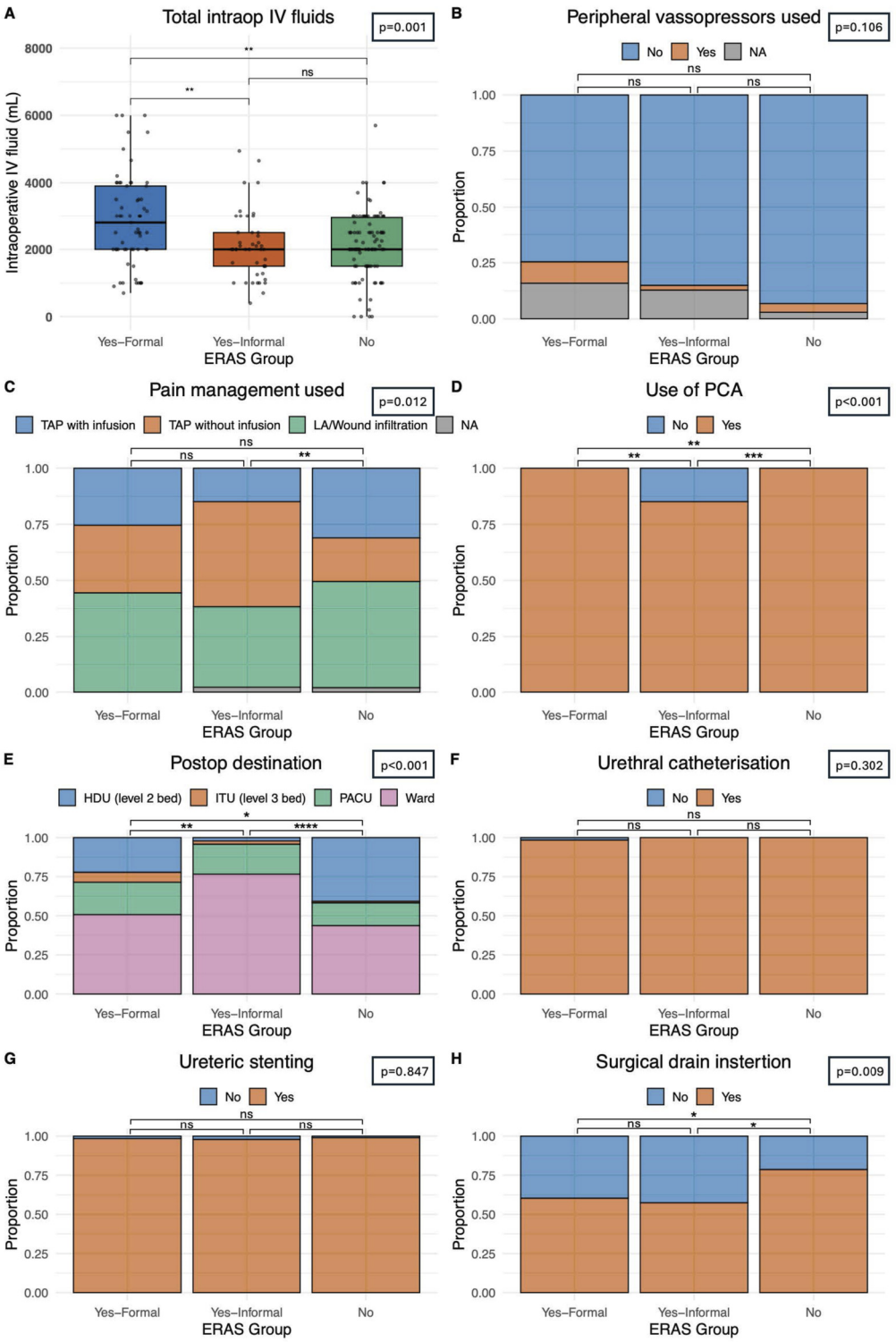


FIGURE 1 | Delivery of perioperative care. **(A)** Intraoperative intravenous fluid usage in mL. **(B)** Intraoperative peripheral vasopressor usage. **(C)** Intraoperative pain management strategy including Transversus Abdominis Plan (TAP) block with or without infusion of local anaesthetic or local anaesthetic only. **(D)** Use of patient-controlled analgesia technique post-operatively. **(E)** Patient destination post operatively, including high dependency unit (HDU – level 2 care), intensive treatment unit (ITU – level 3 care), a prolonged stay within a post-anaesthetic care unit (PACU) or immediate ward-based care. **(F)** Incidence of urethral catheterisation pre- or intra-operatively. **(G)** Incidence of intraoperative ureteric stenting. **(H)** Incidence of surgical drain insertion. Bars indicate p-values from pairwise comparisons (Wilcoxon rank-sum test for continuous, and Chi-squared test for categorical variables). Significance levels: *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, ****p ≤ 0.0001.

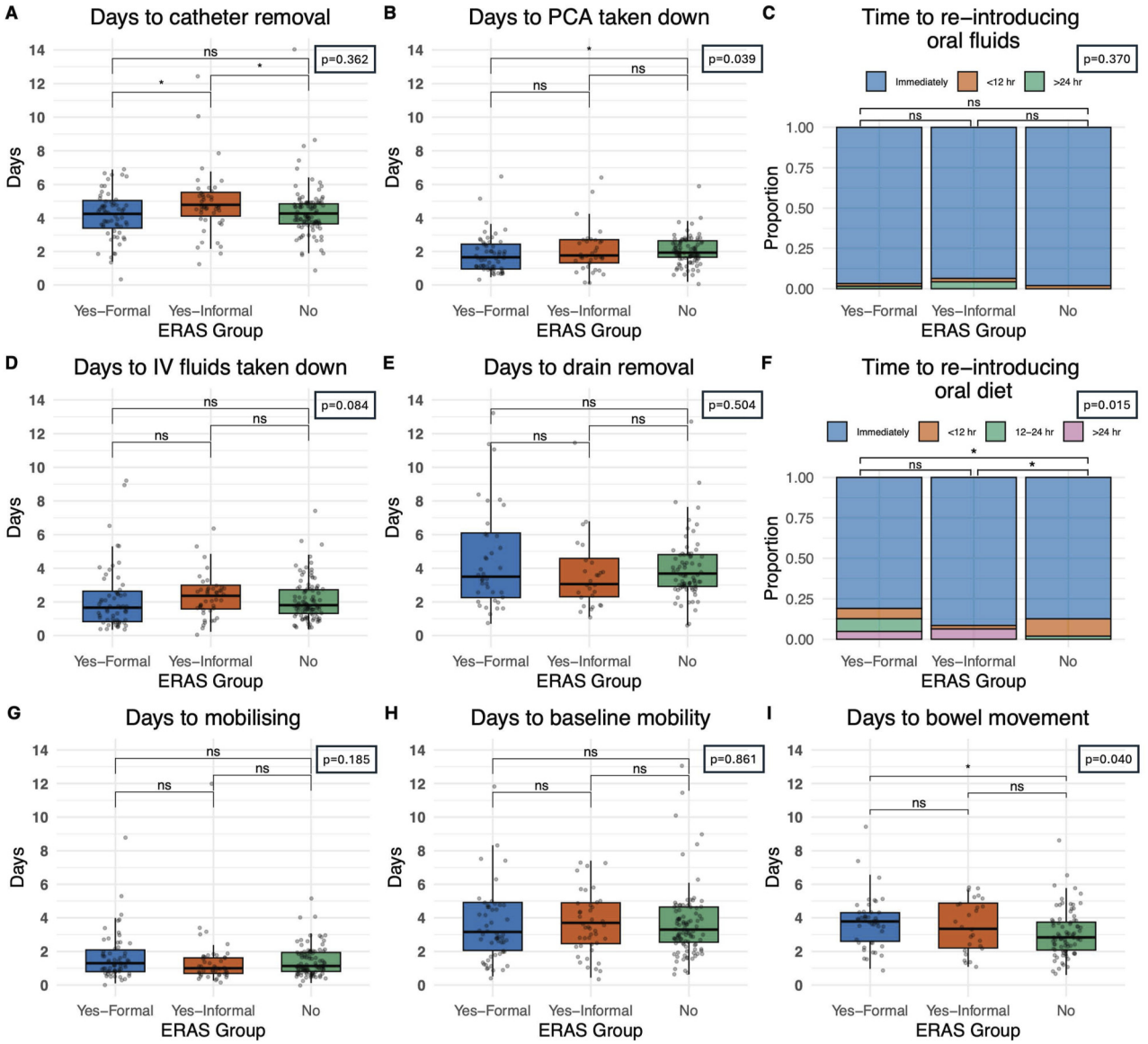


FIGURE 2 | Impact of perioperative care approach on post-operative course. **(A)** Time until catheter removal, measured in days. **(B)** Time until patient controlled analgesia (PCA) taken down in recipients who were given a PCA. **(C)** Time until oral fluids reintroduced categorized as immediately post-operative, within 12 hours and greater than 24 h **(D)** Time until intravenous fluids taken down in days **(E)** Time until drain removal, measured in days **(F)** Time until re-introduction of oral diet categorized as immediately post-operatively, within 12 h, 12–24 h and greater than 24 h. **(G)** Time until the patient first mobilises, measured in days post-operatively **(H)** Time until patient returned to baseline mobility, measured in days **(I)** Days until first documented bowel movement, measured in days. Bars indicate p-values from pairwise comparisons (Wilcoxon rank-sum test for continuous, and Chi-squared test for categorical variables). Significance levels: *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, ****p ≤ 0.0001.

centre with *no* ERAS programme were statistically significantly less likely to use a TAP block than those with a *formal/informal* programme (p = 0.012) **Figure 1C**. Patient controlled analgesia was utilised in 96.7% of transplants (n = 206). Of the seven patients who did not receive a PCA they were all within a single *informal* ERAS centre which was statistically significant (p < 0.0001), **Figure 1D**. Patients who received *formal* ERAS care were statistically significantly more likely to go back to the ward post-operatively (50.8%, n = 32), as were those who underwent *informal* ERAS care (76.6%, n = 36) when compared to those without an ERAS programme (43.7%, n = 45), p < 0.0001, **Figure 1E** where they were more likely to go to the high dependency unit. Those who underwent *formal or informal* ERAS care were also statistically significantly less likely to have a surgical drain inserted (p = 0.009). 60.3% of *formal* ERAS patient (n = 38) had a drain inserted, 57.4% (n = 27) in an *informal* centre and 78.6% (n = 81) in centres with *no* ERAS programme, **Figure 1H**. Comparable rates of peripheral

