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TRANSPLANT TRIAL WATCH
published: 31 May 2024
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Transplant Trial Watch

John M. O'Callaghan[1,2]* *and Keno Mentor*[2]*

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Keywords: randomised controlled trial, liver transplantation, hepatorenal syndrome, solid organ transplantation, hospitalization costs

To keep the transplantation community informed about recently published level 1 evidence in organ transplantation ESOT and the Centre for Evidence in Transplantation have developed the Transplant Trial Watch. The Transplant Trial Watch is a monthly overview of 10 new randomised controlled trials (RCTs) and systematic reviews. This page of Transplant International offers commentaries on methodological issues and clinical implications on two articles of particular interest from the CET Transplant Trial Watch monthly selection. For all high quality evidence in solid organ transplantation, visit the Transplant Library: www.transplantlibrary.com.

RANDOMISED CONTROLLED TRIAL 1

Decreased Need for RRT in Liver Transplant Recipients After Pretransplant Treatment of Hepatorenal Syndrome-Type 1 With Terlipressin.

by Weinberg, E. M., et al. Liver Transplantation 2023 [record in progress].

Aims

This *post hoc* analysis of the CONFIRM trial aimed to examine whether terlipressin was effective in reducing the need for renal replacement therapy (RRT) and improving posttransplant outcomes in liver transplant recipients.

Interventions

Participants in the CONFIRM trial were randomised to receive either terlipressin plus albumin or placebo.

Participants

300 liver transplant recipients from the CONFIRM trial.

Outcomes

The main outcomes of interest were the incidence of hepatorenal syndrome-type 1 (HRS-1) reversal, need for RRT (pretransplant and posttransplant), and overall survival.

Follow-Up

12 months.

CET Conclusion

by Keno Mentor

Hepatorenal syndrome (HRS) resulting in renal dysfunction results in poorer outcomes following liver transplantation (LT). The efficacy of Terlipressin in reducing HRS in liver failure patients was investigated

Transplant Trial Watch

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in the CONFIRM trial, which showed significantly improved rates of HRS, but no difference in mortality at 90 days. This *post hoc* analysis of the CONFIRM trial aimed to determine the difference in renal outcomes (pre and post LT) and 1-year survival in patients who had Terlipressin versus those who did not. The analysis found significant improvements in renal outcomes and 1-year survival in the Terlipression group. However, sub-group analysis showed that patients with more severe liver and renal disease showed poorer outcomes with terlipressin use, indicating a need for careful patient selection. Further trials will be required to better define the patient sub-group that will derive the most benefit from Terlipressin therapy.

Trial Registration
ClinicalTrials.gov—NCT02770716.

Funding Source
No funding received.

RANDOMISED CONTROLLED TRIAL 2

Cytomegalovirus Related Hospitalization Costs Among Hematopoietic Stem Cell and Solid Organ Transplant Recipients Treated With Maribavir Versus Investigator-Assigned Therapy: A US-Based Study.

by Schultz, B. G., et al. Transplant Infectious Disease 2024 [record in progress].

Aims
The aim of this study was to use the data from the randomised controlled trial, SOLSTICE, to estimate the cytomegalovirus (CMV) related healthcare resource utilization (HCRU) costs of maribavir (MBV) versus investigator-assigned therapy (IAT), among hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients.

Interventions
Participants in the SOLSTICE trial were randomised to either receive IAT or MBV therapy.

Participants
352 patients that had either HSCT (40%) or SOT (60%).

Outcomes
The key outcomes were the cost of hospitalisation with IAT versus MBV therapy, and cost difference (i.e., cost savings) with MBV.

Follow-Up
N/A.

CET Conclusion
by Keno Mentor

CMV infection which is refractory to standard treatment is a challenging clinical problem, resulting in patient morbidity and increased healthcare costs, mainly due to prolonged and repeat admissions. In the SOLSTICE trail, Maribavir was shown to be more effective than standard treatment protocols for refractory CMV infection in post-transplant patients. This *post hoc* analysis of the SOLISTICE trial used trial data to calculate the reduction in healthcare costs that could be achieved by using Maribavir in this patient population. The analysis demonstrated a third to two-thirds reduction in costs over an 8-week period when using Maribavir. Healthcare cost analyses are complex and subject to many assumptions, which the authors acknowledge introduces significant bias. However, the most striking omission from the analysis is the cost of the Maribavir treatment itself, which is significantly higher than standard therapy. With the additional limitation of a short duration of study, the reliability and applicability of the reported cost savings cannot be readily determined.

Trial Registration
Not reported.

Funding Source
Industry funded.

CLINICAL IMPACT SUMMARY

by John O'Callaghan

This paper represents further work from the SOLSTICE study, published in 2022. This RCT investigated the treatment of refractory CMV in organ transplant and stem cell transplant recipients. In the previous paper, Maribavir was shown to be significantly better at clearing CMV than standard treatment, with less nephrotoxicity than foscarnet and less myelosuppression than valganciclovir/ganciclovir.

The current paper focusses on the cost-effectiveness of using Maribavir in this patient group (40% stem cell and 60% solid organ recipients). The potential cost savings are predicated not only on the increased effectiveness of Maribavir, but also on the improved safety profile and reduced complications associated. Clinical data inputs were taken from the SOLSTICE study. Daily costs were derived from the Centers for Medicare and Medicaid Services online price database. Facility-level costs reported by each of the participating facilities in the look-up tool were averaged to yield a representative daily cost.

The authors then used annualised mean length of hospital stay for Maribavir and standard treatment groups using length of stay estimates for ICU and non-ICU beds to calculate a mean Per-Patient-Per-Year (PPPY) hospital-care-related cost. The costs presented in the paper do not take into account any difference in the price of Maribavir compared to standard treatments and so should be viewed in that context. The mean PPPY costs of overall hospitalization was lower in the Maribavir group: $67,205 compared to $145,501. From the

results of the previous SOLSTICE paper, and the information in this paper, the use of Maribavir in this population is supported in terms of clinical recovery and safety profile. With regards to the cost effectiveness, it is completely possible that any potential reduction in healthcare associated costs is abrogated by a difference in the treatment cost. A weeks' course of Maribavir currently costs several thousand US dollars.

The paper was funded by Takeda pharmaceuticals USA Inc. and both first authors are employees of Takeda Pharmaceuticals USA Inc., with stocks in the company.

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

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

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ORIGINAL RESEARCH
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Women Are Also Disadvantaged in Accessing Transplant Outside the United States: Analysis of the Spanish Liver Transplantation Registry

Marta Tejedor[1], Fernando Neria[2], Gloria De La Rosa[3], Carolina Almohalla Álvarez[4], María Padilla[3], Andrea Boscà Robledo[5], Yiliam Fundora Suárez[6], Francisco Sánchez-Bueno[7], Miguel Angel Gómez-Bravo[8] and Marina Berenguer[9,10]**

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Sex inequities in liver transplantation (LT) have been documented in several, mostly US-based, studies. Our aim was to describe sex-related differences in access to LT in a system with short waiting times. All adult patients registered in the RETH-Spanish Liver Transplant Registry (2000–2022) for LT were included. Baseline demographics, presence of hepatocellular carcinoma, cause and severity of liver disease, time on the waiting list (WL), access to transplantation, and reasons for removal from the WL were assessed. 14,385 patients were analysed (77% men, 56.2 ± 8.7 years). Model for end-stage liver disease (MELD) score was reported for 5,475 patients (mean value: 16.6 ± 5.7). Women were less likely to receive a transplant than men (OR 0.78, 95% CI 0.63, 0.97) with a trend to a higher risk of exclusion for deterioration (HR 1.17, 95% CI 0.99, 1.38), despite similar disease severity. Women waited longer on the WL (198.6 ± 338.9 vs. 173.3 ± 285.5 days, $p < 0.001$). Recently, women's risk of dropout has reduced, concomitantly with shorter WL times. Even in countries with short waiting times, women are disadvantaged in LT. Policies directed at optimizing the whole LT network should be encouraged to guarantee a fair and equal access of all patients to this life saving resource.

Keywords: sex inequity, waiting list, survival, access to transplantation, women, Spanish Liver Transplant Registry (RETH)

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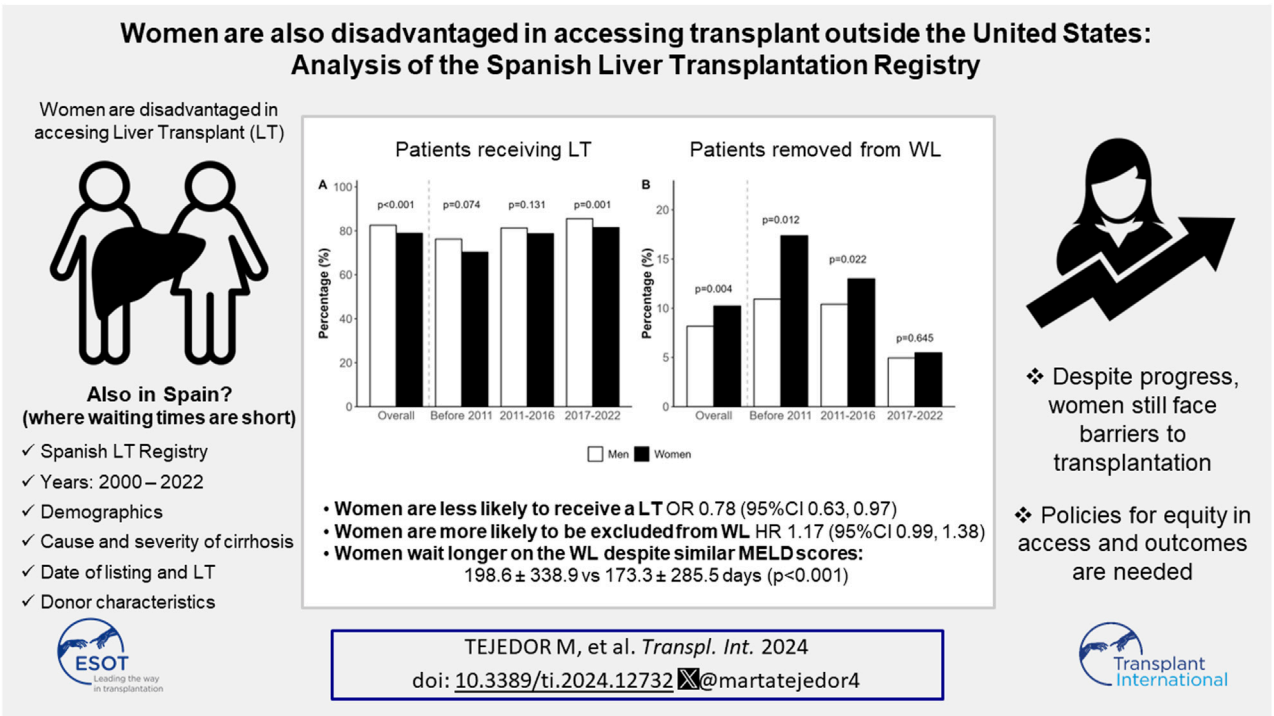
Abbreviations: AIH, autoimmune hepatitis; ANOVA, analysis of variance; CORE, Spanish Registry for Donation and Transplantation; DBD, donation after brain death; DCD, donation after cardiac death; HCC, hepatocellular carcinoma; HR, hazard ratio; Kg, kilograms; LD, living donation; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; ONT, Organización Nacional de Trasplantes (National Transplant Organization); OR, odds ratio; RETH, Registro Español de Trasplante Hepático (National Spanish Liver Transplant Registry); US, United States; vs., versus; WL, waiting list.



GRAPHICAL ABSTRACT

INTRODUCTION

In recent years, noticeable health disparities between men and women have emerged, extending into various domains, including the transplant arena. Indeed, although sex differences exist from biological and physio-pathological perspectives, these have rarely been considered when proposing prognostic models or when applying and evaluating treatments. Because the demand for organs has always exceeded the supply, the transplant community has long recognized the need to ensure equity and efficiency of the organ allocation system. With this in mind, it is imperative to recognize inequities to then further develop policies that have the potential to ensure that women have equitable access to transplantation. In that sense, providing national data is crucial as poorer access to liver transplantation (LT) for women compared to men might be explained by different analytical approaches or different national contexts, and has two facets, biological and sociocultural [1, 2]. Sex inequities in LT including the type of liver disease that leads to the need of transplantation, the referral pattern to transplant centres, access to waiting lists (WL) and transplantation itself as well as post-transplant outcomes have been recently documented in several, mostly US-based, studies [1–5]. The reduced need of LT, mainly explained by the different prevalence of chronic liver disease in women and men, particularly refers to viral cirrhosis and liver cancer, more frequently found in men [1–4, 6]. However recent changes in epidemiology due to the advent and penetration of direct antiviral agents as well as the obesity epidemics can modify this scenario and are known to vary substantially based on local epidemiology [7, 8]. Several hypotheses attempt to elucidate the higher likelihood of death on the WL, removal from the list due to an illness precluding transplant, and the lower likelihood of receiving a liver graft. Factors such as limitations in the model for end-stage liver disease (MELD) score and donor-recipient size mismatch are implicated [9–15], and these variables strongly correlate with local allocation systems and general characteristics of the local population. In summary, our transplant population (including transplant candidates and recipients) may have substantial differences from that of the US, related to both transplant indications as well as baseline features of the population.

The so called "Spanish Model in Organ Donation and Transplantation" has positioned our country as a global leader in terms of donation and transplantation. The key features of this model include its three-tiered governing structure, close and collaborative relationships with the media, dedicated professional roles, a comprehensive reimbursement strategy, and intensive tailored training programs for all personnel. Throughout the years, the pool of donors has expanded, with a significant rise in donation after circulatory death (DCD). The program is driven by a culture of research, innovation, and continuous commitment and is complemented by successful strategies in prevention of end-stage liver and renal disease [16, 17]. As in most Eurotransplant countries, exception points are assigned to some indications where WL mortality risk is not accurately predicted by MELD, particularly hepatocellular carcinoma (HCC). The registered MELD scores

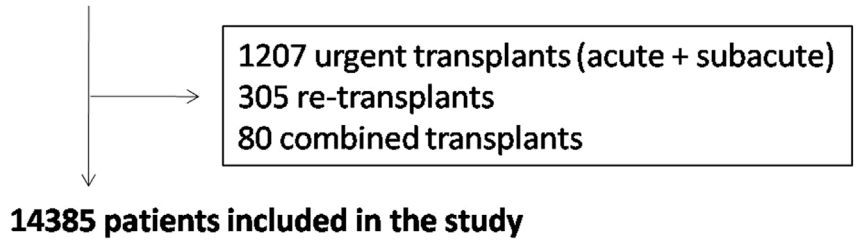


FIGURE 1 | Flowchart of the study.

TABLE 1 | Liver transplant candidates baseline demographics, overall and by sex.

Variable	Overall (*n* = 14,385)	Men (*n* = 11,115)	Women (*n* = 3,270)	P[a]
Age (years)	56.2 ± 8.7	56.5 ± 8.2	55.5 ± 10.2	**<0.001**
Weight (kg)	77.3 ± 15.7	80.6 ± 14.7	66.1 ± 13.7	**<0.001**
Height (cm)	168.4 ± 8.6	171.0 ± 7.1	159.2 ± 7.0	**<0.001**
MELD[b]	16.6 ± 5.7	16.6 ± 5.7	16.6 ± 5.7	0.953
Blood group				**0.010**
· A	6,540 (45.5%)	5,084 (45.7%)	1,456 (44.5%)	
· O	5,872 (40.8%)	4,464 (40.2%)	1,408 (43.1%)	
· B	1,380 (9.6%)	1,094 (9.8%)	286 (8.8%)	
· AB	593 (4.1%)	473 (4.3%)	120 (3.7%)	
Aetiology				**<0.001**
· Alcohol	6,260 (43.5%)	5,538 (49.8%)	722 (22.1%)	
· Viral	4,356 (30.3%)	3,429 (30.9%)	927 (28.4%)	
· Cholestatic	801 (5.6%)	313 (2.8%)	488 (14.9%)	
· MASLD	514 (3.6%)	306 (2.8%)	208 (6.4%)	
· AIH	317 (2.2%)	91 (0.8%)	226 (6.9%)	
· Other	2,137 (24.8%)	1,438 (12.9%)	699 (21.3%)	
HCC	4,937 (34.3%)	4,230 (38.1%)	707 (21.6%)	**<0.001**

Continuous variables are expressed as Mean ± SD; categorical variables are expressed as n (%).
[a]Welch Two Sample t-test for comparison between men and women (continuous variables); Pearson's Chi-squared test (categorical variables).
[b]MELD data only available for 5,475 patients. MASLD, metabolic dysfunction-associated steatotic liver disease; AIH, autoimmune hepatitis; HCC, hepatocellular carcinoma.
The bold values represent p values that are significant statistically.