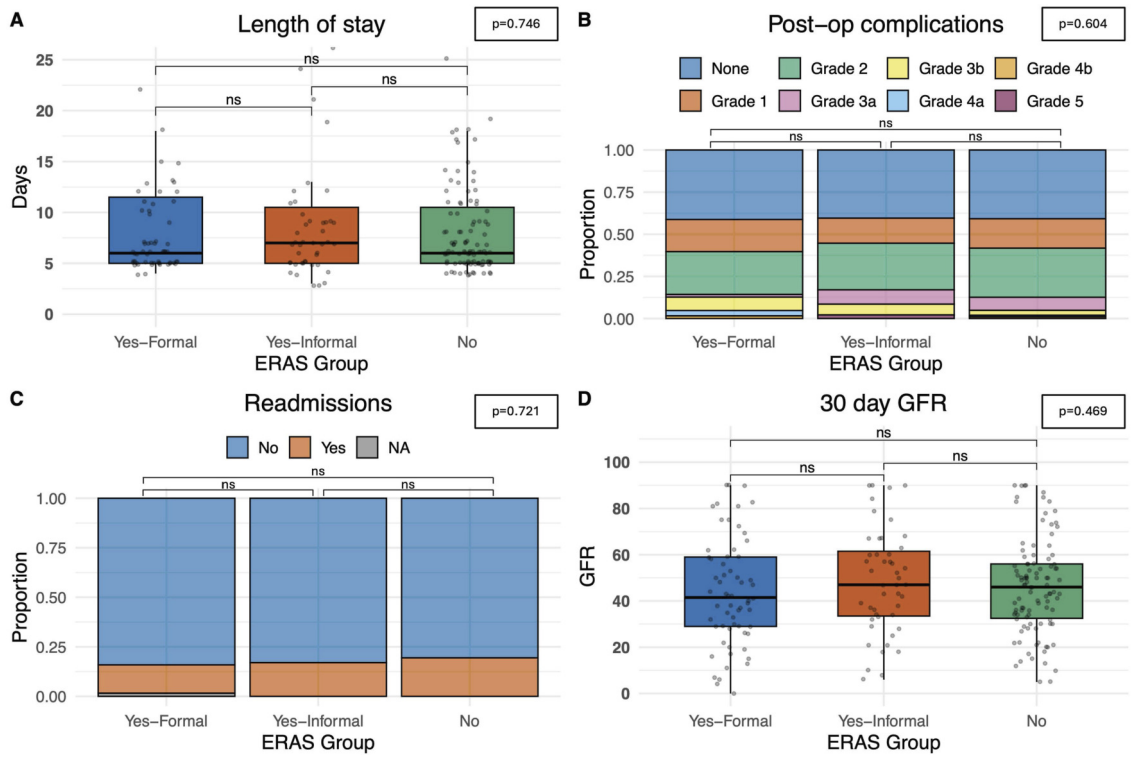


FIGURE 3 | Postoperative outcomes. **(A)** Length of stay, measured in days from admission. **(B)** Total complications noted, categorised by Clavien-Dindo grading score. **(C)** Number of readmissions within a 30-day time-period. **(D)** eGFR at 30 days. Bars indicate p-values from pairwise comparisons (Wilcoxon rank-sum test for continuous, and Chi-squared test for categorical variables). Significance levels: *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, ****p ≤ 0.0001.

vasopressor use (p = 0.106), **Figure 1B**, urethral catheterisation (p = 0.302), **Figure 1F**, and ureteric stenting (p = 0.847), **Figure 1G**, was seen in all centres.

Post-Operative Management of Drains and Lines

Patients in centres with a *formal* ERAS protocol had earlier catheter removal (4.3 days IQR: 3.4–5.1) than those with an *informal* programme (4.8 days IQR: 4.1–5.5) and comparable catheter removal to centres with *no*-ERAS (4.3 days IQR: 3.7–4.9) protocol, **Figure 2A** (p = 0.036). Oral diet was introduced at a later stage in recipients who underwent a *formal* ERAS protocol (12.7%, at 24 h or more) when compared to centres with an *informal* programme (6.4%) or *no* ERAS programme (0%) (p = 0.015), **Figure 2F**. Centres with *no* ERAS protocol had a statistically significant shorter period of time post-operatively until documentation of bowel movement (2.8 days, IQR: 2.1–3.7), when compared to *formal* centres (3.8 days, IQR:2.6–4.2) and *informal* centres (3.3 days, IQR: 2.2–4.9) (p = 0.040) **Figure 2I**. Patients in a *formal* ERAS centre had their PCA taken down earlier (1.7 days IQR: 0.8–2.6) when compared to centres with *informal* programmes (1.8 days IQR:1.3–2.7) and *non*-ERAS centres (1.9 days IQR: 1.7–2.7), this reached statistical significance but is unlikely to be clinically significant given the actual values (p = 0.036), **Figure 2B**. The time from operation to re-introducing oral fluids (p = 0.370) **Figure 2C**, and IV fluids being taken down (p = 0.084), **Figure 2D** was comparable. Days until drain removal was also comparable (p = 0.504), and on average centres were removing drains after 3.6 days, **Figure 2E**. There were comparable outcomes when analysing the number of days from operation to mobilisation, those in a *formal* ERAS program mobilised at 1.3 days (IQR: 0.8–2.1), an *informal* programme 1.0 days (IQR: 0.7–1.6) and *no* ERAS programme 1.1 days (IQR: 0.8–1.9) (p = 0.185), **Figure 2G**. They also returned to baseline mobility at comparable timeframes, 3.2 days for patients in a *formal* ERAS programme (IQR: 2.1–4.9), 3.7 days in the *informal* programme (IQR: 2.5–4.9) and 3.3 days for patients with *no* ERAS programme (IQR: 2.5–4.6), (p = 0.861), **Figure 2H**. Patients in the non-ERAS centres opened their bowels sooner than patients in formal ERAS centres (p = 0.040), **Figure 2I**.

Post-Operative Outcomes

The primary outcome measured in this study was the length of stay (days since transplant) and no statistically significant differences on univariate analysis were observed between *formal* ERAS centres, or *informal* ERAS centres when compared with *non*-ERAS units (p = 0.746). The average length of stay in centres with a *formal* ERAS programme was 6.0 days (5.0–11.5), 7.0 days (5.0–10.5) in centres with *informal* ERAS and 6.0 (5.0–10.5) days in centres without an ERAS protocol, **Figure 3A**. A comparable rate of post-operative

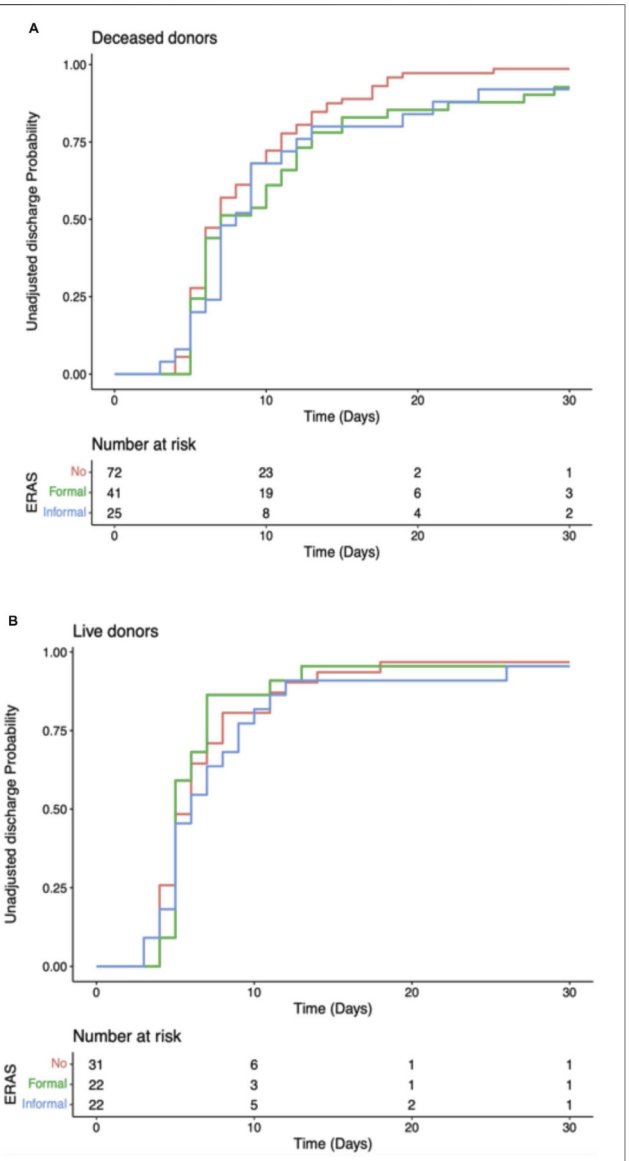


FIGURE 4 | Cumulative unadjusted discharge probability after transplantation, stratified by transplant unit ERAS group. **(A)** Recipients of deceased donor kidney. **(B)** Recipients of live donor kidney.

complications (categorised using the Clavien-Dindo Grading system) (p = 0.604), were observed. 14.3% (n = 9) patients in the *formal* ERAS programme had a Grade 3 or higher Clavien-Dindo complication, comparable to the 17% (n = 8) in the *informal* ERAS programme and 12% (n = 12) in centres with *no* ERAS programme, **Figure 3B**.

The recipients also had comparable rates of readmission at 30 days. In centres with a *formal* ERAS programme 14.3% (n = 9) patients were readmitted, 17% (n = 8) in centres with *informal* ERAS programmes and 19.4% (n = 20) in centres without an ERAS programme (p = 0.721), **Figure 3C**. Median eGFR 30 days post-operatively was also comparable. In *formal* ERAS centres median 30 days eGFR was 41.5 mL/min/1.73 m^2 (IQR: 29.0–59.0), 47.0 mL/min/1.73 m^2 in *informal* centres (IQR: 33.5–61.5) and 46.0 mL/min/1.73 m^2 (IQR: 32.5–56.0), (p = 0.469), **Figure 3D**. Univariate analyses were also performed delineating recipients who received a graft from a deceased donor (DBD/DCD graft) and those who received a graft from a living donor. These models showed comparable time until discharge irrespective of whether the centre described themselves as having a *formal* ERAS protocol, and *informal* protocol or *no* ERAS protocol. This trend was similar in both deceased and live donors (**Figure 4**).

TABLE 4 | Multivariable hierarchical Cox regression model for length of stay, with random effect term for transplant centre.

Variable	HR (95%CI)	P value
ERAS - none	1	
ERAS - formal	0.753 (0.543–1.045)	0.090
ERAS - informal	0.628 (0.435–0.906)	0.013
Live	1	
DBD	1.051 (0.748–1.476)	0.774
DCD	0.462 (0.326–0.656)	0.000
WHO performance status 1	0.586 (0.423–0.811)	0.001
WHO performance status >1	0.544 (0.328–0.904)	0.019
Random effect for transplant centre	Random effect	0.916

Length of hospital stay is modelled as time to discharge, and therefore hazard ratios lower than 1 represent prolonged hospital stay. ERAS – Enhanced Recovery After Surgery; DBD – donation after brainstem death; DCD – donation after circulatory death.

Multivariable Analysis of Impact of ERAS on Length of Stay

A multivariable model was created to analyse the impact of ERAS protocols within the context of other recipient and donor factors including type of transplant (DBD/DCD/Live Donor) as well as patient frailty (based on the WHO performance status), **Table 4**. In the multivariable hierarchical Cox regression model, ERAS status was statistically significantly associated with length of stay (Wald p = 0.030). This was demonstrated by a lower HR for discharge (formal ERAS aHR = 0.753, 0.543–1.045, p = 0.090 and informal ERAS aHR = 0.628, 0.435–0.906, p = 0.013; **Table 4**); adjusted length of stay was longer in the centres with ERAS programmes compared to those without ERAS programmes. The multivariable models also demonstrated patients with WHO performance status ≥1 (frailer patients) had longer LOS, **Table 4**. A sensitivity analysis adjusting for pre-emptive transplant as a confounder was performed which demonstrated similar results. A further sensitivity analysis was performed excluding the two centres which used a mixture of ERAS and no ERAS; results were in keeping with the model in **Table 4**. Finally, we repeated the model shown in **Table 4**, instead categorising ERAS status into "formal ERAS" versus "no formal ERAS" (combining the "no ERAS" and "informal ERAS" groups). There was no significant difference in length of stay between "formal ERAS" and "no formal ERAS" (aHR = 0.888, 0.647–1.219, 0.462).

DISCUSSION

ERAS was conceptualised within colorectal surgery and has since been adopted across various surgical disciplines, with specialty-

specific adaptations to complement the demographic of patients and the operations being performed. In this study, across multiple UK kidney transplant centres, we demonstrate that the uptake of a specific ERAS protocol in renal transplant has been variable. However, despite this, the delivery of perioperative care was very similar across centres irrespective of how the centres categorised themselves with all centres tending towards ERAS-style care. From the study we noted that regardless of a centres classification, the cautious use of IV fluids, vasopressors, patient controlled analgesia, avoidance of epidurals and strategic drain insertion were commonplace. This likely represents a wider culture change across all surgical specialties as ERAS principles have become embedded in standard UK surgical practice. This lack of difference in the real-world delivery of perioperative care may also explain the similar length of stay between cohorts.

Of note, pre-operative ERAS style care was found to be less well embedded within practice. Few centres offered nutritional support, or pre-operative carbohydrate loading drinks and less than half of centres offered weight advice and blood pressure optimisation. Exercise programmes were also sparsely available. Those with formal ERAS protocols had a greater propensity for smoking cessation programmes than centres without. These differences may reflect the relatively unpredictable nature of deceased donor transplantation.

The renal transplant recipient population are generally more comorbid than those undergoing other elective general surgery, in part as a consequence of end stage renal disease, and therefore organ support in the form of chronic dialysis dependence. Additionally, there are changing demographics within the kidney recipient population, over time–tending towards greater numbers of older, co-morbid transplant recipients [18], as the population ages. This study found that recipients with a worse WHO performance status had an associated increased length of stay, as would be expected. As such this would suggest that the ERAS elements of pre-operative optimisation and prehabilitation which are less well implemented across the board, may aide improvements in a patient's functional status and may represent another target to improve outcomes.

Donor and recipient demographics were largely comparable between centres with a *formal* ERAS programme, an *informal* ERAS programme and *no* ERAS programme, thus demonstrating that our cohorts were well matched for comparison with no one group having a high proportion of pre-emptive live donor transplants which would artificially skew length of stay data. There were two differences within the donor demographic group which reached statistical significance, donor terminal eGFR and the use of NRP. For donor terminal eGFR centres with an informal ERAS programme accepted grafts from donors with a statistically significantly poorer terminal eGFR ($p = 0.040$). Whilst statistically significantly different we do not think the difference in eGFR noted would be clinically significant when looking at the absolute values. Terminal eGFR is also a single value and therefore does not discriminate between an acute injury to the kidney that may be recoverable, precipitated by the mechanism of death in the donor, versus chronic kidney disease. With regards to the use of normothermic regional perfusion (NRP), this is an emerging technique with limited centres of expertise and no centralised funding. Grafts from donors who underwent NRP were statistically significantly less likely to be accepted by programmes with an *informal* ERAS programme. We believe this is likely coincidental secondary to the geography of the retrieval units routinely performing NRP rather than directly related to the ERAS programme. Recipient demographics were similar between all centres which provides confidence when comparing our primary and secondary outcomes.

This study provides a unique snapshot of real-world perioperative care delivery in kidney transplantation across multiple centres. Importantly, our findings indicate that whilst only 27% of centres would describe themselves to have a formal ERAS programme, most UK renal transplant centres are delivering perioperative ERAS-type care. The average length of stay for all patients in the study was 6 days. A prior study using data from 2020 showed an average of 10 days stay, which could be improved to 5–7 days in units with an active ERAS programme [10]. This suggests that the principles of ERAS have been widely adopted into routine clinical practice, which is reflected in the improved lengths of stay, and a broader trend towards optimizing management in kidney transplantation.

Despite the widespread adoption of ERAS-type care, our univariate unadjusted analysis found no significant association between the implementation of a *formal* ERAS protocol and reduced complications, length of stay (LOS), or readmissions. However, the adjusted analysis did demonstrate an increased length of stay in the *informal* ERAS cohort. This could be explained by the fact that centres without ERAS protocols may already operate with a relatively short LOS, hence there is no need to introduce an ERAS protocol, limiting the potential for further reductions. Notably, the median length of stay across the different cohorts was relatively acceptable at 6 days. This is a considerable reduction from 20 years ago when often renal transplant recipients would often have significantly longer lengths of stay, with over 20% of US recipients staying in hospital for more than 2 weeks post-transplant [19]. This highlights how the culture change has become embedded within all renal transplant centres to encourage early discharge.

These findings also highlight the paucity of preoperative optimization efforts which may represent an area for improvement. Rather than solely emphasizing intraoperative ERAS implementation, we suggest future strategies should prioritize addressing patient-related factors that impact recovery. Specifically, prehabilitation and frailty management for at-risk patients on the transplant waiting list could provide a more effective means of improving perioperative outcomes. Prehabilitation has been described as a process where a patient's functional capacity is enhanced prior to surgery in preparation for the known upcoming stressor which is surgery [20].

There are four main aspects of prehabilitation which include: medical optimisation, nutritional support, increasing physical exercise, and psychological support. Medical optimisation focusses on smoking cessation to improve post operative wound healing [21] and weight management – for both obese and underweight patients, both of whom are at risk of malnutrition [22]. Patient malnutrition is associated with

increased length of stay, infection, increased readmissions and mortality [23] and strategies to improve nutrition, including preoperative carbohydrate loading drinks and a high protein diet in the weeks prior to surgery to reduce insulin resistance and improve immune responses [24]. Physical exercise is well documented to have improved benefits post-surgery, including decreasing length of stay, but is notoriously challenging with regards to patient uptake [25]. In transplantation, the unpredictable and variable timing from listing to transplant makes the delivery of prehabilitation difficult as patients need to be able to maintain the gains made throughout a potentially extended waiting period for an organ offer to become available. This may be more achievable in live donor transplantation as a planned elective operation and prompts the question should we be encouraging more of our comorbid and frail recipients to go for this approach alongside targeted prehabilitation? This could be combined with the known benefits of pre-emptive transplantation to avoid the compounded effect of dialysis in this at-risk cohort [26].

Study Limitations

The main limitation of our study is its observational nature, consequently assessments of causality cannot clearly be made. Additionally, we acknowledge that the follow up period, is limited: the study was actively recruiting for 30 days and had a further 30 days of follow up which is a relatively short time period. This was deliberately chosen to be pragmatic, as our contributors were trainees who often move centre during training. Despite this, we had well matched cohorts across 20 different centres with over 200 patients and for the majority of patients a 30 days follow up period is more than adequate to capture outcomes of interest in the early postoperative period that were of interest in this scenario e.g., length of stay, readmission and complications. The study was designed as a prospective service evaluation study which allowed for multiple centres to be involved due to the simpler registration and approval processes. Again, this was a pragmatic decision, as the real world costs associated with running a multicentre randomised control trial of an ERAS protocol would be prohibitive, not to mention challenging to ensure adherence. As such, this is the largest prospective study to date assessing the role of ERAS care in renal transplantation, which provides a clear snapshot of perioperative practice across the UK and potential insights for future improvements.

Conclusion

In conclusion, while intraoperative ERAS principles have been widely integrated into routine kidney transplant care, formal ERAS protocols were not associated with significant improvements in post-transplant outcomes. This study found few centres offered prehabilitation strategies. Future efforts should focus on identifying high-risk patient populations and implementing prehabilitation strategies to enhance recovery and reduce complications. Further research is needed to explore how this would impact patient outcomes specifically within transplant patients and how we can achieve the same culture change for preoperative care that we have seen in the perioperative care setting to further optimize transplant outcomes effectively.

DATA AVAILABILITY STATEMENT

Anonymized raw data supporting the conclusions of this article will be made available on reasonable request.

ETHICS STATEMENT

This study was conducted as a national service evaluation project and local audit and research governance approvals were obtained for all participating centres by the responsible principal investigators. No changes to clinical care nor patient-identifiable data were stored in the REDCap™ system, and all data were anonymized before analysis. We used the NHS HRA decision tool https://www.hra-decisiontools.org.uk/research/ which deemed this study not to need REC review.

AUTHOR CONTRIBUTIONS

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

GROUP MEMBERS OF THE CRAFT STUDY COLLABORATORS

Lauren Hackney, Damian McGrogan, Clara Tohill, Shauna McBride, Isobel Austin, Belfast City Hospital; Kayani Kayani, Dilan Dabare, Ugochukwu Okafor, Raja Rashid, Poppy Brown, Irena Radnaeva, Tariq Ghattas, Birmingham Queen Elizabeth Hospital; Ahmed Radwan, Harry VM Spiers, Catriona Walker, Paula Appleton, Cambridge Addenbrooke's Hospital; Charlie Brown, Christopher Chalklin, Laszlo Szabo, Cardiff University Hospital of Wales; Farhan Ahmad, Hamza Ahmad, Keno Mentor, Coventry University Hospital; Katie L Connor, Rachel Thomas, Karen Clark, Neil McKane, Eksha Gupta, Edinburgh Royal Infirmary; Robert Pearson, Emma Aitken, Aldo Alonso-Becerra, Glasgow Queen Elizabeth University Hospital; Jessica Weemes, Adam Barlow, Sadia Tasleem, Sunil Daga, Melissa Bautista, Amirh Azhar, Leeds St James' University Hospital; George Nita, Petra Goldsmith, Caitlin Jordan, Liverpool Royal University Hospital; Benedict Phillips, Hannah Maple, Ahmed Hussein, Yasaman Nikooiyan, Fayyad Jaradat, London – Guy's Hospital; Zoja Milovanovic, Rebecca Matthews, Mohammad Ayaz Hossain, Fiona McCaig, Baven Blanderan, James Sweatman, London – The Royal Free Hospital; Christopher Seet, Muhammad Khurram, Ben Lindsey, Ismail Mohamed, Laura Clementoni, London – The Royal London Hospital Barts; Ruth Owen, Hussein Khambalia, Malcom Greenwood-Morgan, Orus Erum, Manchester Royal Infirmary; Emily Thompson, Aimen Amer, Carrie Scuffell, Tzer En Yap, Eleanor Kissane, Laura Kenny, Batool Almoosawi, Joe Dobbins, Sam Tingle, Jenny Nur, George Kourounis, Sarah Abdelbar, Newcastle Freeman Hospital; Hatem Sadik, Mohamed Aly M. El Shafei El Zawahry, Srikanth Reddy, Thomas Whitehead, Nasir Al-Karboolee, Muhammad Sheharyar Khan, Faraaz Khan, Oxford Churchill Hospital; Balaji Mahendran, Charlotte Hitchins,

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CONFLICT OF INTEREST

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

GENERATIVE AI STATEMENT

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DARC and Anti-Duffy Antibodies in the Line of Fire: The Challenges in Pinpointing the Etiology of Microcirculation Inflammation to a Distinct Entity

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***Correspondence**
Farsad Eskandary,
farsad.eskandary@meduniwien.ac.at