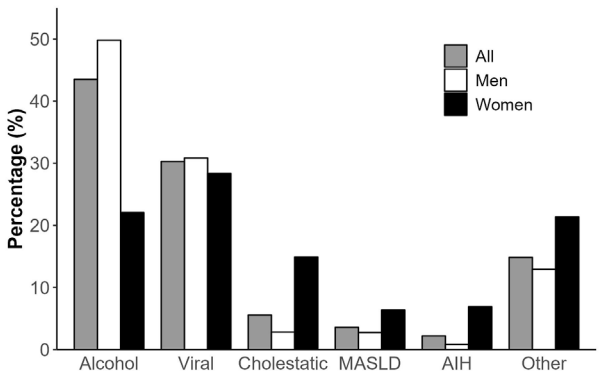


FIGURE 2 | Aetiology of liver disease, overall and by sex. MASLD, metabolic dysfunction-associated steatotic liver disease; AIH, autoimmune hepatitis.

for HCC patients have been adjusted over time to facilitate access to LT while avoiding disadvantages for non-HCC patients. Overall, patients listed for HCC can be registered at a MELD score equivalent to a 15% probability of patient death within 3 months and upgraded every 90 days to a MELD score that reflects an increase in mortality by 10% [18].

The MELD system was progressively adopted in different regions of Spain since 2003 becoming the allocation method of choice in most of the country in 2011. Previously, a combination of time on WL and Child-Pugh score were used to allocate organs.

The aim of our study was to describe the recipient profile over time in Spain, particularly with regards to potential sex-related differences in access to LT in a system with short waiting times.

MATERIAL AND METHODS

Study Population

All adult (18 years old or older) patients registered in the Spanish Registry for Donation and Transplantation (CORE), managed by the Organización Nacional de Trasplantes (ONT), from 2000 to 2022 were included in this study. Urgent transplants, due to acute or subacute liver failure, were excluded as the criteria to allocate this group differs significantly from those with chronic end-stage

TABLE 2 | Evolution of the wait list (WL) demographics by period.

Variable	2000–2010 (*n* = 1,786)	2011–2016 (*n* = 6,640)	2017–2022 (*n* = 5,959)
Age (years)	53.9 ± 8.7	55.5 ± 8.6	57.8 ± 8.5
Weight (kg)	75.5 ± 14.8	77.1 ± 15.4	78.1 ± 16.1
Height (cm)	167.7 ± 8.8	168.5 ± 8.7	168.4 ± 8.6
MELD[a]	19.2 ± 5.2	16.8 ± 5.7	16.2 ± 5.8
Blood group			
· A	824 (46.1%)	3,031 (45.7%)	2,685 (45.1%)
· O	767 (43.0%)	2,687 (40.5%)	2,418 (40.6%)
· B	136 (7.6%)	643 (9.7%)	601 (10.1%)
· AB	59 (3.3%)	279 (4.2%)	255 (4.3%)
HCC	523 (29.3%)	2,373 (35.7%)	2,041 (34.3%)

Continuous variables are expressed as Mean ± SD; categorical variables are expressed as n (%). One-way ANOVA $p < 0.05$ *for each variable between periods.*
[a]*MELD data only available for 5,475 patients. HCC, hepatocellular carcinoma.*

liver disease [19, 20]. Combined transplants were also excluded as the concurrence of extra-hepatic organ failure requiring transplantation may influence waiting times and may require non-standard exception points or specific organ allocation policies [21–23]. We also excluded re-transplants, as standard allocation systems may not apply in all the Spanish system. Registrants were followed from the time of inclusion on the WL until the 31st of December 2022, LT, removal from the list or death, whichever occurred first. Reasons for removal included being too sick for transplantation or improvement such that LT was no longer needed, although our analysis focused on patients excluded for deterioration or death.

Variables analysed were: baseline demographics (age, sex, blood group, weight and height), presence of HCC, cause and severity of liver disease resulting in end-stage liver disease, date of listing on the LT WL and date of transplantation. Donor baseline characteristics were also analysed: age, sex, weight, height, and type of donation [donation after brain death (DBD), DCD, living donation (LD), domino].

Three time periods were analyzed: from 2000 to 2010, from 2011 to 2016, and from 2017 to 2022. Since MELD was adopted by most of the country as the preferred allocation system from 2011, this date was chosen for the first cut-off. The remaining time was divided into two equally long periods to assess the evolution of the WL.

This research was conducted in accordance with both the Declarations of Helsinki and Istanbul. We retrospectively explored data collected from the Spanish Liver Transplant Registry (Registro Español de TrasplanteHepático, RETH). RETH is a multicenter registry that recruits data from all liver transplant units in Spain with periodic auditing. This study was based on data routinely collected at a national level for organ allocation and to assess the efficacy and safety of the LT program. For that reason, the requirement for a formal ethics committee review was waived by the National Transplant Organization (Organización Nacional de Trasplante, ONT). The data analyzed in this study is subject to the following licenses/restrictions: datasets belong to Spanish Liver Transplant Society and are managed and administered by the National Transplant Organization.[1]

[1]Requests to access these datasets should be directed to www.ont.es.

Statistical Analysis

Continuous variables are expressed as mean and standard deviations. T-test or ANOVA test were used as appropriate. Categorical variables were compared using the Chi-square test when appropriate. A multiple regression analysis was performed to assess transplantation odds ratio (OR). A Cox proportional hazards multiple regression analysis was performed to determine whether sex was associated with the likelihood of removal from the list due to worsening or death; this approach was used to account for differences in follow-up times after inclusion in WL. All analyses were stratified by sex and adjusted where appropriate by age, blood group and height, and MELD when available, at time of LT. A p-value <0.05 was considered statistically significant. Sub-analyses were performed in case missing information was significant for a specific variable (i.e., MELD). All statistical analyses were performed with the software R version 4.2.3.

RESULTS

Baseline Characteristics of Patients on the WL

Out of 16,828 adult patients included in the CORE registry, a total of 14,385 patients meeting the inclusion criteria were analysed (**Figure 1**). Baseline characteristics of those included vs. those excluded are shown in **Supplementary Table S1**. Most listed patients were men (77%). Differences between included men and women are shown in **Table 1** and **Figure 2**. As expected, several significant differences were observed by sex. In particular, men were older, heavier and taller. They suffered more of alcohol-related liver disease and HCC than women, who were more likely affected by cholestatic and autoimmune liver diseases.

Evolution of the WL

A change in the WL was observed over time; with candidates becoming older and heavier (**Table 2**). Alcohol-related liver disease and metabolic dysfunction-associated steatotic liver disease (MASLD) have become more frequent indications for LT, as opposed to a decrease in viral hepatitis (**Figure 3**).

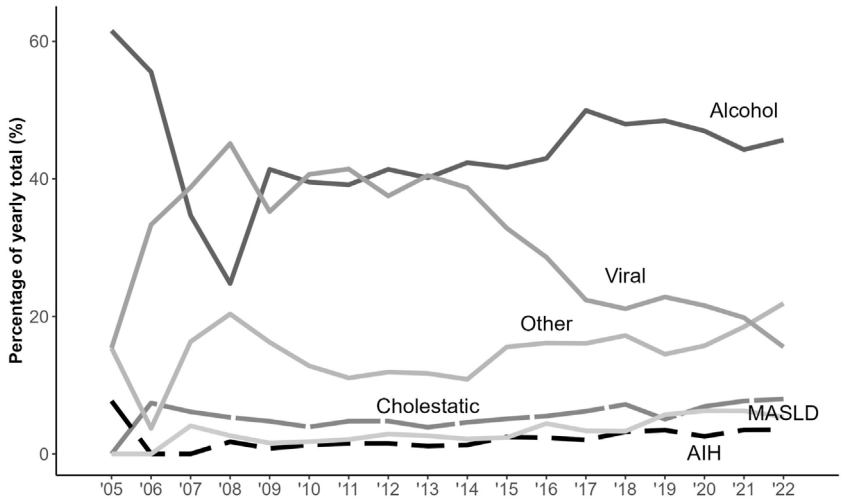


FIGURE 3 | Changes in aetiology of liver disease over time. MASLD, metabolic dysfunction-associated steatotic liver disease; AIH, autoimmune hepatitis.

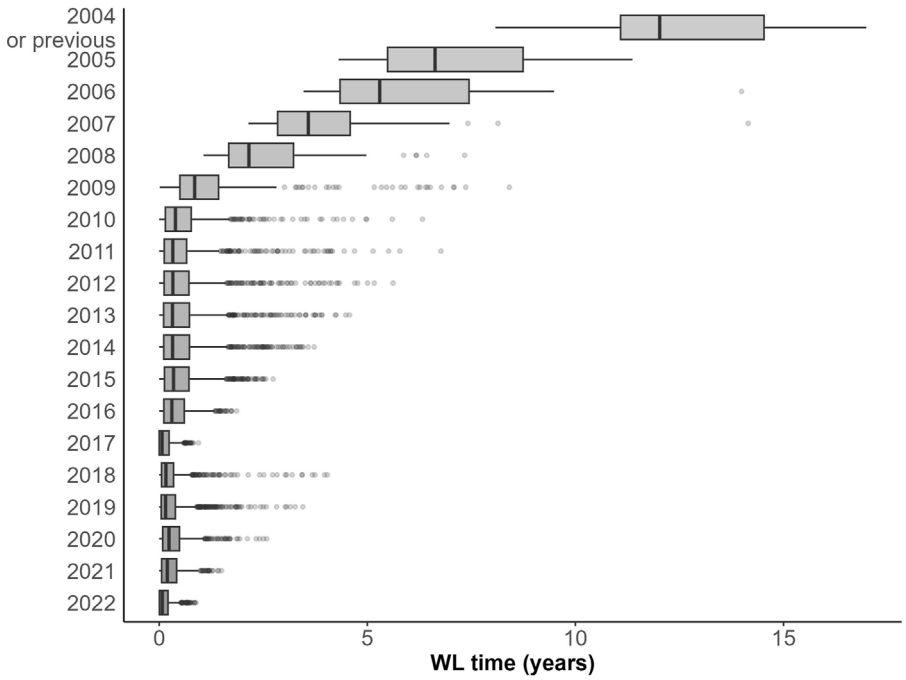


FIGURE 4 | Evolution of waiting times over time.

Time on the WL has shortened from 424.3 ± 619.6 days in the first period (2000–2010), to 190.9 ± 229.6 days in the second period (2011–2016) and to 92.3 ± 126.0 days in the third period (2017–2022) ($p < 0.001$) (**Figure 4**). The progressive shortening of waiting times coincided with a progressive increase in the likelihood of receiving a transplant: compared to the first period, HR was 1.97 (95% CI 1.84, 2.11; $p < 0.001$) in the second period and 3.99 (95% CI 3.72, 4.28; $p < 0.001$) in the third period.

MELD was recorded in a non-systematic way in the national database from 2011 and was available for 5,350 of the 12,599 included patients (43%) after 2011. To ensure that all patients included in the WL after this date were comparable, differences between patients with available and unavailable MELD score were analysed and are shown in **Supplementary Table S2**. No difference was found in access to transplant by availability of MELD in the database in the last two periods (2011–2016: HR 1.19 [95% CI 0.97, 1.45]

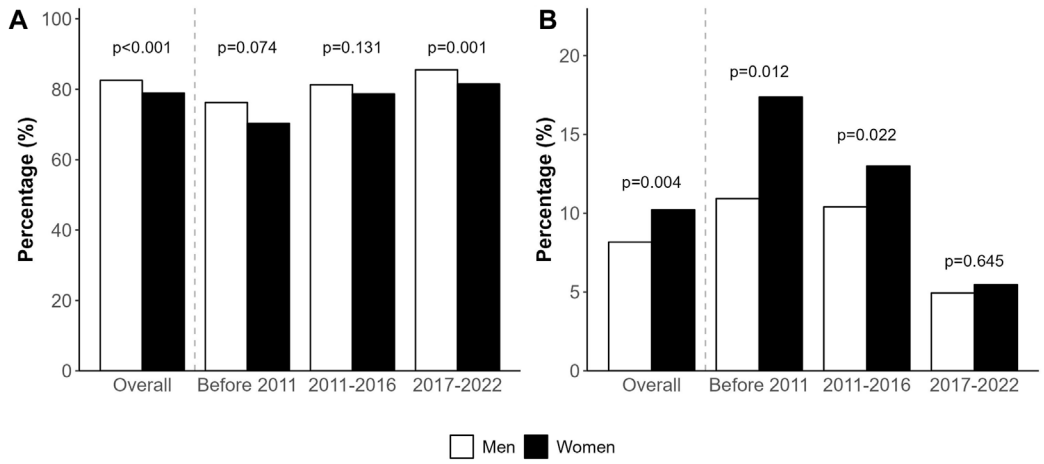


FIGURE 5 | (A) Transplanted patients by sex, overall and by period. **(B)** Exclusion from the waiting list due to deterioration or death by sex, overall and by period.

TABLE 3 | Time on waiting list by sex and period.

Period	Waiting time (days)		
	Men	Women	P[a]
2000–2010	408.4 ± 593.1	473.6 ± 693.7	0.078
2011–2016	186.5 ± 223.1	207.0 ± 251.0	**0.005**
2017–2022	88.7 ± 118.2	104.2 ± 148.2	**<0.001**

All results are expressed as mean ± SD. One-way ANOVA p < 0.001 for the comparison between periods both for men and for women.
[a]Welch Two Sample t-test for the comparison between men and women.
The bold values represent p values that are significant statistically.

TABLE 4 | Time on waiting list by sex in patients included since 2011 with available MELD.

MELD score	Waiting time (days)		
	Men	Women	P[a]
<16	160.0 ± 198.6	167.8 ± 206.8	0.455
16–20	183.3 ± 184.5	223.4 ± 234.5	**<0.001**
>20	100.4 ± 168.4	125.4 ± 220.1	0.129

All results are expressed as mean ± SD.
[a]Welch Two Sample t-test for the comparison between men and women.
The bold values represent p values that are significant statistically.

p = 0.093; and 2017–2022: HR 1.08 [95% CI 0.88, 1.32] p = 0.475). Percentage of patients with available MELD per year is presented in **Supplementary Table S3**.

Analysis of the Donor Pool

Donor characteristics are described in **Supplementary Table S4**. A steady increase in the number of donations has been seen in our study since 2014, coinciding with an expansion in the use of DCD livers (from 2.4% before 2011 to 15.8% after this date, $p < 0.001$). The COVID-19 pandemic explains the brisk drop in donations in 2020, now in recovery (**Supplementary Figure S1**). Men were more likely to receive a graft from a male donor (58.7%) while women received grafts from female donors more often (56.5%, $p < 0.001$ for the difference). Female donors were shorter than male donors (164.6 ± 11.8 vs. 168.2 ± 10.4 cm, $p < 0.001$). There were no differences in allocation of DCD or DBD livers by sex of the recipient, although female recipients received split livers more frequently (1.9% in female vs. 0.9% in male recipients, $p < 0.001$).

Influence of Sex in Access to LT in Spain

Overall, fewer women received a LT (79% vs. 82%, $p < 0.001$) and a greater proportion were excluded (10% vs. 8%, $p = 0.004$) from the WL compared to men. Even though still present, these differences have decreased in recent years (**Figure 5**).

The overall probability of women undergoing LT was lower (OR 0.78, 95% CI 0.63, 0.97; $p = 0.022$) after adjusting for age, height, blood group and MELD score. These differences have attenuated in the last decade. After adjusting for recipient's age, height and blood group, the probability of being transplanted was lower for women before 2011 (OR 0.68, 95% CI 0.49, 0.96; p = 0.026). In this first period, MELD data were scarce and could not be added to the model. However, in the last two periods, after adding MELD to the model, no significant differences in access to liver transplantation were found by sex (2011–2016: OR 0.82 [95% CI 0.60, 1.13] p = 0.216; and 2017–2022: OR 0.77 [95% CI 0.57, 1.05] p = 0.094). Time on the WL did not seem to influence the risk of women undergoing transplant (HR 0.95 [95% CI 0.90, 1.01] p = 0.093).

The risk of exclusion from the WL due to deterioration or death was higher for women after adjusting for age, height and blood group, although the result did not reach statistical significance (HR 1.17 [95% CI 0.99, 1.38] p = 0.060). After adding MELD to the model, differences were no longer present (HR 1.01 [95% CI 0.75, 1.36] p = 0.928). When analysed by period, this inequity has subsided over time. Before 2011 (MELD not included in the model), the risk of being excluded from the WL was higher for women (HR 1.49 [95% CI 0.99, 2.25] p = 0.054). In the second

(2011–2016) and third (2017–2022) periods, including MELD in the analysis, HR were 0.93 [95% CI 0.64, 1.36] (p = 0.716), and 0.93 [95% CI 0.57, 1.51] (p = 0.769), respectively.