†ORCID:
Farsad Eskandary
orcid.org/0000-0002-8971-6149
Günther F. Körmöczi
orcid.org/0000-0002-5490-9987
Johannes Kläger
orcid.org/0000-0001-5761-0713
Nicolas Kozakowski
orcid.org/0000-0001-9180-620X
Stephan Segerer
orcid.org/0000-0002-1936-9719
Konstantin Doberer
orcid.org/0000-0002-8036-7042
Georg A. Böhmig
orcid.org/0000-0002-7600-912X
Heinz Regele
orcid.org/0000-0003-2929-6135

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Farsad Eskandary[1]†, Günther F. Körmöczi[2†], Marlies Schönbacher[2], Gottfried Fischer[2], Ingrid Faé[2], Sabine Wenda[2], Daniela Koren[2], Rainer Oberbauer[1], Roman Reindl-Schwaighofer[1], Andreas Heinzel[1], Johannes Kläger[3†], Nicolas Kozakowski[3†], Stephan Segerer[4†], Konstantin Doberer[1†], Luis G. Hidalgo[5], Helga Schachner[3], Georg A. Böhmig[1†] and Heinz Regele[3†]*

[1]Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria, [2]Department of Blood Group Serology and Cell Therapy, Medical University of Vienna, Vienna, Austria, [3]Department of Pathology, Medical University of Vienna, Vienna, Austria, [4]Division of Nephrology, Dialysis and Transplantation, Kantonsspital Aarau, Aarau, Switzerland, [5]Histocompatibility and Immunogenetics Laboratory, University of Alabama at Birmingham, Birmingham, AL, United States

Antibody-mediated rejection (ABMR) due to non-HLA alloantibodies has gained substantial attention in transplantation research. One candidate for such non-HLA reactivity is the Duffy blood group carrier molecule DARC, which is not only expressed on erythrocytes, but also on kidney microvascular endothelial cells and is postulated as a potential transplantation-relevant alloantigen. However, *in vivo* observation of anti-Duffy antibodies as trigger of microvascular inflammation (MVI) is lacking. Here we propose a direct relationship between preformed anti-Duffy (anti-Fy^a) antibodies, complement deposition (C4d) in peritubular capillaries (PTC), and MVI. Double immunofluorescence for DARC and C4d in sequential biopsies revealed a striking overlap of DARC expression and C4d staining that was completely restricted to the peritubular capillaries. Remarkably, MVI was confined to PTC with complete absence of glomerulitis and lack of preformed anti-HLA DSA. Retrospective analysis revealed a self-limiting posttransplant flare of a low-level anti-DQ8 DSA after blood transfusions and a high missing-self KIR ligand constellation. Concomitant occurrence of non-HLA and anti-HLA reactivities next to missing-self constellations substantially complicates the assessment of individual

Abbreviations: ABMR, antibody-mediated rejection; BKPyVAN, polyomavirus-associated nephropathy; CDCXM, cytotoxicity-dependent crossmatch; DARC, Duffy antigen receptor for chemokines; DGF, delayed graft function; DSA, donor-specific antibody; FXCM, flow cytometric crossmatch; HLA, human leukocyte antigen; ISBT, international society for blood transfusion; KIR, killer cell immunoglobulin-like receptor; MVI, microvascular inflammation; MLPTC, multilayering of peritubular capillary basement membranes; MMDx™, molecular microscope diagnostic system; PTC, peritubular capillaries; RBC, red blood cell transfusion; SAB, single antigen bead; SOT, solid organ transplantation; TCMR, T cell-mediated rejection; vPRA, virtual panel-reactive antibodies.

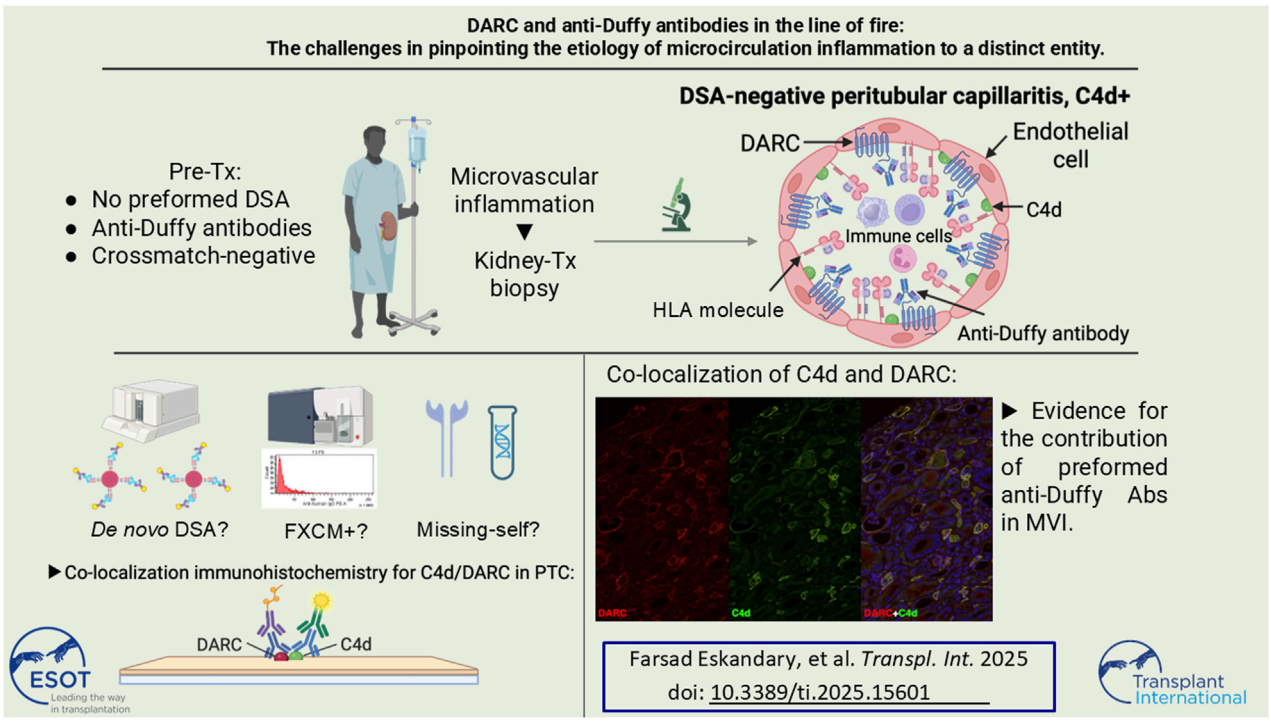
contributions for the development and propagation of MVI. Due to the strictly confined distribution of DARC to PTC our report provides *in vivo* evidence that anti-Fy^a alloantibodies may associate with MVI.

Keywords: antibody-mediated rejection (AMR), humoral rejection, DSA, donor specific antibodies, Duffy blood group

INTRODUCTION

Antibody-mediated rejection (ABMR) constitutes one of the major causes for late allograft loss after kidney transplantation [1, 2]. While the majority of ABMR cases is positive for anti-HLA donor-specific antibodies (DSA), some evidence also supports a role of non-HLA antigens as primary targets of alloantibodies [3]. Clinicians usually only search for such antibodies, when serologic evidence of anti-HLA DSA is lacking despite typical ABMR lesions in biopsies. Detection of non-HLA alloantibodies is challenging, as only a limited number of validated assays are commercially available. Furthermore, the most comprehensive Luminex-based non-HLA antibody assays failed to correlate in a substantial proportion, hindering the development of recommendations for their routine testing [4, 5]. The occurrence of ABMR lesions in anti-HLA DSA-negative patients has recently been introduced as a diagnostic category of the Banff classification termed "microvascular inflammation (MVI) DSA and C4d negative," because some studies observed its detrimental impact on graft survival [6, 7]. In this context it is of interest that particular donor/recipient HLA class I mismatches may trigger NK cells via KIR's through the 'missing-self' pathway, leading to MVI through antibody-independent mechanisms [8].

The glycoprotein "Duffy antigen receptor for chemokines" (DARC) encoded on chromosome 1 constitutes a transfusion-relevant blood group system, belongs to the family of seven-transmembrane proteins, and exhibits clinically relevant Duffy blood group antigens (Fy^a or Fy^b, depending on genotype) [9]. Its expression in the kidney vasculature is almost exclusively limited to the endothelium of peritubular capillaries (PTC) and postcapillary venules [10]. DARC was shown to be upregulated during kidney transplant rejection processes and its expression correlated with the extent of interstitial fibrosis in biopsies showing ABMR [11, 12]. Also, in gene expression profiling of kidney transplant biopsies [Molecular Microscope Diagnostic System (MMDx™) and NanoString®], DARC appeared as one of the most prominent ABMR-associated transcripts [13, 14]. Apart from a possible role in rejection, DARC has also been proposed as a transplantation-relevant antigen due to the fact that Duffy alloantibodies can form after sensitizing events [15, 16]. DARC genotype-mismatch constellations in kidney transplantation showed varying associations with respect to the occurrence of rejection, enhanced fibrosis and reduced graft survival. However, *in vivo* proof of such antibodies to directly contribute to ABMR are lacking [17–19].



GRAPHICAL ABSTRACT |

Here we present the case of a patient with preformed anti-Fy^a, who received a kidney transplant from a Fy(a+b-) donor and subsequently developed early C4d+ microvascular inflammation (MVI), at that time without the evidence of any anti-HLA DSA in serum. We retrospectively performed double immunofluorescence for C4d and DARC in biopsies to assess a potential co-localization of the antigens and their spatial relation to histologic signs of rejection. In this paper we describe the process of corroborating our findings, thorough retrospective workup of patient sera revealed the complexity of the observed MVI with respect to a causative role of anti-Fy^a antibodies.

METHODS

Biopsies

All biopsies were graded according to the 2022 update of the Banff classification. For C4d immunohistochemical and immunofluorescence staining we used a polyclonal anti-C4d antibody (BI-RC4D; Biomedica, Vienna, Austria) and for DARC immunofluorescence we used a mouse monoclonal anti-human DARC-Fy6 antibody (a generous gift from the laboratory of Prof. Yves Colin, INSERM). The detailed protocol of our DARC and C4d double-immunofluorescence is provided in the **Supplementary Appendix**.

Anti-Duffy Antibody Titration

Anti-Fy^a titration was performed using indirect antihuman globulin technique in gel matrix (MicroTyping system, Bio-Rad, Vienna, Austria).

Anti-HLA Antibody Assessment, HLA and KIR Typing

HLA antibody detection was performed at our ISO-certified HLA laboratory, using LABscreen single-antigen flow-bead assays (One Lambda, Canoga Park, CA). Details with respect to donor/recipient high-resolution HLA typing, anti-HLA reactivities, HLA eplet mismatch, KIR typing and missing-self and are provided in the **Supplementary Appendix**.

FXCM Crossmatch

A detailed technical description of the FCXM is provided in the **Supplementary Appendix**. In brief, mononuclear cells from donor spleen were extracted using LymphoprepTM density medium. After pronase digestion to deplete unspecific binding, sera were incubated with B and T lymphocytes and incubated with corresponding antibody-mixes. Controls were performed to account for unspecific binding, enzymatic digestion and equal HLA distribution on cell surfaces. Positivity threshold for FXCM results was >6000 MFI above the mean of negative control values.

RESULTS

In 2017, a 45-year-old male on peritoneal dialysis with a history of opioid abuse and hepatitis C-associated membranoproliferative glomerulonephritis (nucleic acid test-negative since 2015), received his first ABO-compatible deceased donor kidney transplant from a 51-year-old male. HLA mismatch was 0/1/1/1/1/1 (A/B/C/DR/DQ/DP), pretransplant CDCXM was negative and single antigen bead (SAB) testing revealed no preformed anti-HLA DSA (latest vPRA for HLA class I and II: 0%, highest historic vPRA: 7%). Anti-IL2 receptor antibody basiliximab was administered on days 0 (d0) and d4 (20 mg each) and maintenance immunosuppression consisted of standard triple immunosuppression with tacrolimus, mycophenolate-mofetil and steroids.

Upon transplant offer, previously identified donor-specific anti-Fy^a IgG was detectable, with an anti-Fy^a antibody titer of 64 (donor and recipient *DARC* genotypes *FY*A* and *FY*B*, respectively). Anti-Fy^a immunization was most likely due to prior RBC transfusion because of an episode of idiopathic autoimmune hemolytic anemia in 2005. We decided against any desensitization scheme, but to liberally perform transplant biopsies in case of graft dysfunction. The post-transplantation course was complicated by delayed graft function (DGF) most likely due to peri-renal hematomas that impaired global allograft perfusion, requiring two surgical revisions within the first week, and hemodialysis on day four (d4). A concomitant allograft biopsy on d4 contained very little cortical tissue, but showed severe tubular injury with tubular necrosis without signs of rejection and was C4d-negative. A second biopsy on d14 showed resolving tubular injury without TCMR, but now diffuse peritubular capillaritis (ptc2) and minimal linear C4d in PTC (C4d1), suggestive of antibody-mediated injury. Anti-HLA DSA were not detected. Meanwhile, the anti-Fy^a antibody titer had decreased to just above the detection level. Due to this early complicated course, with serum creatinine values stabilizing at around 1.5 mg/dL and absence of albuminuria/proteinuria, no anti-rejection treatment was initiated. At month three serum creatinine increased to >2 mg/dL, which prompted us to administer a steroid bolus before performing a biopsy, that still showed diffuse ptc2, but this time also a strong linear C4d-positivity in PTC (C4d2). There was still no sign of TCMR, but surprisingly we found mild diffuse interstitial fibrosis (ci3, affecting 70% of cortex) without chronic tubular damage (ct0); in electron microscopy no doubling of PTC basement membranes was found (MLPTC0). Repeated testing confirmed the absence of anti-HLA DSA, an anti-Fy^a titer decreasing below the detection limit and serum creatinine remaining at around 2 mg/dL. We decided to not further intensify immunosuppression, as our patient appeared prone to infectious complications (paralytic ileus with sepsis 4 months and pneumonia with subsequent right-sided surgical decortication for empyema 7 months post transplantation). Tacrolimus trough-level goal was set between 4 and 8 ng/mL and was mostly achieved with singular outliers in the upper and lower ranges (Median tacrolimus level day 14 until month ten after transplantation: 5.9 ng/mL, IQR: 4.3–6.4 ng/mL). Mycophenolate-mofetil was switched to azathioprine at month two because of gastrointestinal side effects. Torque-Teno-Virus PCR was assessed as a measure for global immunosuppression and was in the range of 10^4 and 10^8 copies, indicating no excessive immunosuppressive effect.

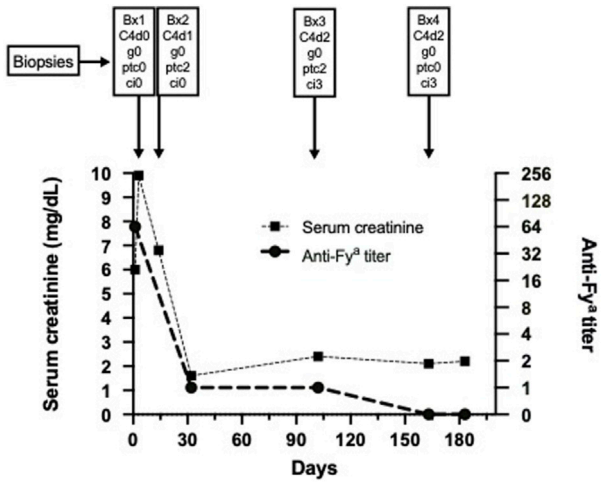


FIGURE 1 | Serum creatinine course and anti-Fy^a antibody titer over time together with corresponding biopsy results. Abbreviations: Bx, biopsy; g, glomerulitis; ptc, peritubular capillaritis; ci, chronic interstitial fibrosis; C4d, complement split product C4d.

At month five BK-viremia (max: 6.5×10^3 copies/mL) together with decoy cells in urine (max: 90% of epithelial cells) were noted and a fourth biopsy at month seven showed BKPyVAN with positive multifocal SV40-positive nuclei, surprisingly together with moderate C4d in PTC (C4d2). Mild chronic interstitial fibrosis was now even more diffuse (ci3, affecting 100% of cortex), tubulitis and interstitial inflammation (i1, t3, ti1) were present, but in the absence of clinical deterioration were interpreted as signs of resolving BKPyVAN. Immunosuppression had already been reduced and BK-viremia together with decoy cell amount resolved gradually. Graft function stabilized at a creatinine of 1.6 mg/dL without any proteinuria. Since 2019 our patient was followed up at a remote center, where lung cancer was diagnosed and he died in mid-2020 with a functioning allograft. The serum creatinine and anti-Fy^a antibody titer trajectories in the context of biopsy results are provided in **Figure 1**. Detailed biopsy findings and representative histologic images are provided in the **Supplementary Appendix**, **Supplementary Table S1** and **Supplementary Figures S1A–D**.

Due to the continuous presence of MVI in PTC without anti-HLA DSA but with endothelial C4d deposition, a causal relationship with the donor-specific anti-Fy^a antibodies was suspected and we therefore retrospectively performed double immunofluorescence for C4d and DARC in all four biopsies. In all three biopsies with linear C4d deposition, C4d was only positive in PTC, but not in glomeruli. DARC staining was only positive in PTC and absent in glomeruli. Most strikingly, and as illustrated in **Figure 2** and **Supplementary Figure S2**, C4d and DARC showed a high degree of co-localization and similar staining intensity. This finding was considered highly suggestive of anti-DARC antibody-mediated C4d deposition in PTC.

In order to corroborate our suspicion of ABMR mediated through anti-DARC antibodies, we performed detailed retrospective analysis of sera and NK cell genetics to rule out other contributors for MVI. As depicted in **Figure 3** and shown in **Supplementary Tables S2, S3** we were able to identify a transient and short-lived low-level anti-DQ8 DSA (MFI 1,300) around month three. Next, we retrospectively performed serial B and T FXCM using frozen cells from the kidney donor in order to pinpoint SAB results to biological relevance. We found that the transient DQ8 reactivity also coincided with a positive B cell FXCM (**Supplementary Figures S3A–G**), all other FXCM remained negative. Clinical workup showed that the occurrence of anti-DQ reactivities was closely related to the administration of RBC's (**Figure 3**) and disappeared spontaneously without any treatment. A thorough description and interpretation of our SAB findings can be found in the **Supplementary Appendix**.

The option of MVI potentially being triggered by missing self, prompted us to perform donor/recipient KIR typing that revealed a high missing-self constellation for two established ligands (A11/KIR3DL2 and C2/KIR2DL1, **Supplementary Table S4**).

In follow-up biopsies MVI and C4d remained constantly high and interstitial fibrosis progressed without overt functional graft deterioration, again with no sign of glomerulitis or chronic glomerular lesions.

DISCUSSION

This is the first description of a potential *in vivo* relationship between the non-HLA antigen DARC, preformed anti-Duffy antibodies and histologic ABMR features in a kidney transplant. Immunofluorescent double-labelling revealing co-localization of DARC and C4d further supported anti-Duffy antibodies as potential cause of ABMR.

The combination of a recipient with preformed anti-Fy^a antibodies receiving an Fy^a-positive donor kidney in the absence of anti-HLA alloreactivity is a rare event. We found only one report of a patient with preformed anti-Duffy antibodies who developed CDCXM-negative mixed rejection with crescentic GN, rendering the interpretation of Duffy-specific ABMR without SAB testing almost impossible as also upregulation of DARC during crescentic GN has already been demonstrated [20, 21].

Our findings are consistent with DARC acting as a non-HLA antigen potentially leading to clinically relevant rejection in kidney allografts. Our observation that interstitial fibrosis increased rapidly over time does confirm our previous findings showing that DARC expression on the transcriptome level, but also in IHC correlated well with fibrosis [11]. However, this study included patients with late ABMR, where DARC expression was investigated as a surrogate marker for ABMR and not as primary alloantibody target. DARC expression may lead to increases in cytokine levels within capillaries and thereby attract immune cells contributing to inflammation and potentially enhance subsequent fibrosis [22, 23]. One may argue that in this specific situation, preventive measures such as plasmapheresis or immunoadsorption could have been applied to prevent rejection due to anti-Fy^a antibodies, whereas declining

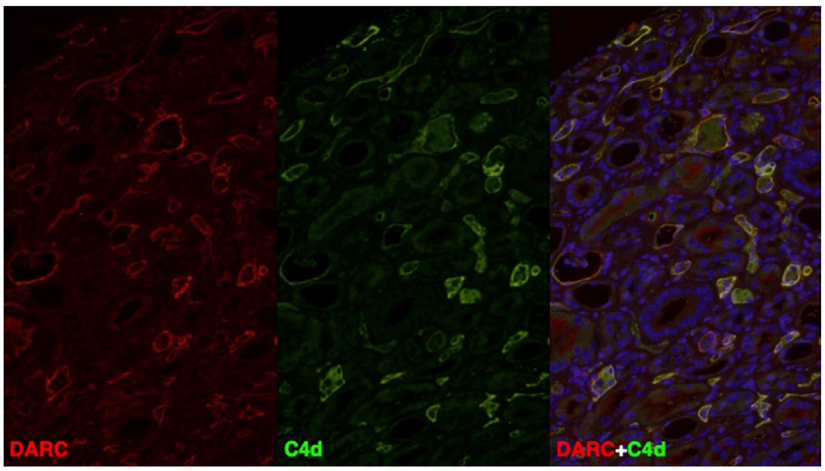


FIGURE 2 | DARC (red) and C4d (green) and DAPI (blue) immunofluorescence staining in a representative biopsy specimen (Bx No. 3) fulfilling the Banff 2022 criteria for antibody-mediated rejection. On the right, double immunofluorescence is shown, where all areas with co-localization staining of DARC and C4d show high overlap (yellow = double positive) with respect to the positive area in PTC. Abbreviations: C4d, complement split product C4d; DARC, Duffy antigen-receptor of chemokines.

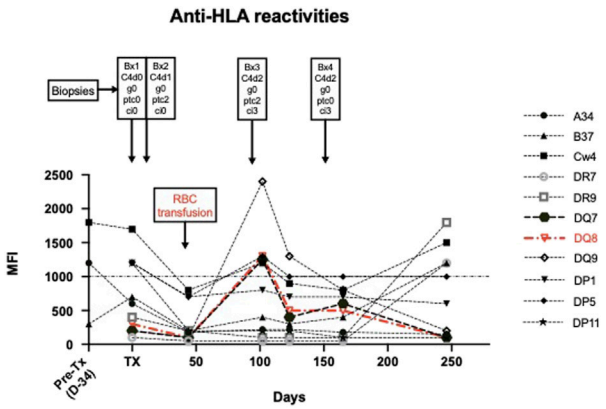


FIGURE 3 | Illustrates anti-HLA reactivities over time in the context of biopsy results and the administration of RBC transfusions. Donor-specific antibody reactivities are shown in Red. A detailed discussion on the interpretation of SAB findings can be found in the **Supplementary Appendix**.

this organ in order to wait for a Fy^a-negative donor (approximately 32% of Caucasians) would not have been an ideal option [24]. With respect to the literature we found no strong recommendation regarding desensitization, but our report indicates that it may be warranted in such a case [15].