Overall, mean waiting times for women were longer (198.6 ± 338.9 days for women vs. 173.3 ± 285.5 for men, p < 0.001). Over the last two decades, waiting times have shortened for both sexes, but women still wait longer than men (**Table 3**). In particular, women with intermediate MELD scores [16–20] waited significantly longer than men with similar scores (**Table 4**). In this subgroup of women with intermediate MELD scores, despite longer waiting times, there was no significant difference in access to transplant (HR 1.10, 95% CI 0.82, 1.48; p = 0.534) or risk of being excluded from the WL for deterioration or death (HR 0.98, 95% CI 0.61, 1.57; p = 0.925).

Among patients with HCC, there were no differences in access to LT by sex (data not shown).

DISCUSSION

Our study presents national Spanish data on WL demographics over the last 20 years, confirming an aging population and a shift in aetiologies towards less viral hepatitis and more MASLD-related liver disease. Waiting times in our country have significantly decreased over time. Women were found to have lower access to transplant and a higher risk of exclusion due to worsening or death compared to men, although these differences have reduced in recent years, in parallel with shorter waiting times.

In our cohort, only 23% of patients on the WL were females. This percentage remained stable throughout the study period. Female representation in the Spanish WL is slightly lower than the 40% reported in the literature in other countries [1, 6]. Not only women were under-represented on the WL, but they were also less likely to receive a LT and had a higher risk of being excluded from the WL for being too sick for LT. This is in keeping with several US based-studies showing women to be at higher risk of death or drop-out on the WL and less likely to receive an organ [1, 24].

There is no published information as to the burden of decompensated cirrhosis in Spanish women, but data from a recent systematic analysis allows us to estimate a 40% prevalence of decompensated cirrhosis in Spanish women and 60% in men, similar to other regions of the world [25]. Yet only around 20% of women and 80% of men finally access LT waitlists in Spain. This difference with other series could be explained by the high number of HCC indications in our country (34%), compared, for instance, to the most recent OPTN report in the US showing that HCC was the primary diagnosis for 10.5% of waitlist candidates [26]. Indeed, HCC is more frequent in men (38% vs. 22% in our study, p < 0.001). A traditionally healthier lifestyle in women has translated into lower rates of alcohol-related liver disease, hepatitis C infection and HCC, although this might change in the future with the increase of MASLD in women. One important finding in our study is the decreasing rate of mortality and exclusion due to deterioration in our WL, both in males and females, with differences between sexes disappearing in recent years (**Figure 5**).

Several changes have occurred in the LT field over the last decade in Spain that help interpret our results. Firstly, public health interventions have resulted in a decrease in the number of patients listed for a LT. In particular, universal treatment of hepatitis C from 2015 has allowed our country to witness a decreased number of indications for LT associated with hepatitis C-related diseases [27], as depicted in **Figure 3**. This national plan to eradicate hepatitis C decreased the number of patients requiring a transplant, resulting in shorter waiting times a few years later (**Figure 4**) [27]. Secondly, Spain consistently reports the highest rates of deceased donation in the world (14,383 valid donors during our study period), based on the implementation of the so called "Spanish Model in Organ Donation and Transplantation" that has been well described in the literature [16, 28]. Over the last years, the implementation of innovative measures such as the standardization of intensive care to facilitate organ donation, the expansion of donor eligibility criteria and the incorporation of DCD (with the systematic use of normothermic regional perfusion) has further allowed to increase the availability of livers for clinical use [29]. In fact, the global percentage of DCD use in our study was 14.3%. The COVID-19 pandemic impacted significantly in donation rates and transplant programs, but this is now in recovery. Finally, MELD was progressively adopted in different regions of Spain since 2003 and became the allocation method of choice in the majority of the country from 2011.

Around the world, adoption of MELD derived systems as the preferred allocation policy translated into a decrease in global mortality on the WL [30, 31]. While implementation of MELD based systems in other countries was associated with a further reduction in rates of transplantation among women compared with the previous era (9% vs. 14% reduction rate in the pre vs. post MELD era) [3], we found the opposite (**Figure 5A**), with a growing number of women accessing transplant. The most accepted explanation for the sex-based difference in access to LT is the use of creatinine, which underestimates renal dysfunction in women because of their lower muscle mass [9–11, 32] and their smaller stature [13, 15]. Similar studies performed in North America show that differences between sexes in terms of transplantation, death or removal from list are small during the first months after listing but grow progressively after 1 year of waiting and remain stable after 3 years [10]. We found an association between a longer time on the WL in women and the risk of exclusion for worsening or death prior to 2011 (HR 1.49, 95% CI 0.99, 2.25; p = 0.054) that disappeared after this date (HR 1.11, 95% CI 0.92, 1.33; p = 0.277). As mentioned above, many changes occurred in the LT field after 2011, which makes it difficult to point to a single explanation for the observed improvement in sex-related inequities. In our particular scenario, for instance, where access to transplantation occurs in less than 6 months, patients listed with HCC may not gain enough points to reach the top of the list, which could minimize the differences between men and women. As previously noted, overall waiting times are very short, which probably contributes to women not being penalized with higher drop-out rates due to worsening or death despite longer waiting times than men, in particular those with intermediate MELD scores.

The main strength of our study is the use of a large national database including a large number of patients with long follow up. It is also one of the few works addressing access to LT by sex outside the United States. It has, however, some limitations. MELD data are incomplete, and although there does not seem to be any significant difference between patients with reported MELD and those without from 2011, there is a risk of measurement or information bias, and caution should be exerted when interpreting and extrapolating the results. The MELD system was progressively, but non-homogeneously, adopted in different regions of Spain since 2003 becoming the allocation method of choice in most of the country in 2011. However, the collection of this piece of information, despite its importance, is not mandatory in the current Registry. This, in addition to the retrospective nature of the study dating up to 20 years ago, explain the incomplete and fragmented MELD data (see **Supplementary Table S3** for the evolution of MELD registration). The Spanish LT community should take this opportunity to engage in appropriate data collection, so that Registry studies can offer solid evidence as to how our excellent system performs. No other relevant predictors of WL mortality [33] have been explored, due to the retrospective nature of the study. Finally, there are, still nowadays, significant differences in WL times and donation rates between regions in Spain. However, we have described the global results of one of the most praised transplant systems in the world. Recently, MELD 3.0 was proposed as the official allocation policy in the United States [34]. Future studies in our setting where waiting times are short should address its usefulness.

In summary, even in countries with short waiting times, women wait longer and have a lower access to transplant and higher risk of exclusion from the WL. Policies directed at optimizing the whole LT network should be encouraged to guarantee a fair and equal access of all patients to this life saving resource.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The requirement of ethical approval was waived by Organización Nacional de Trasplante for the studies involving humans because this study was based on data routinely collected at a national level for organ allocation and to assess the efficacy and safety of the LT program. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board also waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this study was based on data routinely collected at a national level for organ allocation and to assess the efficacy and safety of the LT program.

AUTHOR CONTRIBUTIONS

MB designed the study. GD, CA, and MP granted Access to the national database and helped with data extraction. FN performed the statistical analysis. MT, FN, and MB developed the content of the article. MT wrote the initial draft of the manuscript. All authors discussed the results and contributed to the final manuscript.

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CONFLICT OF INTEREST

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

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To all the liver transplant groups, the ONT, the SETH, the donors and their families.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.12732/full#supplementary-material

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SYSTEMATIC REVIEW AND META-ANALYSIS
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Simultaneous Heart and Kidney Transplantation: A Systematic Review and Proportional Meta-Analysis of Its Characteristics and Long-Term Variables

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Patients with end-stage heart disease who undergo a heart transplant frequently have simultaneous kidney insufficiency, therefore simultaneous heart and kidney transplantation is an option and it is necessary to understand its characteristics and long-term variables. The recipient characteristics and operative and long-term variables were assessed in a meta-analysis. A total of 781 studies were screened, and 33 were thoroughly reviewed. 15 retrospective cohort studies and 376 patients were included. The recipient's mean age was 51.1 years (95% CI 48.52–53.67) and 84% (95% CI 80–87) were male. 71% (95% CI 59–83) of the recipients were dialysis dependent. The most common indication was ischemic cardiomyopathy [47% (95% CI 41–53)] and cardiorenal syndrome [22% (95% CI 9–35)]. Also, 33% (95% CI 20–46) of the patients presented with delayed graft function. During the mean follow-up period of 67.49 months (95% CI 45.64–89.33), simultaneous rejection episodes of both organ allografts were described in 5 cases only. Overall survival was 95% (95% CI 88–100) at 30 days, 81% (95% CI 76–86) at 1 year, 79% (95% CI 71–87) at 3, and 71% (95% CI 59–83) at 5 years. Simultaneous heart and kidney transplantation is an important option for concurrent cardiac and renal dysfunction and has acceptable rejection and survival rates.

Keywords: transplant, multiorgan transplant, simultaneous heart and kidney transplantation, heart transplantation, kidney transplantation

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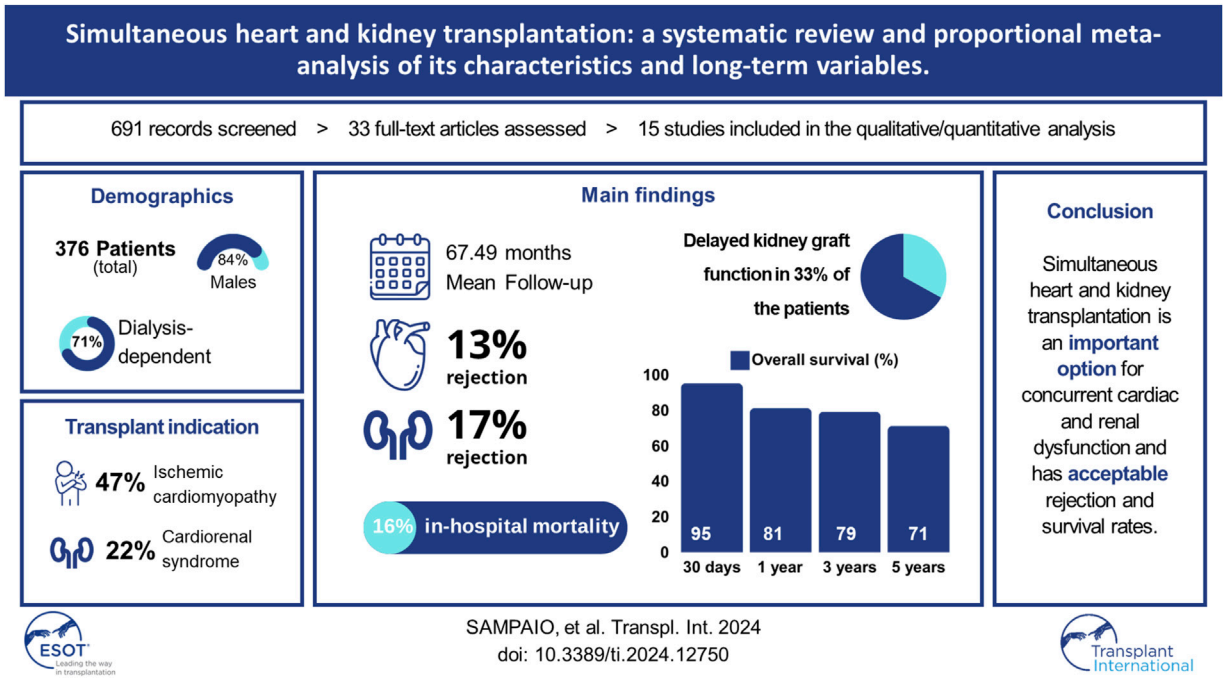

GRAPHICAL ABSTRACT |

INTRODUCTION

Patients with end-stage heart disease who undergo heart transplantation alone (HTx) frequently have simultaneous kidney insufficiency, leading to an outcome of reduced survival [1], as kidney failure is a predictor of morbidity and mortality in patients after HTx [2]. Since simultaneous heart and kidney transplantation (sHKTx) was first described in 1978 by Norman et al [3], it has become a recognized therapy for simultaneous end-stage cardiac and renal failure, with increased numbers since 2010 and representing more than 5% of the total number of HTx performed in the United States currently [4].

Indications for sHKTx are challenged by difficulties in differentiating those patients with cardiorenal syndrome without intrinsic renal disease, who could present renal recovery after HTx, from those with intrinsic advanced kidney disease who would benefit most from sHKTx [4]. Current evidence [1] supports that the simultaneous procedure is strongly recommended for heart transplantation candidates with pre-transplant renal dysfunction that leads to an estimated glomerular filtration rate (eGFR) under 30 mL/min/1.73 m [2]. Although the indications for sHKTx remain unclear, it is known that patients with simultaneous end-stage heart and renal disease who went through sHKTx have similar mortality when compared with HTx [5] and present a lower incidence of cardiac rejection [6].

The limitations of the existing sparse literature on the indications and outcomes of sHKTx highlight the critical need for studies dedicated to filling these gaps. Presently, the primary studies in this domain mainly center on retrospective analyses of the OPTN/UNOS database. However, this approach is limited as it excludes data from international centers performing this procedure. Therefore, this systematic review and meta-analysis was designed to synthesize the global evidence on the indications and outcomes of sHKTx, addressing this particular gap in the literature.

METHODS

This systematic review and meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) 2020. The study protocol was registered in AsPredicted (119472).

Literature Search and Study Selection

We searched for relevant studies in PubMed, Embase, Lilacs, Scopus, Ovid Medline, and Web of Science updated to February 03, 2023. Two researchers (author 2 and author 3) searched works independently with a combination of the following terms: "heart kidney transplantation," "simultaneous heart kidney transplantation" and "combined heart kidney transplantation," and any discrepancies regarding the selection of studies were resolved by them. The reference lists of all eligible studies were reviewed for further identification of potentially relevant studies. The title and abstract of each identified publication were screened, and only publications that followed the selection criteria were fully read and included in the review.

Selection Criteria

The inclusion criteria were as follows: 1) published clinical studies in English, Portuguese, or Spanish that investigated indications and outcomes of sHKTx patients only; 2) studies including patients that underwent sHKTx as a result of simultaneous end-stage heart disease and concomitant kidney disease; 3) studies that had reported at least one of the outcomes of interest (mean donor age, mean recipient age, recipient body mass index, left ventricular ejection fraction, pre-operative serum creatinine, heart failure etiology, renal failure etiology). The exclusion criteria were: 1) studies with incomplete or unavailable data of interest; 2) studies not involving human subjects; 3) studies that included both the staged procedure and the simultaneous procedure in the same analysis group. If multiple studies were published from the same center, with overlapping patients' data and follow-up periods, only the most complete reports with the longest follow-up period were included for assessment.

Data Extraction and Outcomes

The data extraction was performed with standardized processes conducted independently by two researchers (MDF, LVSV). Extracted data included study characteristics, such as title, type of study, first author, year of publication, center, study date, and the number of subjects that underwent sHKTx. The baseline demographics of the patients (donor age, recipient age, gender, cardiac and renal failure etiology, BMI, LVEF, pre-operative serum creatinine, inotrope usage, and dialysis dependency), as well as perioperative outcomes (overall allograft ischemic time, cardiac and kidney allograft ischemic times, delayed graft function, and in-hospital mortality) were also included. The assessment of warm allograft time was not feasible due to the lack of reporting of these parameters in the selected studies, although cold ischemic allograft time data was collected. The immunosuppression strategies adopted by each study were assessed and included solely in the qualitative synthesis. Five long-term outcomes (duration of follow-up period, serum creatinine at follow-up, overall, cardiac and renal rejection episodes), were assessed for quantitative synthesis. Cumulative 30-day, 1-, 3- and 5-year overall survival rates were also extracted for assessment for the study. The Newcastle-Ottawa Scale (NOS) - a tool to assess the quality of studies in meta-analyses, with a score from zero to nine, with zero being the worst outcome and nine classifying the paper as the best quality, developed by the Universities of Newcastle, Australia, and Ottawa, Canada [7] - was adopted to evaluate the quality of evidence in each included study by two researchers independently (author 1 and author 4) and they resolved any discrepancies in quality scoring.

Statistical Analysis

A meta-analysis of proportions was conducted for the available recipient demographics and perioperative and postoperative variables with logit transformation. The R software version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for all data analysis and visualization. Heterogeneity was evaluated using the I2 test. As a guide, I2 $<25\%$ indicated low, 25%–50% moderate, and >50% high heterogeneity [8]. If there was low or moderate statistical heterogeneity, a fixed-effect model was used. Otherwise, a random-effect model was adopted to evaluate variables with high heterogeneity. The meta-analysis was performed with the *metafor* package for R. Statistical significance was judged by p values under 0.05. Continuous data were estimated using mean with 95% confidence intervals (CI), and dichotomous data were reported using percentages with 95% CI. For some studies adopting median and range for parameters, estimated mean and standard deviation (SD) were obtained by adopting the formulas proposed by Hozo et al [9].

RESULTS

Characteristics of the Selected Literature

A total of 781 articles were identified based on the literature search criteria and 15 eligible papers were included in qualitative synthesis and meta-analysis [10–24], including 376 patients who underwent the procedure from 1996 to 2019. All articles were single-center retrospective studies from 15 different transplantation centers in Austria, Belgium, the United States of America, the United Kingdom, Germany, Taiwan, Italy, New Zealand, Argentina, Spain, France, and Brazil. The literature search and study characteristics description are reported in **Figure 1** and **Table 1**, respectively. The complete results table, including heterogeneity and the number of studies used to access each pooled variable, is reported in Table A in **Supplementary Material**.

Baseline Characteristics

This proportional meta-analysis included 376 patients, of whom 84% (95% CI 80–87, $p = 0.06$) were men. The mean donor age was 32.97 years (95% CI 28.21–37.73, $p < 0.01$) whereas the mean recipient age was 51.10 years (95% CI 48.52–53.67, $p < 0.01$). Regarding recipient demographics, the mean BMI was 24.42 kg/m2 (95% CI 23.42–25.41, $p = 0.04$), mean LVEF was 23.32% (95% CI 16.62–30.02, $p < 0.01$), and pre-operative serum creatinine was 4.53 mg/dL (95% CI 3.04–6.02, $p < 0.01$). Overall, 71% (95% CI 59–83, $p < 0.01$) of the patients were dialysis-dependent and 33% (95% CI 17–50, $p = 0.02$) were inotrope-dependent before transplantation.

The predominant heart failure etiology was ischemic cardiomyopathy in 47% (95% CI 41–53, $p = 0.04$) of the patients, followed by dilated cardiomyopathy in 43% of the patients, (95% CI 29–57, $p < 0.01$), and idiopathic cardiomyopathy in 28% of the patients (95% CI 20–35, $p = 0.59$). The sum of these percentages results in a value above 100% because of the variability in the assessment of each etiologies in the number of studies included, which can be verified in Table A in **Supplementary Material**.

Although the diagnosis methods were not registered, renal failure etiology was mostly due to cardiorenal syndrome (22% of the patients, 95% CI 9–35, $p < 0.01$), followed by glomerulonephritis (16% of the patients, 95% CI 2–30, $p < 0.01$), nephritis (14% of the patients, 95% CI 3–26, $p = 0.01$), drug-related toxicity (14% of the patients, 95% CI 9–19, $p = 0.17$),

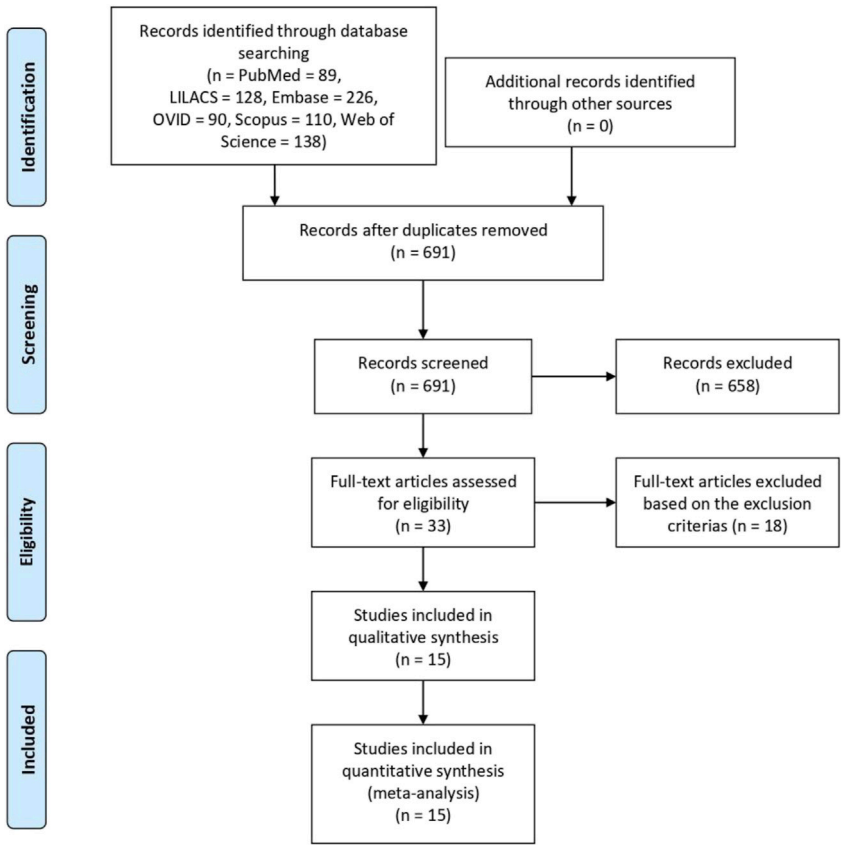

FIGURE 1 | Flow diagram of literature search and study selection.

polycystic kidney disease (7% of the patients, 95% CI 4–11, p = 0.56), and diabetes-related (7% of the patients, 95% CI 4–11, p = 0.13). The sum of these percentages results in a value above 100% for the same reason mentioned before.

Operative Variables

An immunosuppressive regimen based on induction and maintenance therapy was registered in ⅔ of the studies, and the remaining ⅓ only properly reported the use of maintenance therapy. Although it was not possible to associate the specific use of different immunosuppressive regimens with sHKTx outcome, the studies reported, as induction therapy, the use of one or more of the following: thymoglobulin, anti-thymocyte globulin, muromonab-CD3, methylprednisolone, prednisone, and basiliximab. As maintenance therapy, the studies reported the single or combined use of tacrolimus, azathioprine, mycophenolate mofetil, cyclosporine, everolimus, sirolimus, methylprednisolone, belatacept, and prednisone.

The overall cardiac allograft ischemic time was 180.46 min (95% CI 170.48–190.44, p = 0.01), and the overall kidney allograft ischemic time was 11.68 h (95% CI 7.87–15.48, p < 0.01). The studies did not define clearly how ischemic time was assessed and did not specify the difference between cold and warm ischemic time.

After transplantation, the mean ICU length of stay was 14.19 days (95% CI 1.87–26.51, p < 0.01). The rates of infection and sepsis were, respectively, 31% (95% CI 14–48, p < 0.01) and 12% (95% CI 7–17, p = 0.48). Delayed graft function for kidney transplantation (KTx) was presented by 33% of the patients (95% CI 20–46, p = 0.01), and in the hospital, mortality was 16% (95% CI 11–21, p = 0.17). Although not all the studies clarify the definition of how they assessed the early kidney graft function, the delayed graft function definition included requiring more than one hemodialysis. Subsequently, kidney function could be assessed by analyzing serum creatinine, eGFR, and creatinine clearance, and exclusion of any kind of rejection by biopsy. The heart graft function was reported as evaluated with the use of echography.

Long-Term Variables

After a mean follow-up period of 67.49 months (95% CI 45.64–89.33, p < 0.01), serum creatinine was 1.50 mg/dL (95% CI 1.37–1.62, p = 0.16). Overall a cardiac allograft rejection episode was reported in 17% (95% CI 12–23, p = 0.21) of the patients (**Figure 2**), and a renal allograft rejection episode was also reported in 13% (95% CI 7–18, p = 0.38) of the patients (**Figure 3**). A simultaneous rejection episode of both organs' allografts was described in 1 case by Col et al [11] and in 4 cases by

TABLE 1 | Study characteristics and quality assessment.

Title	Type of study	Author and year	Institution	Country	Study date	Number of patients	New-Castle Ottawa Score (0–9)
Combined heart and kidney transplantation using a single donor: a single left's experience with nine cases	Retrospective cohort	Kocher et al. 1998	University of Vienna	Austria	1990–1997	9	6
Combined heart-kidney transplantation: report on six cases	Retrospective cohort	Col et al. 1998	University of Louvain Medical School	Belgium	1986–1995	6	8
Simultaneous Heart and Kidney Transplantation in Patients with End-stage Heart and Renal Failure	Retrospective cohort	Leeser et al. 2001	Temple University Hospital	United States	1990–1999	13	8
Short- and long-term outcomes of combined cardiac and renal transplantation with allografts from a single donor	Retrospective cohort	Luckraz et al. 2002	Papworth Hospital	United Kingdom	1986–2002	13	8
Freedom From Graft Vessel Disease in Heart and Combined Heart- and Kidney-transplanted Patients Treated With Tacrolimus-based Immunosuppression	Retrospective cohort	Groetzner et al. 2005	Ludwig Maximilians University Hospital Grosshadern	Germany	1995–2003	13	6
Combined Heart–Kidney Transplantation: The University of Wisconsin Experience	Retrospective cohort	Hermsen et al. 2007	University of Wisconsin School of Medicine and Public Health	United States	1999–2006	19	7
Effect of simultaneous kidney transplantation on heart-transplantation outcome in recipients with preoperative renal dysfunction	Retrospective cohort	Hsu et al. 2009	National Taiwan University Hospital	Taiwan	1993–2006	13	8
Combined Heart and Kidney Transplantation: Long-Term Analysis of Renal Function and Major Adverse Events at 20 Years	Retrospective cohort	Bruschi et al. 2010	Niguarda Ca' Granda Hospital	Italy	1989–2009	9	8
Outcomes of simultaneous heart–kidney and lung–kidney transplantations: the Australian and New Zealand experience	Retrospective cohort	Ruderman et al. 2015	4 centres across Australia and New Zealand	Australia, New Zealand	1990–2014	35	7
Combined cardiorenal transplant in heart and advanced renal disease	Retrospective cohort	Lastras et al. 2015	Hospital Universitario Fundación Favaloro	Argentina	2006–2014	20	8
Clinical Characteristics and Long-Term Outcomes of Patients Undergoing Combined Heart-Kidney Transplantation: A Single-Center Experience	Retrospective cohort	López-Sainz et al. 2015	Complejo Hospitalario Universitario A Coruña	Spain	1995–2013	22	8
Combined Heart and Kidney Transplantation: Clinical Experience in 100 Consecutive Patients	Retrospective cohort	Awad et al. 2018	Cedars-Sinai Medical Center	United States	1992–2016	100	8
Renal outcome after simultaneous heart and kidney transplantation	Retrospective cohort	Toinet et al. 2019	8 French academic lefts	France	1998–2017	73	8
Simultaneous heart-kidney transplantation results in respectable long-term outcome but a high rate of early kidney graft loss in high-risk recipients—a European single left analysis	Retrospective cohort	Beetz et al. 2021	Hannover Medical School	Germany	1987–2019	27	8
Combined Heart and Kidney Transplantation: Initial Clinical Experience	Retrospective cohort	Atik et al. 2022	Instituto de Cardiologia do Distrito Federal	Brazil	2007–2019	4	8

Groetzner et al [14]. Allograft rejection episodes were defined after performing a renal or endomyocardial biopsy in the majority of the included studies. Overall patient survival rates of 30 days, 1-, 3-, and 5-years were, respectively: 95% (95% CI 88–100, $p = 0.78$), 81% (95% CI 76–86, $p = 0.45$), 79% (95% CI 71–87, $p = 0.12$), and 71% (95% CI 59–83, $p < 0.01$). The survival

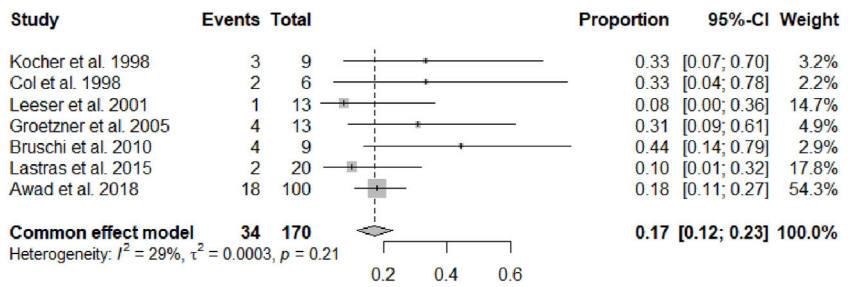

FIGURE 2 | Forest plot representing the pooled occurrence of cardiac allograft rejection episode.

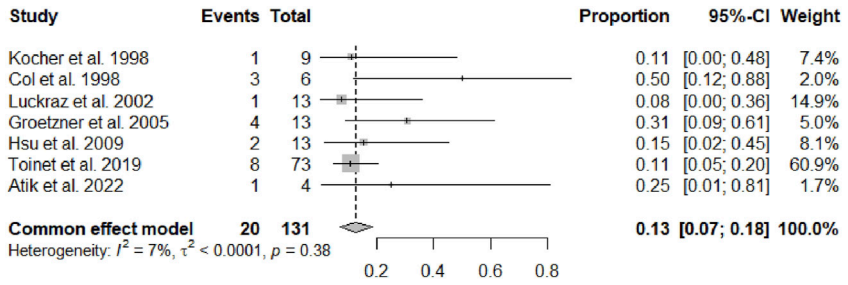

FIGURE 3 | Forest plot representing the pooled occurrence of kidney allograft rejection episode.

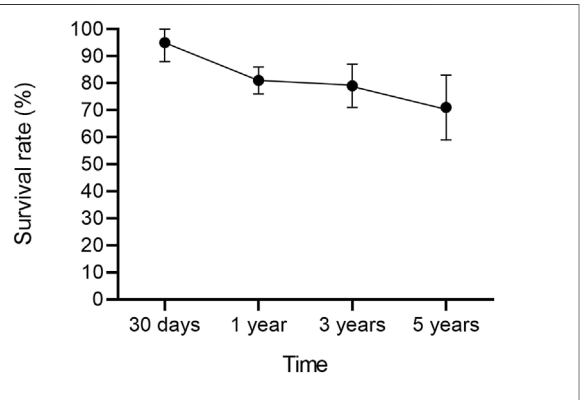

FIGURE 4 | Overall survival analysis after sHKTx with 95% CI.

analysis is presented in **Figure 4**. We could not assess the specific allograft survival because of the lack of report of this information in the included studies. The patient and cardiac survival were equivalent, but the data did not describe kidney transplant survival.

DISCUSSION

Multi-organ transplantation is a lifesaving surgical procedure for patients with multiple organ failure and is a therapeutic option for select patients who may otherwise not survive [25, 26]. Based on the obtained results and discussion, despite its major technical and logistical challenges, we have formulated the hypothesis that this procedure delivers acceptable mortality and rejection rates. The significance of these findings lies in the fact that patients suffering from end-stage heart disease, who undergo HTx, can experience concurrent kidney insufficiency. As a consequence, their outcomes are generally unfavorable if they only receive an HTx, thereby emphasizing the need to consider KTx for these individuals, which highlights the need for studies focusing on understanding sHKTx indications and outcomes.

Although sHKTx has very scarce data in the literature, United Network for Organ Sharing (UNOS) data has shown that the number of patients on the waiting list for this procedure has progressively increased over the years [27, 28]. Our study met the recommendation of donor age to be younger than 45 years proposed by The International Society for Heart and Lung Transplantation (ISHLT) Guidelines for the Care of Heart Transplant Recipients in 2022 [29], as the mean donor age was found to be 32.97 years. However, two included studies [12, 23] described no association between donor age and better outcomes after HKTx ($p < 0.01$). In the consensus conference on sHKTx that took place on June 1, 2019, in Boston, Massachusetts, the discussion of adopting possible age cutoffs on sHKTx donors and recipients was not supported due to ethical principles [4].

Regarding the etiology of organ failure, a previous study based on the UNOS platform [30] reported ischemic cardiomyopathy (35%) and diabetes mellitus (15%) as the leading etiologies of heart and kidney failure, respectively. The results of this previous analysis are comparable with ours concerning heart failure etiology, as the main etiology for this disease was found to be ischemic cardiomyopathy in 47% of the patients included in our

analysis. Although diabetes was found to be the main cause of renal failure in this previous study [30], diabetes-related kidney failure accounts for only 7% of kidney failure etiologies in our cohort, and the main etiology for this organ failure was the cardiorenal syndrome. In this syndrome, severe heart failure leads to decreased kidney perfusion and venous congestion, which consequently leads to reduced eGFR and a rise in serum creatinine [4], resulting in a cascade of feedback mechanisms that causes damage to both the organs and is associated with adverse clinical outcomes [31]. Our result is interesting because, although considered reversible, the cardiorenal syndrome was found to be the leading etiology of kidney failure in our cohort. However, regardless of the etiology of organ failure, current evidence supports the need to focus on measuring the kidney and heart function before sHKTx [15, 19, 21, 22, 32].