The co-localization of DARC and C4d within PTC suggests that DARC might be a relevant non-HLA antigen, with anti-Fy^a antibodies being capable of mediating ABMR. However, a caveat to our hypothesis is the fact that patients with anti-Fy^a antibodies, generally sensitized by blood transfusions, have a chance to also be sensitized against HLA. In our case in-depth analysis indeed revealed a low-level anti-DQ8 DSA after administration of RBC transfusions early posttransplant, which was confirmed by corresponding B cell FXCM reactivity. However, subsequently all anti-DQ reactivities faded without treatment, which is not supporting the occurrence of a memory response or *de novo* DSA formation. The appearance of transfusion-specific anti-HLA class II antibodies that also may act as DSA has been demonstrated earlier, but it has not been documented whether these reactions cause long-term or only short-term memory as it happened in our case [25]. In addition, this also did not lead to clinical deterioration, new onset of proteinuria or aggravation of MVI, even though we retrospectively demonstrated a high degree of "missing-self" constellation. It is interesting that despite having two degrees of missing-self, this failed to manifest glomerular MVI, making DARC expression the primary reason for MVI in PTC. A possible explanation for a milder course of ABMR due to anti-Duffy antibodies might be the fact, that DARC is - if at all - only very weakly expressed in glomeruli, which would explain the lack of proteinuria despite early renal deterioration in our patient [12]. This is also supported by the absence of glomerulitis, and C4d deposition being exclusively restricted to the PTC compartment.

This report illustrates the challenges associated with establishing the diagnosis of non-HLA-mediated ABMR on the basis of an actual clinical case. Despite having made use of our full current diagnostic armamentarium - with the exception of a lack of molecular biopsy diagnostics due to insufficient remaining material - and in order to perform a deep dive into the different potential immunologic processes that might have contributed to MVI in our patient, it seems almost impossible to provide definite evidence for a causal relationship between a non-HLA DSA and MVI in our representative case. Of note, the different potential triggers of MVI are not mutually exclusive, and other conditioning factors such as DGF and ischemia might also have played a role in this specific scenario.

Nevertheless, our findings strengthen a potential association of preformed anti-Fy^a antibodies with MVI, but our report also

highlights the caution that is warranted to exclude the remaining causes of MVI, rendering it a highly complex task to prove causality [26].

DATA AVAILABILITY STATEMENT

Original datasets are available upon request to the corresponding author.

ETHICS STATEMENT

Ethical approval was not required for the studies involving humans because Patient has deceased before project. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by-product of routine care or industry. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article because Patient has deceased before research project was started.

AUTHOR CONTRIBUTIONS

FE, GK, and HR designed the study and wrote the manuscript draft. MS, HS, and DK carried out experiments. GF, IF, and SW helped with interpretation of the data and experiments. RO, RR-S, AH, JK, NK, SS, KD, LH, and GB worked on the manuscript draft and helped with interpretation of the results. 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.2025.15601/full#supplementary-material

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LETTER TO THE EDITOR
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Stabilization of Kidney Graft Function Following SGLT2 Inhibitor Treatment in Non-Diabetic Kidney Transplant Recipients

Diana Rodríguez-Espinosa, Ricardo Parra, Blerina Mataj, Jonay García, Elena Cuadrado-Payán, Vicens Torregrosa, Nuria Esforzado, Ignacio Revuelta, Pedro Ventura-Aguiar, David Cucchiari, Enrique Montagud-Marrahí, Alicia Molina-Andújar, Carolt Arana, Ángela González, José Jesús Broseta and Fritz Diekmann*

Department of Nephrology and Renal Transplantation, Hospital Clínic of Barcelona, Barcelona, Spain

Keywords: chronic allograft dysfunction, chronic kidney disease (CKD), kidney allograft, nephroprotection, SGLT2 inhibitors

Dear Editors,

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have demonstrated nephroprotective effects in patients with chronic kidney disease (CKD) regardless of diabetes. However, their efficacy and safety in non-diabetic kidney transplant recipients (KTR) is limited [1, 2].

This was a single-center, retrospective study of adult KTR patients prescribed an SGLT2i between January 2021 (when the drug was first approved for its use in our health area) and September 2024, followed through September 2025, to analyze the annual decline rate in estimated glomerular filtration rate (eGFR) before and after SGLT2i initiation. Only patients with a transplant vintage of at least 12 months before SGLT2i initiation were included. Those who discontinued treatment or experienced an episode of rejection or recurrent glomerulonephritis within the preceding 12 months were excluded to focus on clinically stable recipients not recovering from acute events or under the influence of prophylactic trimethoprim–sulfamethoxazole, which can transiently affect serum creatinine levels. This study was conducted in accordance with the principles of the Declaration of Istanbul on Organ Trafficking and Transplant Tourism and the ethical guidelines of the host institution.

The primary endpoint was the within-patient difference in the 12-month eGFR slope [3] before and after receiving an SGLT2i, expressed in mL/min/1.73 m^2 and calculated with the CKD-EPI formula [4]. The secondary endpoint was the change in the urinary albumin-to-creatinine ratio (UACR), if available over the same period and ≥30 mg/g at baseline, expressed as mg/g. eGFR slopes were calculated for each patient and compared using the Wilcoxon signed-rank test. A linear mixed model for repeated measures was used to analyze changes in eGFR over time. A general linear model was used to adjust the post-SGLT2i eGFR slope for covariates.

Regarding UACR reduction, the association between time (pre-vs. post-SGLT2i) and the probability of response was evaluated using a generalized estimating equation model with a binomial distribution, accounting for repeated measures within subjects. Odds ratios (OR) with 95% confidence intervals (CI) were estimated. A two-tailed p-value < 0.05 was considered statistically significant. Analyses were performed using SPSS Statistics (version 25.0, IBM Corp, Armonk, NY, United States).

A total of 82 non-diabetic KTR were prescribed an SGLT2i during the mentioned period. Fifteen patients were excluded due to treatment discontinuation, two had a biopsy proven graft rejection and three a glomerular disease recurrence within 12 months of treatment initiation, and four lacked sufficient paired data. The reasons for discontinuation included: death (2), graft loss (5), renal

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***Correspondence**
José Jesús Broseta,
jjbroseta@clinic.cat

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TABLE 1 | Baseline and clinical characteristics of the study population.

Variable	Study population
	n = 58
Recipient age, median (IQR)	50.5 (39.3–61)
Donor age, median (IQR)	53 (43–59)
Recipient male sex, n (%)	34 (58.6)
Recipient BMI, Kg/m^2, median (IQR)	26.1 (21.6–29.9)
Donor BMI, Kg/m^2, median (IQR)	25.8 (23.5–28.6)
Immunosuppression, n (%)	
MPA, n (%)	36 (62.1)
mTORi, n (%)	21 (36.2)
CNI, n (%)	48 (82.8)
Belatacept, n (%)	6 (10.3)
RAASi, n (%)	33 (56.9)
ACEi, n (%)	9 (15.5)
ARB, n (%)	24 (41.4)
Transplant number	
First, n (%)	45 (90.4)
Second, n (%)	7 (9.8)
Third, n (%)	4 (5.9)
Fourth, n (%)	2 (3.9)
Type of donor	
Living donor, n (%)	25 (43.1)
Deceased, n (%)	33 (56.9)
DBD, n (%)	24 (41.4)
DCD, n (%)	9 (13.8)
Baseline eGFR, mL/min/1.73m^2, median (IQR)	43 (34–52)
Baseline UACR, mg/g, median (IQR)	145 (10–567)
GN recurrence	0
BPAR	17 (29.3)
TCMR, n (%)	12 (70.5)
AMR, n (%)	2 (11.8)
caAMR, n (%)	3 (17.6)

AMR, antibody-mediated rejection; BMI, body mass index; BPAR, biopsy-proven allograft rejection; CI: confidence interval; caAMR, chronic-active AMR; CNI, calcineurin inhibitor; DBD, dead brain donor; DCD, donor after circulatory death; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; RAASi, renin-angiotensin-aldosterone inhibitors; TCMR, T-cell mediated rejection. Patients with biopsy-proven rejection or glomerulonephritis recurrence within the 12 months prior to SGLT2i initiation were excluded from the study.

function decline (1), diarrhea (1), erythrocytosis (1), dyspnea (1), intolerance (2), non-adherence (1), and other/unknown reasons (1). Baseline demographic and clinical characteristics of the 58 included patients are detailed in **Table 1**.

In the repeated-measures analysis of eGFR, there was a significant overall effect of time (F = 6.3, p = 0.003). Pairwise comparisons adjusted for immunosuppressive treatment and the use of renin-angiotensin-aldosterone inhibitors (RAASi) showed a progressive decline in kidney function during the pre-SGLT2i period (p = 0.002), while there was no statistical difference between baseline eGFR and 12 months after starting the medication (p = 1). The median annual eGFR slope in the pre-SGLT2i period was - 3.–-7 – 0) mL/min/1.73 m^2, while in the post-SGLT2i period it was −1 (−5.5–4) mL/min/1.73 m^2 (p = 0.003). In the adjusted general linear model, there was no correlation between slope and RAASi, age, transplant vintage, rejection, or immunosuppressive regimen.

In the repeated-measures analysis of the 30 patients with baseline UACR ≥30 mg/g, there was no significant overall difference between periods (F = 2.4, p = 0.067). However, the odds of achieving a ≥30% reduction in UACR increased after initiation of an SGLT2i. In the 12 months preceding treatment, 14% of patients (3/21) achieved a ≥30% UACR reduction, compared with 47% (14/30) at 12 months post-initiation, corresponding to an OR of 5.3 (95% CI 1.2–23.3; p = 0.027).

Regarding adverse events, four patients developed genitourinary fungal infections, with two events occurring before and two after SGLT2i initiation. In addition, five patients experienced a UTI, four before and one after the start of SGLT2i therapy.

Our findings contribute to the expanding, albeit still limited, body of evidence regarding the use of SGLT2i in KTR. Most previous studies have concentrated on diabetic KTR [5, 6] In contrast, pivotal trials involving non-transplant CKD populations [1, 2] have shown that SGLT2i consistently slow the decline in kidney function across both diabetic and non-diabetic patients.

Our cohort demonstrates that kidney function stabilized after initiation of SGLT2i, suggesting that SGLT2i potential nephroprotective effects may extend beyond diabetes. It is important to note that there is currently no universally accepted benchmark for eGFR slope in KTR, with published estimates varying widely from less than 1 to over 7 mL/min/1.73 m^2 per year, depending on the timing and selection of patients [7, 8]. Thus, the observed results should be interpreted with caution. However, the difference between pre- and post-treatment annual eGFR slopes exceeded 0.75 mL/min/1.73 m^2, a magnitude regarded as clinically meaningful in terms of lowering the risk of CKD progression [3].