Pre-transplant dialysis dependence was significantly different between our analysis, which found a high prevalence of pre-transplant dialysis dependence of 71% of the patients, and the UNOS analysis [28] which registered a percentage of 40.2%. In this context, even though the dependence and the time on dialysis could not be fully assessed in the studies due to a lack of data, the pre-transplant dialysis dependence duration may be the best clinical index when determining who should be on the sHKTx transplant list [33, 34]. Patients whose hemodialysis started earlier at a higher eGFR (eGFR >10.5 mL/min per 1.73 m^2) are associated with more comorbidities (hypertension and diabetes), malnutrition (serum albumin lower than 3.5 g/dL), and risk of death [31]. According to the Notice of the Organ Procurement and Transplantation Network (OPTN) Policy Change for Heart-Kidney transplant allocation of 2023 [29], candidates for transplant with CKD, eGFR less than or equal to 60 mL/min for more than 90 consecutive days, and regularly administered dialysis are acceptable for sHKTx.

In our perioperative analysis, attention was given to the allograft ischemic time in sHKTx (p = 0.01), as shorter renal cold ischemic times have been previously proposed as a reason for high long-term graft survival after this procedure [35, 36]. The kidney can be safely transplanted as soon as the heart function is restored, and as quickly as possible [11]. In our analysis, the kidney and heart cold ischemic time was documented in seven studies ($p < 0.01$), with the mean value of heart cold ischemic time of 183.2 min [10, 11, 15–17, 19, 22], and the mean value of kidney cold ischemic time of 11.68 h [10, 11, 15, 17, 19, 22, 23] ($p < 0.001$). It is known that the heart and kidney have different acceptable cold ischemic times without damage, but the increased time can lead to acute rejection, graft loss, and delayed graft function [37–41]. To avoid this complication, the included studies adopted different strategies to reach the lowest overall ischemic time possible, for example, donors were transferred to the same hospital as recipients to reduce heart ischemic time [16, 24]. However, these single-center studies did not assess the significance of the association between cold or warm ischemic time and sHKTx outcomes.

To prevent injury and improve graft function and surgical long-term outcomes, Machine Perfusion (MP) may be used when longer allograft kidney cold ischemic time is anticipated [42]. In our study, we could not determine the impact of MP on patients who had undergone sHKTx. It is important to recognize the many variables that are related to MP, such as the machine type and perfusion time on the machine, which can affect the transplantation outcome [42–49].

In the postoperative analysis, delayed graft function was significant in 8 studies (n = 167 patients), with approximately 33% occurrence. Although sHKTx has an outcome of acceptable delayed graft function [1], previous literature shows no significant difference in patient survival between HTx and sKHTx associated with delayed graft function [15, 19, 22, 23].

Our rejection analysis is in agreement with previous literature that reported in the early days a reduced rejection rate associated with combined transplantation [50], possibly due to an immunoprotective effect of kidney transplantation on the heart allograft [51]. This finding can be explained by the different immunosuppressive strategies that were adopted [14] and their efficacy. For that, although we were not able to analyze the relationship between the immunosuppressive strategies with sHKTx outcomes in our study, we recommend further investigation of this subject [4].

The sHKTx presented a survival rate of 81% at 1 year and 71% at 5 years in our analysis. These results are only slightly lower than the 1-year and 5-year survival rates of HTx alone, which are 84.5% and 72.5%, according to recent data from the registry of the International Society of Heart and Lung Transplantation [52]. Our 5-year survival analysis of this group of studies shows a significant variation (I2 = 69%), which the increased technical complexity of sHKTx could explain, the lack of standardized multiorgan transplantation eligibility criteria across institutions, and the lack of nationwide policies to regulate this procedure [4], that potentially leads to decreased survival rates in the current transplantation era [53].

The limitations of this study include the impossible calculation of pooled pre-transplant eGFR due to the lack of reporting of this parameter in the included studies of our cohort, which mostly reported pre-operative serum creatinine as a parameter of kidney function. For these patients who are not on dialysis, it represents a limitation because eGFR is the best overall index of kidney function [54], and the adoption of serum creatinine to estimate eGFR is not precise [55], potentially leading to the overdiagnosis of chronic kidney disease. We highlight the need for the report of eGFR in a retrospective cohort study about sHKTx, so future studies could understand how this parameter affects sHKTx outcomes.

This study has other limitations since not all the centers included in this analysis used the same patient and donor selection criteria or adopted the same sHKTx techniques and immunosuppressive regimens, so our results must be interpreted carefully. Despite a lack of granularity due to inconsistent data reports in the literature, this study stands out for its comprehensive synthesis of existing research and potential guidance to future studies and valuable insights after identifying gaps in the literature.

Also, our meta-analysis has challenges with the studies' heterogeneity and the lack of clarity in variables such as the types of organs used. Regardless of these limitations, this is an important analysis to be conducted in the current literature to discuss HKTx indications and outcomes, which may help to guide future clinical practice. This study includes a 33-year period of

literature analysis, with significant temporal and regional policy differences, consisting in limitations and unique strengths for this study, since there are clinical experiences from the 1980s up to the present time and so reflect many of the advances in both the surgical and medical management of these high-risk patients.

CONCLUSION

sHKTx appears as an effective option for simultaneous end-stage cardiac and renal failure treatment, as it presents acceptable rejection and survival rates. However, further investigation is warranted to ascertain the specific patient population that would benefit the most from this procedure. We encourage future meticulous studies on this theme, with extended data reported. Additionally, global policies should be established to fortify the implementation of sHKTx and improve its outcomes. Nonetheless, it will be important to determine the physiological characteristics that may lead to renal recovery after Acute Kidney Injury (AKI) related to the cardiorenal syndrome.

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

NS, MF, LV, CT, GL, and SV participated in the design, interpretation of the studies, and analysis of the data and wrote the first manuscript; GB and AM reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.12750/full#supplementary-material

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Outcomes of Lung Transplantation in Patients With Right Ventricular Dysfunction: A Single-Center Retrospective Analysis Comparing ECMO Configurations in a Bridge-to-Transplant Setting

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This study aimed to assess the lung transplantation (LT) outcomes of patients with right ventricular dysfunction (RVD), focusing on the impact of various extracorporeal membrane oxygenation (ECMO) configurations. We included adult patients who underwent LT with ECMO as a bridge-to-transplant from 2011 to 2021 at a single center. Among patients with RVD ($n = 67$), veno-venous (V-V) ECMO was initially applied in 79% (53/67) and maintained until LT in 52% (35/67). Due to the worsening of RVD, the configuration was changed from V-V ECMO to veno-arterial (V-A) ECMO or a right ventricular assist device with an oxygenator (Oxy-RVAD) in 34% (18/67). They showed that lactic acid levels (2–6.1 mmol/L) and vasoactive inotropic score (6.6–22.6) increased. V-A ECMO or Oxy-RVAD was initiated and maintained until LT in 21% (14/67) of cases. There was no significant difference in the survival rates among the three configuration groups (V-V ECMO vs. configuration changed vs. V-A ECMO/Oxy-RVAD). Our findings suggest that the choice of ECMO configuration for LT candidates with RVD should be determined by the patient's current hemodynamic status. Vital sign stability supports the use of V-V ECMO, while increasing lactic acid levels and vasopressor needs may require a switch to V-A ECMO or Oxy-RVAD.

Keywords: lung transplant, ECMO, right ventricular dysfunction, bridge to transplant, survival outcomes

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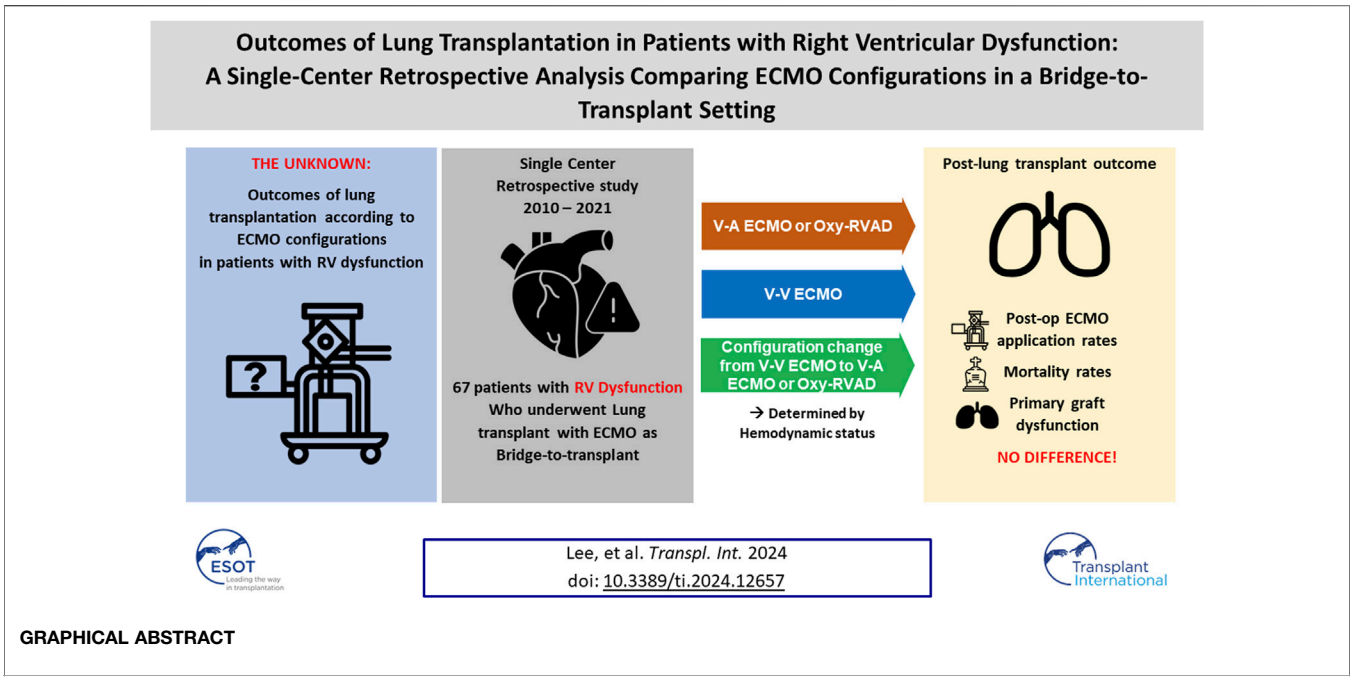
INTRODUCTION

Lung transplantation has become the standard treatment for end-stage lung disease [1]. Many patients awaiting lung transplantation develop right ventricular (RV) dysfunction due to pulmonary hypertension, a consequence of their disease's progression. Secondary pulmonary hypertension is present in up to 66% of patients with end-stage pulmonary disease, particularly reaching up to 84% in patients with idiopathic pulmonary fibrosis [2, 3]. The 2021 guidelines from the International Society for Heart and Lung Transplant recommend listing patients for lung transplantation when they show signs of pulmonary hypertension or RV failure, as these conditions are associated with poorer outcomes [4]. RV systolic dysfunction is also recognized as a risk factor for mortality in patients



GRAPHICAL ABSTRACT

using extracorporeal membrane oxygenation (ECMO) as a bridge to transplantation (BTT) [5]. Therefore, recognizing and managing patients with RV dysfunction effectively is important, placing a special focus on maintaining appropriate volume and hemodynamic support [6].

Mechanical circulatory support strategies while awaiting lung transplantation may differ between patients with end-stage lung disease with secondary pulmonary hypertension and primary pulmonary hypertension based on the severity of their pulmonary failure and cardiac dysfunction [6, 7]. In 2022, the American Association for Thoracic Surgery (AATS) published an expert consensus document on the use of mechanical circulatory support in lung transplantation [8]. According to this consensus, veno-arterial (V-A) ECMO can be a valuable option as a BTT for end-stage pulmonary hypertension with RV failure. However, not all the patients with RV dysfunction were on V-A ECMO at the time of the first ECMO initiation. Research comparing the outcomes of different ECMO configurations in patients with RV dysfunction is limited, and there is no established study on when to initiate V-A ECMO. Also, it is well reported that V-A ECMO can present more complications than V-V ECMO, including a heightened risk of bleeding issues such as surgical site, abdominal, and retroperitoneal hemorrhages, as well as potentially devastating complications, such as systemic thromboembolism-related neurological complications, and limb ischemia [9, 10]. Therefore, the present study aimed to (1) evaluate the lung transplantation outcomes of BTT patients with RV dysfunction, focusing on their specific ECMO configurations, and (2) identify characteristics including timing, lactic acid levels, and vasoactive inotropic doses when initiating V-A ECMO or RV assist devices with an oxygenator (Oxy-RVAD) in patients with RV dysfunction.

MATERIALS AND METHODS

Study Patients and Designs

This retrospective cohort study was conducted at a single-center tertiary hospital in Korea. Among the adult patients (age >18 years) who underwent lung transplantation between 2011 and 2021, those with ECMO as BTT were enrolled in the present study (**Figure 1**). We excluded patients with left ventricular (LV) dysfunction or dilated cardiomyopathy (DCMP) and those who underwent retransplantation due to acute rejection. In all patients, we reviewed the results of preoperative transthoracic echocardiography (TTE) conducted nearest to the date of lung transplantation, and data on RV dysfunction by the official note of cardiologists were collected. RV systolic dysfunction was assessed according to the guidelines of the American Society of Echocardiography [11, 12]. Visual assessment of free wall contractility was performed in all patients, and parameters such as fractional area change (FAC) < 35%, tricuspid annular plane systolic excursion (TAPSE) < 16 mm, tissue Doppler-derived tricuspid lateral annular systolic velocity (S') < 10 cm/s, right ventricular index of myocardial performance (RIMP) > 0.4 by pulsed Doppler, and >0.55 by tissue Doppler were used to define RV dysfunction.

ECMO Strategies in Lung Transplant Candidates

Due to the shortage of lung donors in South Korea, many patients undergo lung transplantation in status 0, which refers to patients on mechanical ventilation or ECMO [13, 14]. When patients on the waiting list develop respiratory failure, they are intubated, started on mechanical ventilation, and uplisted to status 0. If

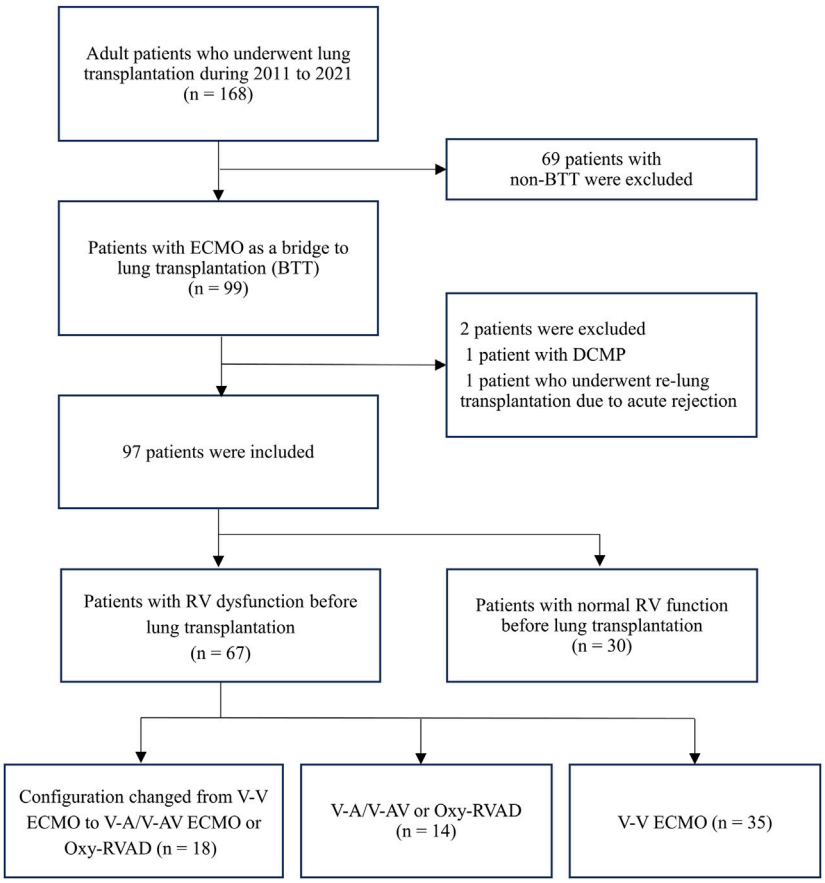


FIGURE 1 | Diagram of patient inclusion flow Abbreviations: ECMO, extracorporeal membrane oxygenation; DCMP, dilated cardiomyopathy; RV, right ventricular; V-V, Veno-venous; V-A, Veno-arterial; V-AV, Veno-arteriovenous; Oxy-RVAD, right ventricular assist device with and oxygenator.

oxygenation and ventilation cannot be maintained by mechanical ventilation alone, and if patients are hemodynamically stable, V-V ECMO is then used [9]. In our center, the right femoral-right internal jugular vein was mainly selected for V-V ECMO configuration. Intensive care physicians routinely performed focused cardiac ultrasound [15], and monitored cardiac enzymes and BNP levels regularly from the time patients were admitted to the intensive care unit (ICU). If patients were hemodynamically unstable with lactic acid levels greater than 4 mmol/L or norepinephrine levels greater than 0.2 mcg/kg/min (or equivalent doses of epinephrine or dobutamine), V-A/V-AV ECMO or Oxy-RVAD was considered after a multidisciplinary team review. While the femoral vein and femoral arterial cannula were usually used in V-A ECMO, an additional femoral arterial cannula was inserted to change the configuration from V-V ECMO to V-AV ECMO. For Oxy-RVAD, a left anterior thoracotomy was performed to place the reinfusion cannula in the pulmonary artery. A bolus of unfractionated heparin (50–70 units/kg) was infused at the start of ECMO support, and heparin was continuously infused to achieve an activated partial thromboplastin time of 40–60 s during V-V ECMO support and 50–75 s during V-A ECMO support. Once patients achieve hemodynamic stabilization, preoperative rehabilitation begins with both mechanical ventilation with early tracheostomy and ECMO support [16]. A few patients underwent lung transplantation as awakening ECMO. If patients with V-V ECMO experienced hemodynamic instability during rehabilitation, the configuration was changed to Oxy-RVAD or V-A/V-AV ECMO. When peripheral V-A ECMO or V-AV ECMO impeded rehabilitation due to cannula position, conversion to central V-A ECMO or Oxy-RVAD was considered [17, 18]. Postoperative ECMO has been used in patients with unstable vital signs or hypoxemia at the end of surgery [6].

Data Collection

We collected the following patient data from the electronic medical records: age, sex, ABO types, height, weight, body mass index (BMI), underlying disease, date of lung transplantation, dates of hospital and ICU admission and discharge, date of death, status of preoperative rehabilitation; TTE results before lung transplantation: left ventricular ejection fraction (LVEF), the ratio of early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity (E/E'), maximal

tricuspid regurgitation velocity (TR Vmax), systolic pressure gradient between the right ventricle and right atrium (RV-RA pressure gradient); Troponin-I, brain natriuretic peptide (BNP), simplified acute physiology score (SAPS) II at lung transplantation day, preoperative and postoperative vasopressor types and doses, dates of mechanical ventilation, date of tracheostomy, ECMO types and configurations, date of ECMO insertion, date of ECMO configuration change, date of ECMO discontinuation. Primary graft dysfunction (PGD) at the 72-h time point was recorded [19]. We reviewed complications during ECMO such as bleeding, ECMO pump clots, ECMO cannula site complications, and continuous renal replacement therapy. We defined "bleeding" as any bleeding site such as gastrointestinal, retroperitoneal, intracranial, tracheostomy site, cannula site, hemoptysis, hemothorax, etc., including major to minor bleeding [20]. We defined "ECMO cannula site complications" as ECMO catheter thrombosis, and wound complications such as wound infection. To quantify the severity of hemodynamic instability, this study measured the Vasoactive Inotropic Score and lactic acid. The vasoactive inotropic score (VIS), which is a weighted sum of all administered vasoactive inotropic agents [21], was calculated just before ECMO insertion, and ECMO change. The lactic acid levels were checked at the same time.

Statistical Analysis

Variables are presented either as means with standard deviations or medians with interquartile ranges, based on their distribution. The included patients were divided into the RV dysfunction group and the normal RV function group. Patients with RV dysfunction were further divided into three groups: 1) V-V ECMO maintenance, 2) configuration change from V-V ECMO to V-A/V-AV or Oxy-RVAD, and 3) V-A/V-AV ECMO or Oxy-RVAD maintenance group. Baseline characteristics and outcomes of patients were compared according to their RV function and ECMO configuration. In addition, VIS and lactic acid levels were compared between initial ECMO insertion and ECMO configuration change. For the comparison of continuous variables, we used the student's t-test. The chi-squared or Fisher's exact tests were chosen for categorical variables. Survival analyses were performed using the Kaplan–Meier method and the log-rank test. All p-values were two-tailed, with the threshold for statistical significance set at a p-value of <0.05. All statistical analyses and graphs were conducted using R 4.2.1 (R Core Team, Vienna, Austria).

Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the Institutional Review Board of our center (IRB number: 2019-0981, approval date: 2019-08-02), which waived the requirement for obtaining patient informed consent due to the observational nature of this study.

RESULTS

Ninety-seven patients who underwent lung transplantation with BTT between 2011 and 2021 were analyzed. Their median days from TTE to lung transplantation was 8 [0.5–15.5] days and most patients had a TTE test within a month from lung transplantation. Of the 97 patients with BTT, 69% (n = 67) had documented RV dysfunction and 31% (n = 30) had normal RV function prior to lung transplantation (**Figure 1**). Among patients with RV dysfunction (n = 67), 53 patients (79%) started V-V ECMO and 14 patients (21%) started V-A/V-AV ECMO or Oxy-RVAD. Thirty-five patients (52%) maintained V-V ECMO, and 18 patients (27%) switched from V-V ECMO to V-A/V-AV ECMO or Oxy-RVAD while awaiting lung transplantation.

Among the BTT patients (n = 97), their median age was 58 years and blood type A was the most common type (35.1%) (**Table 1**). Interstitial lung disease (ILD) patients were the most common (77.3%), and bleeding (39.2%) was the most common complication observed in patients with BTT. When the data between the groups with RV dysfunction and normal RV function were compared, preoperative TTE showed higher TR Vmax (3.4 ± 0.7 vs. 2.8 ± 0.5 m/s, $p < 0.001$) and higher RV-RA pressure gradient (49.0 ± 16.7 vs. 33.5 ± 11.6 mmHg, $p < 0.001$) in the RV dysfunction group. The lactic acid level (3.5 ± 3.3 vs. 2.1 ± 2.5 mmol/L, $p = 0.039$) and VIS (12.5 ± 16.7 vs. 4.9 ± 10.5, $p < 0.008$) at ECMO initiation were also higher in the RV dysfunction group than in the normal RV function group. When the date of lung transplantation, SAPS II was higher (35.7 ± 12.5 vs. 31.1 ± 6.9, $p = 0.022$) and BNP was also higher (537.3 ± 699.6 vs. 122.7 ± 147.5 pg/mL) in patients with RV dysfunction.

Among the BTT patients, 12 patients (12.4%) received ECMO after lung transplantation and patients stayed in the ICU for a median duration of 22 days after lung transplantation (**Table 2**). The 1-year, 3-year, and 5-year crude mortality rates were 21.6%, 33.3%, and 58.0%, respectively. When we compared the postoperative ECMO application rates and the grade and percentage of PGD, we did not observe significant differences according to the presence of RV dysfunction.

We compared the baseline characteristics of the patients grouped according to their ECMO configurations (**Table 3**). All idiopathic pulmonary arterial hypertension (PAH) patients were in the V-A/V-AV ECMO or Oxy-RVAD groups. The lactic acid level (8.2 ± 3.5 mmol/L) and VIS (32.7 ± 20.4) were significantly higher in the V-A/V-AV ECMO or Oxy-RVAD group at the initial ECMO insertion ($p < 0.001$ for each). The complication rate was the lowest (37.1%) in the V-V ECMO group and the highest (78.6%) in the V-A/V-AV or Oxy-RVAD group ($p = 0.029$). Preoperative ECMO duration was similar between the V-A/V-AV ECMO or Oxy-RVAD and configuration change groups (16 [13–30] vs. 17 [9–28]). The median duration from starting ECMO to changing the configuration was 7 days [4.3–62.0 days] in the configuration change group. BNP on the operative day (1,114.5 ± 1,133.0 pg/mL) was significantly higher in the V-A/V-AV ECMO or Oxy-RVAD group ($p = 0.001$).

Among the three ECMO configuration groups, there were no significant differences in the post-lung transplantation outcomes, including mortality rates, postoperative ECMO application rates, and the grade and percentage of PGD (**Table 4**). Survival analysis by Kaplan–Meier curve and log-

TABLE 1 | Characteristics of the patients with and without RV dysfunction before lung transplantation among bridge-to-transplant patients.

	Normal RV function (*n* = 30)	RV dysfunction (*n* = 67)	Total (*n* = 97)	*p*-value
Age, median [IQR]	56.5 [44.0; 63.0]	58.0 [49.0; 63.0]	58.0 [47.0; 63.0]	0.625
Male sex, n (%)	15 (50.0)	25 (37.3)	40 (41.2)	0.342
ABO types, n (%)				0.792
A	12 (40.0)	22 (32.8)	34 (35.1)	
B	7 (23.3)	20 (29.9)	27 (27.8)	
O	4 (13.3)	12 (17.9)	16 (16.5)	
AB	7 (23.3)	13 (19.4)	20 (20.6)	
BMI, kg/m^2, mean ± SD	21.5 ± 3.1	23.5 ± 4.5	22.9 ± 4.2	0.012
Diagnosis, n (%)				
ILD	24 (80.0)	51 (76.1)	75 (77.3)	0.598
BO	1 (3.3)	2 (3.0)	3 (3.1)	
ARDS	5 (16.7)	10 (14.9)	15 (15.5)	
PAH	0 (0.0)	4 (6.0)	4 (4.1)	
Preop rehabilitation, n (%)	22 (73.3)	52 (77.6)	74 (76.3)	0.842
Standing	10 (33.3)	23 (34.3)	33 (34.0)	0.505
Dangling	2 (6.7)	1 (1.5)	3 (3.1)	0.505
Bed exercise	10 (33.3)	28 (41.8)	38 (39.2)	0.505
Transthoracic echocardiography				
LVEF, %, mean ± SD	63.9 ± 6.4	60.6 ± 7.8	61.6 ± 7.5	0.046
E/E′, mean ± SD	8.9 ± 1.4	8.8 ± 3.6	8.9 ± 3.1	0.916
TR Vmax, m/s, mean ± SD	2.8 ± 0.5	3.4 ± 0.7	3.2 ± 0.7	<0.001
PGsys(RV-RA), mmHg, mean ± SD	33.5 ± 11.6	49.0 ± 16.7	44.4 ± 16.8	<0.001
Lactic acid at ECMO insertion, mmol/L, mean ± SD	2.1 ± 2.5	3.5 ± 3.3	3.1 ± 3.1	0.039
VIS at ECMO insertion, mean ± SD	4.9 ± 10.5	12.5 ± 16.7	10.2 ± 15.4	0.008
Preop ECMO duration days, median [IQR]	12.5 [5.0; 22.0]	14.0 [6.5; 27.0]	13.0 [6.0; 24.0]	0.631
Complications during ECMO, (%)	12 (40.0)	34 (50.7)	46 (47.4)	0.447
Bleeding	12 (40.0)	26 (38.8)	38 (39.2)	1.000
ECMO pump clot	1 (3.3)	14 (20.9)	15 (15.5)	0.056
ECMO site complications	2 (6.7)	11 (16.4)	13 (13.4)	0.327
CRRT	0 (0.0)	9 (13.4)	9 (9.3)	0.084
SAPS II at operation day, mean ± SD	31.1 ± 6.9	35.7 ± 12.5	34.2 ± 11.2	0.022
BNP at operation day, pg/mL, mean ± SD	122.7 ± 147.5	537.3 ± 699.6	409.1 ± 616.5	<0.001
Troponin-I at operation day, ng/mL, mean ± SD	0.2 ± 0.6	0.4 ± 0.9	0.3 ± 0.8	0.209

Abbreviations: RV, right ventricular; BMI, body mass index; ILD, interstitial lung disease; BO, bronchiolitis obliterans; ARDS, acute respiratory distress syndrome; PAH, pulmonary arterial hypertension; LVEF, left ventricular ejection fraction; E/E', the ratio of early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity; TR, vmax, maximal tricuspid regurgitation velocity; PGsys(RV-RA), systolic pressure gradient between right ventricle and right atrium; ECMO, extracorporeal membrane oxygenation; VIS, vasoactive inotropic score; SAPS, the simplified acute physiology score; CRRT, continuous renal replacement therapy; SD, standard deviation; IQR, interquartile range.

TABLE 2 | Post-lung transplantation outcomes of the patients stratified based on RV dysfunction among bridge-to-transplant patients.

	Normal RV function (*n* = 30)	RV dysfunction (*n* = 67)	Total (*n* = 99)	*p*-value
Postop ECMO application, n (%)	5 (16.7)	7 (10.4)	12 (12.4)	0.599
Postop ECMO duration days, median [IQR]	4 [4.0; 5.0]	6.0 [3.5; 8.5]	4.5 [3.5; 6.0]	0.324
Postop ICU days, median [IQR]	23.0 [15.0; 36.0]	21.0 [12.0; 35.5]	22.0 [14.0; 36.0]	0.514
Postop hospital days, median [IQR]	88.0 [47.0; 137.0]	79.0 [47.0; 157.5]	82.0 [46.5; 150.0]	0.971
Discharge from hospital, n (%)	27 (90.0)	52 (77.6)	79 (81.4)	0.243
30-day vasoactive drug-free day, median [IQR]	26.0 [24.0; 28.0]	27.0 [22.0; 28.0]	27.0 [23.0; 28.0]	0.997
30-day ventilator-free day, median [IQR]	18.0 [0.0; 24.0]	16.0 [0.0; 24.0]	17.0 [0.0; 24.0]	0.782
30-day mortality, n (%)	2 (6.7)	4 (6.0)	6 (6.2)	1.000
90-day mortality, n (%)	2 (6.7)	8 (11.9)	10 (10.3)	0.668
1-year mortality, n (%)	4/30 (13.3)	17/67 (25.4)	21/97 (21.6)	0.287
3-year mortality, n (%)	4/18 (22.2)	20/54 (37.0)	24/72 (33.3)	0.386
5-year mortality, n (%)	5/10 (50.0)	24/40 (60.0)	29/50 (58.0)	0.830
PGD at T72, n (%)				0.274
Grade 0	15 (50.0)	39 (58.2)	54 (55.7)	
Grade 1	4 (13.3)	9 (13.4)	13 (13.4)	
Grade 2	4 (13.3)	13 (19.4)	17 (17.5)	
Grade 3	7 (23.3)	6 (9.0)	13 (13.4)	

Abbreviations: RV, right ventricular; ECMO, extracorporeal membrane oxygenation; PGD, at T72, primary graft dysfunction at 72-h time point; IQR, interquartile range.

TABLE 3 | Characteristics of patients according to the ECMO configurations before lung transplantation among bridge-to-transplant patients.