Proteinuria reduction represents a key mechanism behind the nephroprotective effects of SGLT2i. Lim et al. reported greater reductions in proteinuria among KTR who experienced an early decline in kidney function after starting SGLT2i [6]. In contrast, we observed no significant overall change in UACR; however, their cohort consisted of diabetic patients, who may have had higher baseline proteinuria than ours (they did not report baseline UPCR values). Notably, patients in our study were more likely to achieve a ≥30% reduction from baseline UACR, which represents the surrogate endpoint recommended by both the American Diabetes Association and the KDIGO guidelines [9, 10].

This study has limitations. It is a retrospective, single-center analysis with a small sample size, which limits generalizability. The exclusion of patients with recent rejection or early discontinuation may have introduced selection bias, though it allowed evaluation of a clinically stable cohort. The absence of a control group and heterogeneous transplant vintage also restrict causal inference, and treatment indication was not standardized, introducing potential confounding despite the within-patient design mitigating interindividual variability. Data on the early eGFR dip were unavailable due to follow-up intervals, and UACR data were incomplete, with heterogeneous assessments. The 12-month follow-up captures only short-term outcomes, and tacrolimus levels were not collected, although prior studies suggest no relevant pharmacologic interaction.

No safety concerns were observed, and the absence of discontinuations due to UTI is reassuring.

In summary, SGLT2i may attenuate eGFR decline in non-diabetic KTR, warranting confirmation in larger prospective studies.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Data can be provided upon reasonable request to the first author. Requests to access these datasets should be directed to DR-E, dmrodriguez@clinic.cat.

ETHICS STATEMENT

The studies involving humans were approved by HCB/2024/0626 Comité de Ética de la Investigación con Medicamentos. H. Clínic Barcelona. 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

Conceptualization, DR-E and JB; methodology, JB; validation, EC-P and CA; formal analysis, DR-E; investigation, RP, JG, BM, VT, and ÁG; resources, PV-A, DC, EM-M, NE, and IR; data curation, AM-A; original draft preparation, DR-E and JB; review and editing JB and FD; supervision, FD and JB. All authors contributed to the article and approved the submitted version.

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LETTER TO THE EDITOR
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Pharmacokinetics of Piperacillin in an Experimental Porcine Liver Model During Normothermic Machine Perfusion

Simon Mathis[1], Gabriel Putzer[1], Judith Martini[1], Thomas Resch[2], Christina Bogensperger[2], Michael Dullnig[1], Jonas Dunz[1], Fariha Nawabi[1], Nikolai Staier[1], Magdalena Bordt[2], Theresa Hautz[2], Julia Hofmann[2], Stefan Schneeberger[2] and Christoph Dorn[3]*

[1]Department of Anaesthesiology and Critical Care Medicine, Medical University of Innsbruck, Innsbruck, Austria, [2]Department of Visceral, Transplant and Thoracic Surgery, OrganLife™ Organ Regeneration Center of Excellence, Medical University of Innsbruck, Innsbruck, Austria, [3]Institute of Pharmacy, University of Regensburg, Regensburg, Germany

Keywords: normothermic machine perfusion, piperacillin, microdialysis, liver transplant, pharmacokinetic analysis

Dear Editors,

Normothermic machine perfusion (NMP) has become a routine technique in liver transplantation, allowing preservation and assessment of grafts prior to implantation [1]. Current commercially approved systems are limited to 24 h, prompting interest in prolonged perfusion to further improve graft conditioning. During extended NMP, microbial contamination is a potential risk, as warm, humid conditions promote bacterial growth [2]. To mitigate this, antimicrobials are commonly added to the perfusate, although the pharmacokinetics under NMP conditions - characterized by a small volume of distribution and absence of renal clearance - remain insufficiently understood.

Piperacillin, a broad-spectrum β-lactam, has been used experimentally for extended NMP [3]. The present study characterizes its pharmacokinetics during liver NMP, including perfusate levels, tissue concentrations via microdialysis, and bile excretion.

In this study, the livers of eight domestic pigs were used and perfused with 1,500 mL leukocyte-depleted whole blood from the donor animal. A microdialysis double lumen catheter with a semi-permeable membrane at the tip was inserted into the liver tissue. Prior to piperacillin administration, the relative recovery of each microdialysis probe was determined by retrodialysis using Ringer's solution (Fresenius Kabi Austria GmbH, Graz, Austria) containing 80 μg mL^{-1} piperacillin. The piperacillin concentrations in the retroperfusate (C_{RP}) and the corresponding retrodialysate (C_{RD}) were used to calculate the relative recovery using the formula: relative recovery = [1 - (C_{RD}/C_{RP})] × 100%.

After calibration, 400 mg piperacillin was added into the reservoir of the NMP system.

The catheter was perfused with Ringer's solution at a flow rate of 1 μL min^{-1} to facilitate the exchange of piperacillin between the liver interstitial space fluid (ISF) and the microdialysis perfusate across the membrane. The piperacillin concentration measured in the resulting microdialysate (C_{MD}), corrected for the relative recovery of the probe, was used to estimate the piperacillin concentration in the ISF (C_{ISF} = C_{MD} × 100%/relative recovery). Microdialysate samples were collected at 20-minute intervals for 2 h and at 60-minute intervals for up to 8 h after piperacillin administration. NMP perfusate samples were collected 5 min, 15, 30, 60 min and 3, 4, 6 and 24 h after piperacillin administration. Bile samples were analyzed 4 and 8 h after piperacillin administration (in four grafts due to technical limitations). The concentrations of piperacillin were determined by HPLC-UV.

Stable perfusion and organ function was achieved over the entire study period. The piperacillin concentration in perfusate samples and ISF of liver tissue during NMP are shown in **Figure 1**. After piperacillin application (t = 0 min), the first samples of NMP perfusate, taken at 5 min (n = 5) or

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***Correspondence**
Gabriel Putzer,
gabriel.putzer@i-med.ac.at

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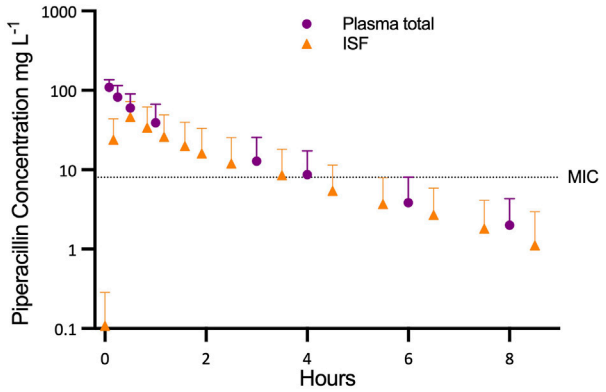

FIGURE 1 | Progression of piperacillin concentration in plasma and interstitial fluid (ISF) in relation to the minimum inhibitory concentration (MIC).

15 min (n = 3) showed the highest measured concentrations of total piperacillin: 109.9 ± 25.1 mg L^{-1} at 5 min (n = 5) or 78.7 ± 29.9 mg L^{-1} at 15 min (n = 3; corresponding to 108.5 ± 36.7 mg L^{-1} at 5 min).

The mean area under the curve (AUC(0.8)) for total piperacillin in NMP perfusate was 135 ± 92.91 mg L^{-1} h, $AUC_{INFINITY}$ was 144 ± 103 mg L^{-1} h, the elimination half-life time was 1.43 ± 0.42 h. The mean volume of distribution was 8.22 ± 4.83 L and the mean clearance of piperacillin was 4.54 ± 3.25 L $h^{-1.}$

The unbound fraction (fu) of piperacillin in NMP perfusate was 93.8% ± 1.31%. Mean *f*AUC(0.8) and *f*$AUC_{INFINITY}$ was 128 ± 86.6 mg L^{-1} h and 136 ± 95.9 mg L^{-1} h, respectively.

Relative recovery of the microdialysis probes was high (95.4% ± 4.67%) and ranged from 83.0% to 100%. Peak concentrations (C_{max}) in ISF were reached at 10 min (n = 1), 30 min (n = 5) or after 50 min (n = 2). Mean C_{max} in ISF amounted to 48.6 ± 26.4 mg L^{-1}. Mean elimination half-life (1.50 ± 0.36 h) was similar to that of the NMP perfusate.

Mean AUC(0.8) and $AUC_{INFINITY}$ for piperacillin in ISF (87.18 ± 76.18 and 90.8 ± 81.3 mg L^{-1} h) were lower than in NMP perfusate (p = 0.016). The penetration ratio, defined as the ratio of the $AUC_{INFINITY}$ for piperacillin in ISF to $AUC_{INFINFINITY}$ for free piperacillin in NMP perfusate ($AUC_{INFINITY\_ISF}$/*f*$AUC_{INFINITY\_perfusate}$), was 0.653 ± 0.300.

The grafts produced 118.25 (±44.74) mL of bile during the first 8 h of perfusion with a mean piperacillin concentration of 1.48 ± 1.11 g L^{-1}, corresponding to 168.15 ± 68.4 mg of piperacillin excreted in bile per graft.

Piperacillin rapidly achieved high concentrations in graft tissue during NMP, followed by swift elimination. Perfusate levels consistently exceeded tissue concentrations, with elimination predominantly occurring via bile in the absence of renal excretion. The reduced volume of distribution inherent to isolated liver perfusion, combined with rapid recirculation of a small perfusate volume, explains both the fast tissue penetration and rapid clearance.

Although piperacillin elimination *in vivo* is largely renal, biliary excretion represents a known alternative route, particularly in renal insufficiency [4]. This pathway likely accounts for the significant biliary concentrations observed in this study despite absent renal clearance.

Protein binding in NMP perfusate was markedly lower than in human plasma (20%–30%), attributed to the leukocyte-depleted whole blood used here [5]. In clinical NMP with red cell concentrates and colloids [6], protein binding would be negligible.

Using the EUCAST minimum inhibitory concentration breakpoint for piperacillin/tazobactam-sensitive strains (8 mg L^{-1}), graft tissue levels were below this threshold within 4 hours of receiving a 400 mg bolus dose [7]. This suggests that a single-dose strategy provides only transient antimicrobial protection during NMP. Continuous infusion could maintain therapeutic levels, but dosing must account for the high inter-graft variability observed (coefficient of variation 72%).

These findings underscore that drug pharmacokinetics during NMP differ markedly from *in vivo* conditions, necessitating dedicated dosing studies for medications administered in this setting. Limitations include the use of an animal model [8], perfusate composition differing from clinical practice (although protein binding was low even with whole blood), and the lack of metabolite measurements.

In summary, piperacillin during NMP demonstrates rapid hepatic penetration and biliary elimination, with therapeutic levels declining within 4 hours. For prolonged or long-term NMP, continuous dosing strategies may be required to ensure sustained antimicrobial protection.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The animal study was approved by Institutional Animal Care and Use Committee of the Medical University of Innsbruck and the Austrian Ministry of Science, Research and Economy (Nr.: 2022-0.386.456). The study was conducted in accordance with the local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

SM participated in research design, performance of research, writing of the paper and data analysis. GP participated in research design, writing of the paper and data analysis. JM participated in research design, writing of the paper and data analysis. TR participated in performance of research and writing of the paper. CB participated in performance of research. MD participated in performance of research. JD participated in performance of research. FN participated in performance of research. NS participated in performance of research. MB participated in performance of research. TH participated in writing of the paper. JH participated in writing of the paper. SS participated in writing of the paper. CD participated in

research design, performance of research, writing of the paper and data analysis. 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.2025.15348/full#supplementary-material

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LETTER TO THE EDITOR
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Due to Increased Immune Therapies, Are Sensitized Heart Transplant Recipients at Increased Risk for Malignancies?