	Initial V-V ECMO (*n* = 53)		V-A ECMO or Oxy-RVAD maintained[b] (*n* = 14)	*p*-value
	V-V ECMO maintained (*n* = 35)	Configuration change to V-A/V-AV ECMO or Oxy-RVAD[a] (*n* = 18)		
Age, median [IQR]	60.0 [52.0; 63.0]	59.0 [47.0; 64.0]	58.0 [38.0; 61.0]	0.72
Male sex, n (%)	22 (62.9)	12 (66.7)	8 (57.1)	0.858
ABO types, n (%)				0.486
A	12 (34.3)	5 (27.8)	5 (35.7)	
B	11 (31.4)	4 (22.2)	5 (35.7)	
O	7 (20.0)	5 (27.8)	0 (0.0)	
AB	5 (14.3)	4 (22.2)	4 (28.6)	
BMI, kg/m^2, mean ± SD	23.4 ± 4.0	23.9 ± 4.1	23.3 ± 6.3	0.911
Diagnosis, n (%)				0.007
ILD	28 (80.0)	15 (83.3)	8 (57.1)	
BO	2 (5.7)	0 (0.0)	0 (0.0)	
ARDS	5 (14.3)	3 (16.7)	2 (14.3)	
PAH	0 (0.0)	0 (0.0)	4 (28.6)	
Preop rehabilitation, n (%)	26 (74.3)	13 (72.2)	13 (92.9)	0.302
Standing	14 (40.0)	7 (38.9)	2 (14.3)	0.076
Dangling	0 (0.0)	0 (0.0)	1 (7.1)	0.076
Bed exercise	12 (34.3)	6 (33.3)	10 (71.4)	0.076
Transthoracic echocardiography				
LVEF, %, mean ± SD	60.6 ± 7.4	58.3 ± 9.3	63.5 ± 6.0	0.199
E/E′, mean ± SD	7.8 ± 2.5	9.3 ± 4.2	10.9 ± 4.6	0.031
TR Vmax, m/s, mean ± SD	3.3 ± 0.7	3.5 ± 0.6	3.4 ± 0.7	0.785
PGsys (RV-RA), mmHg, mean ± SD	48.0 ± 17.0	49.1 ± 16.2	51.4 ± 17.8	0.842
Lactic acid at ECMO insertion, mmol/L, mean ± SD	2.5 ± 2.2	2.0 ± 0.8	8.2 ± 3.5	<0.000
Lactic acid at ECMO configuration change, mmol/L, mean ± SD	NA	6.1 ± 3.2	NA	NA
VIS at ECMO insertion, mean ± SD	7.5 ± 11.8	6.6 ± 7.4	32.7 ± 20.4	<0.000
VIS at ECMO configuration change, mmol/L, mean ± SD	NA	22.6 ± 19.0	NA	NA
Complications during ECMO, n (%)	13 (37.1)	10 (55.6)	11 (78.6)	0.029
Bleeding	9 (25.7)	8 (44.4)	9 (64.3)	0.037
ECMO pump clot	7 (20.0)	3 (16.7)	4 (28.6)	0.701
ECMO site complication	4 (11.4)	4 (22.2)	3 (21.4)	0.514
CRRT	2 (5.7)	2 (11.1)	5 (35.7)	0.02
Preop ECMO duration, days, median [IQR]	10.0 [3.5; 21.5]	17.0 [9.0; 28.0]	16.0 [13.0; 30.0]	0.09
Day to configuration change, median [IQR]	NA	7.0 [4.3; 62.0]	NA	NA
SAPS II at operation day, mean ± SD	35.6 ± 12.0	34.2 ± 12.3	37.9 ± 14.2	0.712
BNP at operation day, mean ± SD	305.9 ± 326.6	538.3 ± 565.9	1,114.5 ± 1,133.0	0.001
Troponin-I at operation day, mean ± SD	0.2 ± 0.3	0.6 ± 1.3	0.7 ± 1.2	0.153

Abbreviations: V-V, Veno-venous; V-A, Veno-arterial; V-AV, Veno-arteriovenous; Oxy-RVAD, right ventricular assist device with an oxygenator; ECMO, extracorporeal membrane oxygenation; RV, right ventricular; BMI, body mass index; ILD, interstitial lung disease; BO, bronchiolitis obliterans; ARDS, acute respiratory distress syndrome; PAH, pulmonary arterial hypertension; LVEF, left ventricular ejection fraction; E/E′, the ratio of early diastolic mitral inflow velocity to early diastolic mitral annular tissue velocity; TR, vmax, maximal tricuspid regurgitation velocity; PGsys(RV-RA), systolic pressure gradient between right ventricle and right atrium; VIS, vasoactive inotropic score; SAPS, the simplified acute physiology score; CRRT, continuous renal replacement therapy; SD, standard deviation; IQR, interquartile range; NA, not applicable.

[a]*Of the 18 patients in the configuration change group, 5 patients were switched to V-A/V-AV ECMO, and 13 patients were switched to Oxy-RVAD.*

[b]*Of the 14 patients in the initial V-A ECMO or Oxy-RVAD, group, 5 patients started V-A ECMO, and 9 patients started Oxy-RVAD.*

rank test showed that there was no difference in the 5-year survival rate between the V-V ECMO, V-A/V-AV ECMO or Oxy-RVAD, and configuration change groups (**Figure 2**).

In the configuration change group of V-V ECMO to V-A/V-AV ECMO or Oxy-RVAD groups, the lactic acid level and VIS were significantly different between the time of initial ECMO start and the time of ECMO configuration change (**Figure 3**; **Table 3**). The lactic acid level was 2.0 ± 0.8 mmol/L when starting V-V ECMO but it increased to 6.1 ± 3.2 mmol/L when the configuration was changed to V-A/V-AV ECMO or Oxy-RVAD ($p < 0.001$). The baseline VIS was also 6.6 ± 7.4 when V-V ECMO was started but it increased to 22.6 ± 19.0 when the configuration changed ($p = 0.009$).

DISCUSSION

In this study, we observed that among BTT patients who successfully underwent lung transplantation, 67% exhibited documented RV dysfunction. We compared the three groups of V-V ECMO, configuration changed from V-V ECMO to V-A ECMO or Oxy-RVAD, and V-A ECMO/Oxy-RVAD in RV

TABLE 4 | Post-lung transplantation outcomes of the patients stratified according to the ECMO configurations among bridge-to-transplant patients.

	Initial V-V ECMO (*n* = 53)		V-A ECMO or Oxy-RVAD maintained (*n* = 14)	*p*-value
	V-V ECMO maintained (*n* = 35)	Configuration change to V-A/V-AV ECMO or Oxy-RVAD (*n* = 18)		
Postop ECMO application, n (%)	3[a] (8.6)	1[b] (5.6)	3[c] (21.4)	0.302
Postop ICU days, median [IQR]	16.0 [12.0; 31.0]	27.0 [16.0; 48.0]	20.5 [11.0; 43.0]	0.335
Postop hospital days, median [IQR]	69.0 [45.0; 129.5]	85.5 [60.0; 199.0]	92.0 [37.0; 178.0]	0.483
Discharge from hospital n (%)	27 (77.1)	14 (77.8)	11 (78.6)	0.994
30-day vasoactive drug-free day, median [IQR]	27.0 [22.5; 28.0]	27.5 [21.0; 29.0]	27.0 [22.0; 28.0]	0.537
30-day ventilator-free day, median [IQR]	19.0 [6.0; 24.5]	12.0 [0.0; 22.0]	15.5 [0.0; 23.0]	0.534
30-day mortality, n (%)	2 (5.7)	1 (5.6)	1 (7.1)	0.978
90-day mortality, n (%)	5 (14.3)	1 (5.6)	2 (14.3)	0.621
1-year mortality, n (%)	10/35 (28.6)	4/18 (22.2)	3/14 (21.4)	0.819
3-year mortality, n (%)	12/34 (35.3)	5/12 (41.7)	3/8 (37.5)	0.925
5-year mortality, n (%)	15/25 (60.0)	6/8 (75.0)	3/7 (42.9)	0.448
PGD at T72, n (%)				0.886
Grade 0	21 (60.0)	10 (55.6)	8 (57.1)	
Grade 1	4 (11.4)	2 (11.1)	3 (21.4)	
Grade 2	69 (17.1)	5 (27.8)	2 (14.3)	
Grade 3	4 (11.4)	1 (5.6)	1 (7.1)	

Abbreviations: V-V, Veno-venous; V-A, Veno-arterial; V-AV, Veno-arteriovenous; Oxy-RVAD, right ventricular assist device with an oxygenator; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; PGD, at T72, primary graft dysfunction at 72 h time point.

[a]*Postoperative ECMO, duration in three patients was 3, 3, and 6 days.*

[b]*Postoperative ECMO, duration in one patient was 1 day.*

[c]*Postoperative ECMO duration in three patients was 6, 11, and 43 days.*

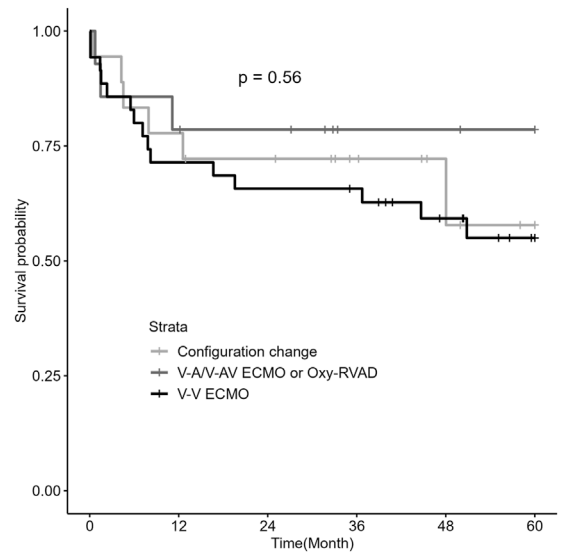


FIGURE 2 | Kaplan–Meier survival analysis by ECMO configurations in patients with RV dysfunction (*n* = 67) Abbreviations: ECMO, extracorporeal membrane oxygenation; RV, right ventricular; V-V, Veno-venous; V-A, Veno-arterial; V-AV, Veno-arteriovenous; Oxy-RVAD, right ventricular assist device with an oxygenator.

dysfunction patients. There was no significant difference in the survival rates and other clinical outcomes among the three ECMO configuration groups. Our results suggest that proper ECMO configurations and management are important for survival in patients with RV dysfunction.

In patients awaiting lung transplantation, management of RV dysfunction is very important because preoperative mortality in this group of patients has been reported to be very high if not adequately managed [18, 22]. Moreover, since RV dysfunction improves in most cases after lung transplantation [23, 24], achieving hemodynamic stability by mechanical circulatory support in the perioperative period is a very important issue. A previous study from a high-volume transplant center suggested initiating V-A ECMO rather than V-V ECMO in patients with secondary pulmonary hypertension [1]. In their study, initial V-A ECMO showed higher survival rates for transplantation than initial V-V ECMO [22]. Therefore, the current expert consensus document recommends V-A ECMO as a BTT in selected patients with end-stage pulmonary hypertension who develop right ventricular failure. However, unlike the existing study, in our cohort, V-V ECMO was initially applied in 79% (*n* = 53) of patients with RV dysfunction, and 52% (*n* = 35) of patients eventually underwent lung transplantation via V-V ECMO. Our results also showed no difference in the short- and long-term post-transplant outcomes in the V-V ECMO group compared with the V-A ECMO or Oxy-RVAD groups, although the complication rate was the lowest in the V-V ECMO group. Therefore, we believe that further larger studies are needed in this area.

In current recommendations for rehabilitation while awaiting with BTT, ambulation and rehabilitation should be aggressively pursued to improve bridge success rates and post-transplant outcomes [8]. In this study, the rate of preoperative rehabilitation, especially standing in V-V ECMO patients was not significantly different from that in other configuration

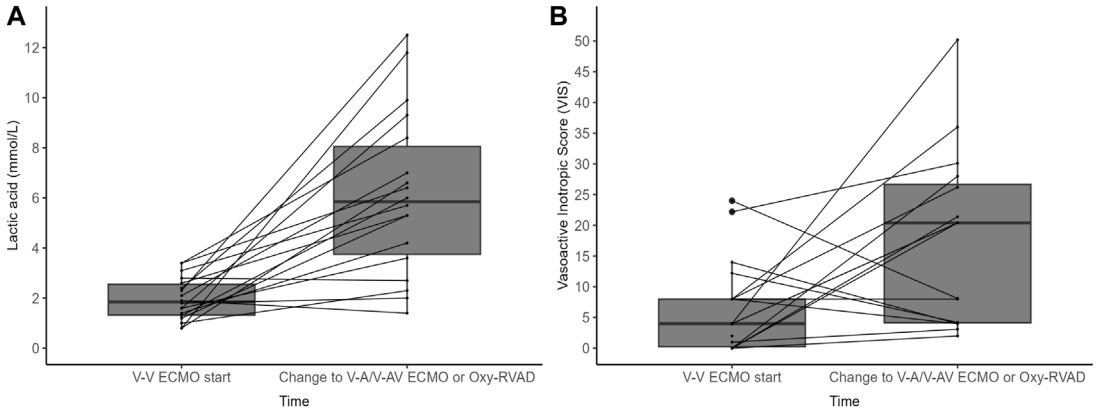


FIGURE 3 | (A) Lactic acid level and **(B)** vasoactive inotropic score (VIS) in the configuration change group (n = 18) Abbreviations: ECMO, extracorporeal membrane oxygenation; V-V, Veno-venous; V-A, Veno-arterial; V-AV, Veno-arteriovenous; Oxy-RVAD, right ventricular assist device with and oxygenator.

groups. This is because when patients with V-V ECMO could not tolerate standing and walking, we changed V-V ECMO to Oxy-RVAD or V-A ECMO to rehabilitate well [17, 18]. Conversely, in cases of hemodynamically stable and compensated RV dysfunction even during mobilization and rehabilitation, proceeding with lung transplantation via V-V ECMO does not affect the post-transplant outcomes. Successful lung transplantation is achieved using only low doses of vasoactive inotropic agents in this group of patients. Finally, our cohort showed similar short- and long-term survival outcomes regardless of ECMO configuration. We suggest that this is because early recognition and prompt adjustment of ECMO configuration in patients who experienced hemodynamic deterioration during V-V ECMO or were unable to tolerate early mobilization and rehabilitation allowed patients with RV dysfunction to survive and successfully undergo lung transplantation.

A noteworthy aspect of this study is the examination of the characteristics in the configuration change group that transitioned from initial V-V ECMO to V-A/V-AV ECMO or Oxy-RVAD. The median duration from V-V ECMO start to configuration change was 7 days. At the time of V-V ECMO insertion, the lactic acid level was 2 mmol/L, and the VIS was 6.6 (equivalent to norepinephrine 0.06 mcg/kg/min), which escalated to a lactic acid level of 6.1 mmol/L and a VIS of 22.6 (equivalent to norepinephrine 0.22 mcg/kg/min) before the configuration change. It is crucial for all BTT patients awaiting lung transplantation to undergo continuous hemodynamic monitoring via arterial line, periodic arterial blood gas analysis, and lactic acid tests to promptly detect any worsening of RV failure and progression to cardiogenic shock. Additionally, transitioning to Oxy-RVAD or V-A ECMO requires involvement from thoracic surgery and ECMO teams; hence, ongoing, close discussions among multidisciplinary teams, including intensivist, ECMO team, and thoracic surgery department, are essential. Failing to change the ECMO configuration in deteriorating hemodynamic situations could lead to progressive organ failure, inhibiting patients from undergoing lung transplantation and potentially leading to mortality.

High doses of vasoactive inotropes were required, and hyperlactatemia may reflect the onset of cardiogenic shock due to RV failure. Patients initially treated with V-A/V-AV ECMO or Oxy-RVAD had significantly higher pre-ECMO lactic acid levels of 8.2 ± 3.5 mmol/L and VIS of 32.7 ± 20.4 (equivalent to norepinephrine 0.33 mcg/kg/min) compared to the other groups. They also experienced the highest rates of bleeding and pump clots, and CRRT application during ECMO was most frequently observed. This suggests a likelihood of accompanying issues, such as DIC or acute kidney injury due to cardiogenic shock. The choice between Oxy-RVAD and V-A ECMO for patients with hemodynamic decompensated RV dysfunction is currently dependent on hospital or physician preference, although the application of Oxy-RVAD is increasing [16]. Oxy-RVAD, requiring left anterior thoracotomy for the placement of the reinfusion cannula in the pulmonary artery, is technically more complex than peripheral V-A ECMO, but it offers several advantages over V-A ECMO, such as enabling systemic circulation with oxygenated blood and showing fewer thromboembolic complications [6, 9]. It also facilitates rehabilitation similar to central V-A ECMO [6, 18, 25]. Hence, its use in patients awaiting lung transplantation is increasingly prevalent. A new device of percutaneous RVAD (Protek Duo, Tandemlife Pittsburgh, PA, United States) could also be a good option for BTT [26]. Further research is necessary regarding the choice between V-A ECMO and Oxy-RVAD in patients with hemodynamic decompensated RV dysfunction.

Limitations

There are several limitations to this study. First, not all RV parameters were measured. Because there were many parameters to define RV systolic dysfunction, not all parameters (TAPSE, tricuspid annulus DTI S′ velocity, FAC, and RIMP) were measured in each of the patients. However, the RV dysfunction used in our study was verified by a cardiologist

after the examination by a cardiac sonographer, lending credibility to the results. Second, this was a single-center study in a setting with a severe lung donor shortage. Many patients are transplanted in status 0 [13, 14]. As a result, the patients are already intubated and on mechanical ventilation due to respiratory failure, and their performance and rehabilitation status may be poorer than those of outpatients, potentially leading to higher long-term mortality rates post-lung transplantation.