*Masaki Tsuji[1,2], Michelle M. Kittleson[1], David H. Chang[1], Evan P. Kransdorf[1], Andriana P. Nikolova[1], Lily K. Stern[1], Mason Lee[1] and Jon A. Kobashigawa[1]**

[1]Department of Cardiology, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA, United States, [2]Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Keywords: cancer after transplant, desensitization, heart transplant, malignancy, sensitized

Dear Editors,

Sensitization leads to the formation of antibodies to human leukocyte antigens (HLA) [1]. Among sensitized heart transplant (HT) candidates, the waiting time for HT is longer along with the risk of adverse events [2]. Moreover, the presence of HLA antibodies reduces rate of survival and increases the risk of rejection and cardiac allograft vasculopathy [3].

These rejection episodes require increased immunosuppression, which in turn raises concerns about adverse effects such as malignancies. Moreover, desensitization, including intravenous immunoglobulin (IVIG), plasmapheresis, and several anti-humoral agents, is performed for highly sensitized patients for an increase in the chances of a negative crossmatch, expansion of the donor pool, and improvement of post-HT outcomes.

However, the relationship between sensitization and post-transplant malignancies (PTM) has not been well understood. Therefore, we investigated the incidence of PTM and the impact of desensitization for PTM in sensitized HT recipients.

This study design is illustrated in **Supplementary Figure S1**. We reviewed the records of adult patients who underwent HT between 2010 and 2023 and excluded those with a history of malignancies and missing data. Sensitization was defined as a panel-reactive antibody (PRA) level (either class I or II) of ≥10%. Highly sensitized patients were considered for desensitization therapy. Desensitization included Rituximab, Eculizumab, Bortezomib, Tocilizumab and Obinutuzumab treatment. Our institutional protocol for post-transplant management has been previously described [4, 5].

The primary endpoint of this study was the incidence of PTM diagnosed based on histological evidence. The secondary end point was all-cause mortality. The study participants were followed up until 31 August 2024. Event-free survival analyses were performed using the Kaplan–Meier method and compared using the log-rank test. A Cox proportional hazard model was constructed, adjusting for sensitization status, age, and sex. Nearest-neighbor propensity matching was performed to generate matched cohort. The propensity score model was developed using the following covariates: recipient age, sex, and history of HT. The study protocol was approved by the Institutional Review Board of Cedars-Sinai. Written informed consent was obtained from all patients.

Among the 1,096 patients who underwent HT, 364 were sensitized and 110 were desensitized. The overall mean age was 55.1 ± 12.9 years, and 801 (73.1%) patients were male. The mean follow-up period was 6.4 ± 3.8 years.

Abbreviations: PRA, panel-reactive antibody; HLA, human leukocyte antigens; HT, heart transplant; IVIG, intravenous immune globulin; PTM, post-transplant malignancies.

***Correspondence**
Jon A. Kobashigawa,
jon.kobashigawa@cshs.org

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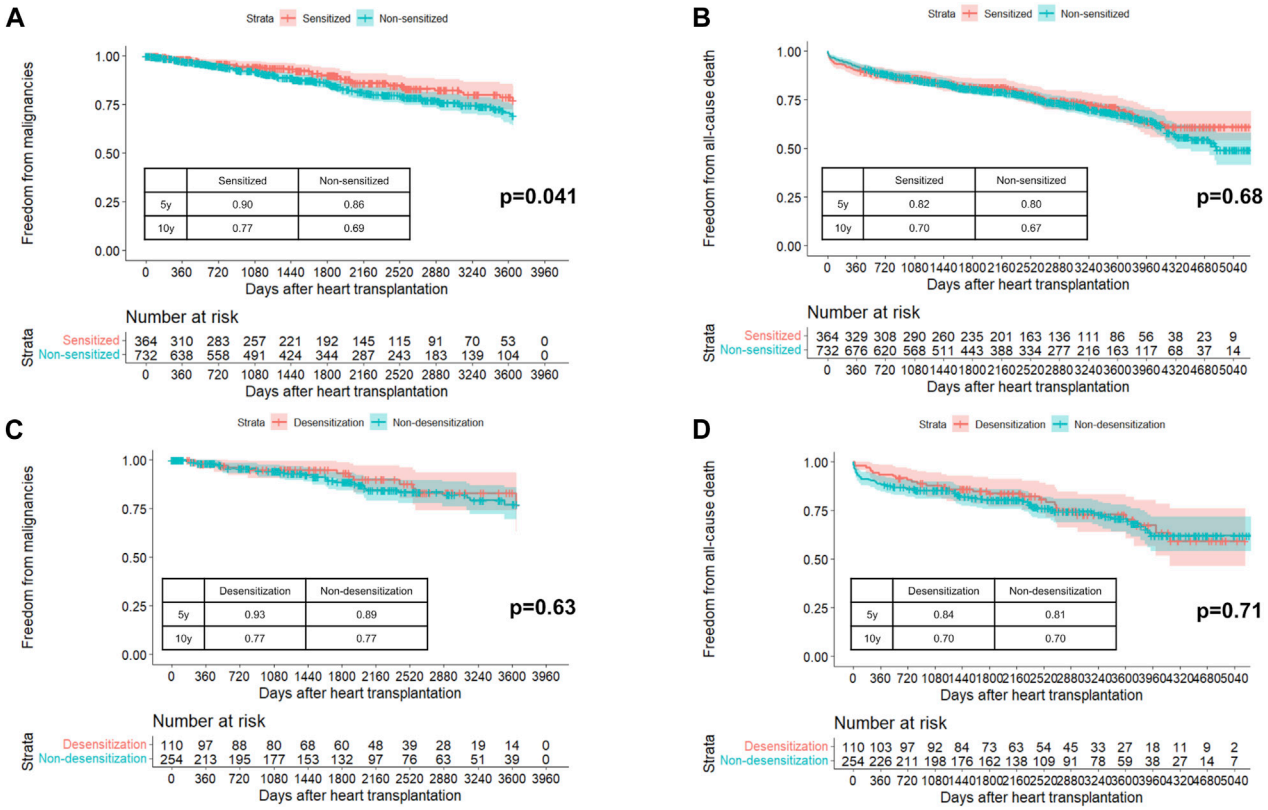

FIGURE 1 | Probability of freedom from post-transplant malignancies **(A)** and all-cause death **(B)** in sensitized and non-sensitized groups. Probability of freedom from post-transplant malignancies **(C)** and all-cause death **(D)** in desensitization and non-desensitization groups in unmatched cohort.

The baseline patient characteristics of the sensitized and non-sensitized groups are presented in **Supplementary Table S1**. The sensitized group was significantly younger, with a higher proportion of female, history of pregnancy, history of blood transfusion, history of HT, and sex mismatch than the non-sensitized group. The mean follow-up period was 6.5 ± 3.9 years in the sensitized group and 6.4 ± 3.8 years in the non-sensitized group (p = 0.68). During the follow-up period, 183 (16.7%) patients developed PTM, with skin cancer being the most common, followed by genitourinary/gynecologic/renal cancers (**Supplementary Table S2**). **Figure 1A** shows the difference in freedom from PTM, which was significant between the sensitized and non-sensitized groups (p = 0.041). The 10-year freedom from PTM was 77% in the sensitized group and 69% in the non-sensitized group. However, the all-cause mortality was similar between the two groups (p = 0.68, **Figure 1B**). In the multivariable Cox analysis, sensitized status was not associated with PTM (**Supplementary Table S3**).

The baseline patient characteristics of the desensitization and non-desensitization groups are presented in **Supplementary Table S4**. Before propensity score matching, the desensitization group was younger, had a higher proportion of females, and had a higher body mass index. The peak PRA value was significantly higher in the desensitization group than in the non-desensitization group. The most common agent for desensitization was rituximab (56.4%) followed by eculizumab (38.2%). The mean follow-up period was 6.9 ± 3.7 years in the desensitization group and 6.4 ± 3.9 years in the non-desensitization group (p = 0.31). In the unmatched cohort, freedom from PTM (**Figure 1C**) and all-cause mortality (**Figure 1D**) were similar between the two groups (p = 0.63 and p = 0.71). After propensity matching with one-to-one pairs, 108 patients in the desensitization group had a higher proportion of multi-organ transplants, whereas age, sex, and body mass index were similar (**Supplementary Table S4**). In the matched cohort, PTM incidence (**Supplementary Figure S2A**) and all-cause death (**Supplementary Figure S2B**) were comparable between the two groups (p = 0.43 and p = 0.58, respectively).

In this study, we identified the following: (1) Sensitized patients were younger, more often female, and had a history of pregnancy, blood transfusion, or HT. (2) The incidence of PTM in sensitized patients was lower than that in non-sensitized patients. (3) Desensitization did not lead to the development of PTM in sensitized patients.

Risk factors for sensitization include prior pregnancy, blood transfusions, infections, presence of homografts/allografts, and use of temporary or durable mechanical circulatory support [3]. Data from the United Network of Organ Sharing dataset for

bridge-to-transplant patients show that sensitized patients tend to be younger and female [6]. Conversely, the risk factors for PTM, as identified in several large cohort analyses, include older age at HT, male sex, infection with oncogenic viruses, re-transplantation, and malignancies prior to HT. The risks of sensitization and PTM are inversely related to age and sex. The lower incidence of PTM in sensitized patients in our study might be explained by their younger age and higher proportion of females.

The safety of desensitization agents in terms of PTM risk is not well established, and reports on the association between desensitization and PTM in solid-organ transplants are limited. Bachelet, et al. found no difference in the incidence of PTM between sensitized kidney transplant recipients treated with Rituximab and those who were not [7]. On the contrary, a report from Taiwan showed that patients who underwent desensitization with Rituximab, plasmapheresis and IVIG in kidney transplant had a higher incidence of PTM, particularly urothelial carcinoma [8]. There are no reports on other desensitization agents beside Rituximab nor are there studies in HT population. To the best of our knowledge, our study is the first to evaluate desensitization and PTM in the field of HT and suggests no significant difference in PTM incidence between groups after adjusting for baseline characteristics.

This study has some limitations. First, this was a retrospective, single-center study with a small cohort. Second, IVIG and plasmapheresis were not defined as desensitization. The general categories of desensitization therapy include mechanical removal of antibodies, IVIG, and immunosuppressive agents targeting antibody production; however, this study focused on immunosuppressive agents targeting antibody production. Third, the targets of the humoral immune pathway for each agent used for desensitization were different, and further investigation of the PTM risk associated with each agent is necessary. Fourth, malignancy-related data, including stage and severity, were missing. Finally, oncogenic viral infections were not identified; therefore, their involvement remained unclear.

In conclusion, our findings suggest that neither sensitization nor desensitization therapies were associated with an increased incidence of PTM in this cohort; however, these results should be interpreted cautiously given the potential for residual confounding and the limitations of the retrospective design.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by Institutional Review Board of Cedars-Sinai. 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

Design of the work: MT and JK. Conduct of the work and data acquisition: MT, MK, DC, EK, AN, LS, ML, and JK. Data analysis and interpretation: MT, MK, DC, EK, AN, LS, ML, and JK. Drafting the work: MT. Reviewing the work and providing input: all authors. Final approval: all authors. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2026.15593/full#supplementary-material

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Editorial Office

Avenue du Tribunal Fédéral 34
CH – 1005 Lausanne
Switzerland

Tel +41 (0)21 510 17 40
Fax +41 (0)21 510 17 01

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