In conclusion, in lung transplant candidates with RV dysfunction, the initial ECMO configuration should be determined based on the patients' current hemodynamic status, including lactic acid levels and the need for vasoactive inotropic support. Patients who maintain stable vital signs with low doses of vasoactive inotropes and low lactate levels even during rehabilitation can continue V-V ECMO until lung transplantation. However, even in patients who are initially stable, an increase in lactic acid levels and the need for vasoactive inotropes may need prompt consideration of a transition to V-A ECMO or Oxy-RVAD. Appropriate changes in ECMO configuration do not lead to an increase in mortality, highlighting the value of a clinically adaptive approach to ECMO management that is customized to each patient's clinical situation.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by the Institutional Review Board of Asan Medical Center (IRB number: 2019-0981, Approval date: 2019-08-02), which waived the requirement for obtaining patient informed consent due to the observational nature of this study. 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

SL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Writing–original draft. JA: Resources, Investigation, Validation, Writing–review and editing. HK: Resources, Investigation, Validation, Writing–review and editing. TS: Resources, Investigation, Validation, Writing–review and editing. P-JK: Resources, Investigation, Validation, Writing–review and editing. GL: Resources, Investigation, Validation, Writing–review and editing. SC: Resources, Investigation, Validation, Writing–review and editing. S-HJ: Resources, Investigation, Validation, Writing–review and editing. S-IP: Resources, Investigation, Validation, Writing–review and editing. S-BH: Conceptualization, Methodology, Resources, Investigation, Validation, Supervision, Writing–review and editing. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

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Pre-Transplant Frequencies of FoxP3$^+$CD25$^+$ in CD3$^+$CD8$^+$ T Cells as Potential Predictors for CMV in CMV-Intermediate Risk Kidney Transplant Recipients

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Cytomegalovirus (CMV) infection detrimentally influences graft survival in kidney transplant recipients, with the risk primarily determined by recipient and donor serostatus. However, recipient CD8$^+$ T cells play a crucial role in CMV control. The optimal preventive strategy (prophylaxis vs. pre-emptive treatment), particularly for seropositive (intermediate risk) recipients, remains uncertain. We investigated CD8$^+$ T cell subpopulation dynamics and CMV occurrence (DNAemia ≥ 100 IU/mL) in 65 kidney transplant recipients, collecting peripheral blood mononuclear cells before (T1) and 1 year after transplantation (T2). Comparing the two timepoints, we found an increase in granulocyte, monocyte and CD3$^+$CD8$^+$ T cells numbers, while FoxP3$^+$CD25$^+$, LAG-3$^+$ and PD-1$^+$ frequencies were reduced at T2. CMV DNAemia occurred in 33 recipients (55.8%) during the first year. Intermediate risk patients were disproportionally affected by posttransplant CMV (N = 29/45, 64.4%). Intermediate risk recipients developing CMV after transplantation exhibited lower leukocyte, monocyte, and granulocyte counts and higher FoxP3$^+$CD25$^+$ frequencies in CD3$^+$CD8$^+$ T cells pre-transplantation compared to patients staying CMV negative. Pre-transplant FoxP3$^+$CD25$^+$ in CD3$^+$CD8$^+$ T cells had the best discriminatory potential for CMV infection prediction within the first year after transplantation (AUC: 0.746). The FoxP3$^+$CD25$^+$ CD3$^+$CD8$^+$ T cell subset may aid in selecting intermediate risk kidney transplant recipients for CMV prophylaxis.

Keywords: kidney transplant, biomarker, cytomegalovirus management, immune cells, valganciclovir

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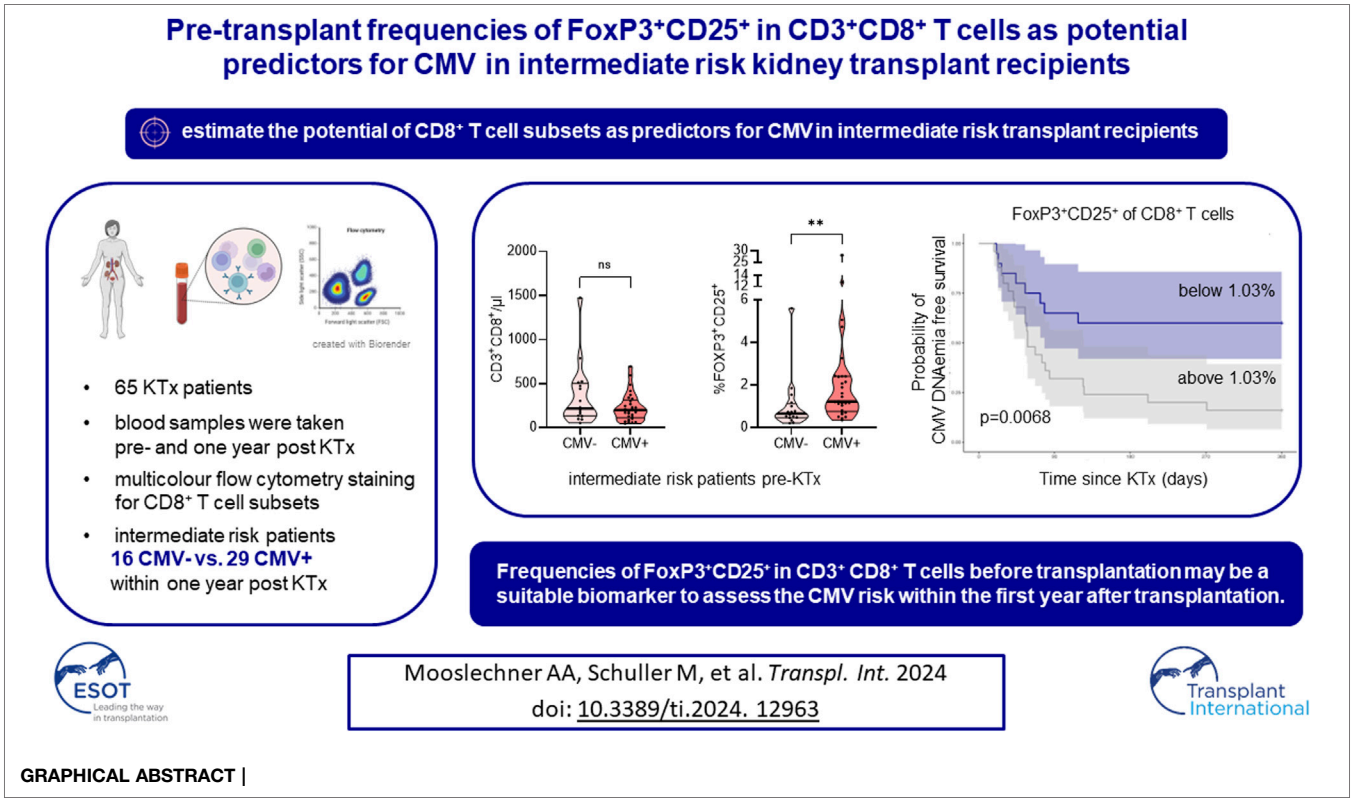

GRAPHICAL ABSTRACT |

INTRODUCTION

Cytomegalovirus (CMV) infection is a common complication in kidney transplant recipients (KTR). The disease spectrum encompasses asymptomatic replication to potentially life-threatening CMV disease, defined as end-organ affection or flu-like symptoms accompanied by fever and hematological abnormalities [1]. Furthermore, indirect effects of CMV include increased rates of transplant rejection, graft loss, and death [2–5].

Following often asymptomatic primary infection, CMV is not eliminated but remains a latent infection in non-hematopoietic cells. $CD8^+$ T cells are crucial for the control of primary infection and reactivation. Antiviral mechanisms of these cells include the production of cytokines and cytotoxic granules directed at infected cells [6]. However, subpopulations of $CD8^+$ T cells, including $FoxP3^+$ cells, are associated with suppressing cytotoxicity, potentially counteracting an efficient antiviral response [7]. CMV drives the terminal differentiation and expansion of $CD8^+$ T cells, leading to long-term changes in the composition of the $CD8^+$ T cell compartment [8].

CMV DNAemia may arise in immunosuppressed individuals [9], and the risk of posttransplant CMV is primarily dependent on the serostatus of the recipient (R) and the donor (D). While either R+/D+ or R+/D− are considered intermediate risk, R−/D+ are at high risk of CMV infection. R−/D− are at the lowest risk of posttransplant CMV [10, 11]. Other risk factors highlight the role of an intact immune system for CMV control and include T-cell depleting immunosuppression, high-dose mycophenolate mofetil (MMF) or mycophenolic acid (MPA), high-dose corticosteroids and lymphocytopenia [10, 11].

A preventive strategy is recommended for those who are at intermediate and high risk of CMV [1, 12]. Both antiviral chemoprophylaxis and preemptive treatment are viable options with different advantages and problems [1, 12]. Whereas prophylaxis is often complicated by post-prophylaxis CMV disease, the treatment threshold for CMV DNAemia is unknown [13]. The preemptive treatment approach requires frequent screening (preferably weekly) and poses a substantial logistic burden [14], while prophylaxis is more costly [15]. Moreover, valganciclovir prophylaxis harbors the risk of myelotoxicity [16, 17], potentially rendering transplant recipients vulnerable to breakthrough CMV and other infections.

Additionally, valganciclovir dosing is dependent on kidney function, and insufficient dosing can lead to breakthrough CMV [18]. Although prophylaxis and preemptive treatment have shown similar efficacy in preventing CMV disease and indirect CMV effects like rejection [19], many centers, including ours, employ a prophylactic strategy for high-risk recipients (R-/D+). Of note, an extended chemoprophylaxis for 200 days compared to 100 days in high-risk patients did not only lead to a reduction of CMV disease, but was also associated with fewer rejections and opportunistic infections [20]. For intermediate risk

constellation, considerable uncertainty regarding the optimal preventive strategy exists. Improved identification of vulnerable individuals would allow for personalized prophylaxis beyond CMV D and R serostatus.

In this study, we followed the dynamics of the peripheral immune cell composition of a cohort of kidney transplant recipients before transplantation and 1 year thereafter. We set a strong focus on the $CD8^+$ T cell compartment and its subpopulations associated with immunoregulatory functions (FoxP3), ageing (CD28), and exhaustion (LAG-3, PD-1). Intrigued by the interplay of CMV and $CD8^+$ T cells, we hypothesized that the pre-transplant peripheral $CD8^+$ T cell pool may harbor prognostic subsets for the susceptibility to CMV DNAemia post-transplantation.

MATERIALS AND METHODS

Study Design and Study Population

We screened 105 CKD G5 patients prior to transplantation, as previously described [21]. Briefly, adult (age ≥ 18 years) kidney transplant recipients without prevalent immunosuppression who received an organ from a deceased donor after obtaining written informed consent were included. Blood samples were drawn before the dialysis session before transplant surgery (T1) and 1 year after transplantation (T2). Only those with complete follow-up and intact graft at T2 were included in the final analysis.

The study protocol was approved by the Institutional Review Board of the Medical University of Graz, Austria (28- 514ex15/16). The study was registered as #DRKS00026238 in the German Register of Clinical Studies.

CMV Prophylaxis, Screening, and Treatment

According to local standards, individuals at high risk of CMV, including R+/D-constellation, following anti-thymocyte globulin (ATG) induction or ATG rejection treatment, were selected for 3 months of CMV prophylaxis with valganciclovir. The valganciclovir dose adjustment was performed as recommended in the package insert for impaired kidney function.

CMV positive (CMV+) individuals were defined as CMV PCR ≥ 100 international units (IU)/mL in EDTA-plasma at least once during the first posttransplant year measured by cobas® 5800 (Roche Holding, Basel, Switzerland) at the Diagnostic and Research Institute of Hygiene, Microbiology, and Environmental Medicine at the Medical University Graz. CMV PCR testing in peripheral blood was performed at every regular outpatient visit during the first year. Routine visit frequencies according to the local center standard are month 1—weekly, month 2–3—every 2–3 weeks, month 4–6—monthly, month 6–12—every 4–6 weeks. If clinically indicated, patients were checked more frequently including CMV PCR testing.

Those without any CMV PCR ≥ 100 IU/mL in the first year were defined as CMV negative (CMV−).

In case of CMV DNAemia with ≥ 100 IU/mL, potential strategies encompassed observation of viral replication, dose reduction or temporary discontinuation of MMF/MPA and/or the initiation of therapeutic dose valganciclovir. The selected strategy was subject to the discretion of the treating physician and was contingent upon the specific clinical circumstances. Antiviral treatment was administered until two consecutive PCR results showed < 100 IU/mL.

Duration of CMV positivity describes the interval between the first PCR result ≥ 100 IU/mL and the last PCR result ≥ 100 IU/mL. Any subsequent PCR with ≥ 100 IU/mL after the initial episode was defined as relapse. If there was a solitary PCR with ≥ 100 IU/mL, the duration of CMV positivity was designated as 1 day. The definition of CMV disease adhered to current recommendations [1]. The highest PCR measurement in IU/mL during the first year was designated as CMV peak.

PBMC Isolation and Flow Cytometry

Peripheral blood mononuclear cells (PBMC) were isolated at T1 and T2 as described previously [21]. Briefly, fresh heparinized whole blood samples were collected in BD vacutainer tubes containing lithium heparin (Becton Dickinson, Franklin Lakes, NJ, United States) and diluted at 1:1 ratio with phosphate-buffered saline (PBS), and then carefully layered into a tube preloaded with Lymphoprep density gradient media (Stemcell Technologies, Vancouver, Canada). Following a density gradient centrifugation process (20 min, 800 × g at room temperature), the PBMC layer was collected and subsequently washed with PBS. Viability and cell count were determined using an automated dual fluorescence cell counter (LUNA-FL, Logos Biosystems, Anyang, South Korea) prior to multi-parameter staining of 1×10^6 cells per fluorescence-activated cell sorting (FACS) panel. Additionally, 0.5×10^6 cells were designated for an unstained control. Furthermore, 50 µL of fresh whole blood was subjected to staining with anti-CD45 APC-H7 antibodies (Becton Dickinson), with the addition of 123 count eBeads (Thermo Fisher Scientific, Waltham, MA, United States) for analyzing absolute numbers of leukocyte subpopulations. Absolute cell numbers were calculated according to manufacturer's instructions. Absolute numbers of subpopulations were determined by multiplying the absolute counts of lymphocytes by the respective frequencies of each subpopulation relative to total lymphocytes.

BD Lyse/Fix buffer (Becton Dickinson) was used for surface panel staining according to the manufacturer's protocol. All antibodies were obtained from BD and details are summarized in **Supplementary Table S1**. Sample acquisition occurred on a four-laser BD FACS Fortessa SORP instrument (Becton Dickinson). Data analysis was performed using FlowJo software Version 10.10.0 (Becton Dickinson). Compensation utilized UltraComp eBeads (Thermo Fisher Scientific), and fluorescence minus one (FMO) controls were implemented. Our gating strategy is illustrated in **Supplementary Figures S1, S2**.

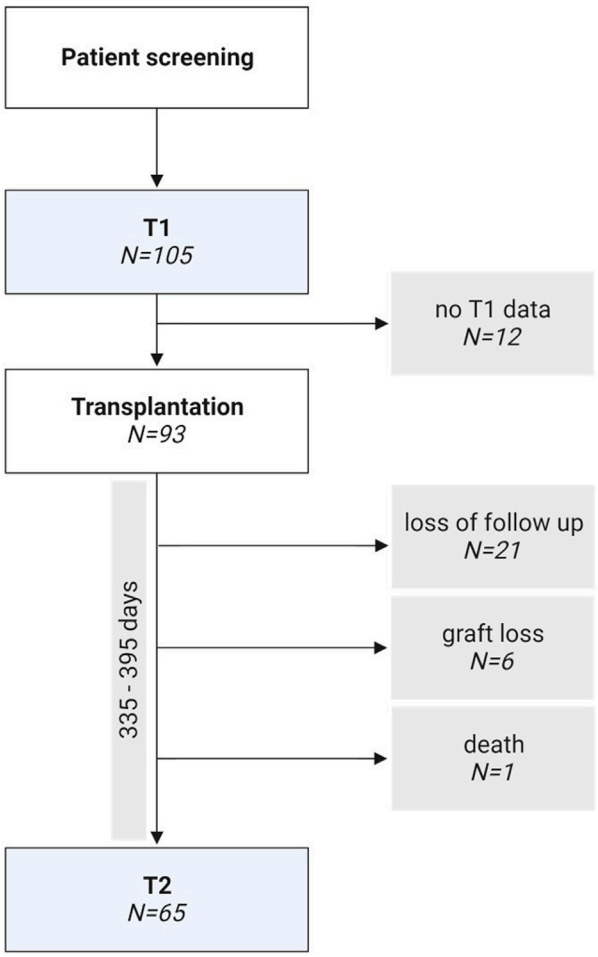

FIGURE 1 | Flow chart of the study design.

TABLE 1 | Descriptive statistics of KTRs with 1-year follow up.

N	**65**
Age (years)	56 (47–63.5)
Caucasian Ethnicity	59 (90.8)
Male gender	40 (61.5)
BMI (kg/m^2)	26.1 (21.8–29.3)
Preemptive	4 (6.2)
HD/PD	50/11 (76.9/16.9)
Diabetes mellitus	12 (18.5)
Donor Age (years)	55 (47.5–70.5)
ECD	35 (53.8)
HLA Mismatches	
0	2 (3.1)
1	4 (6.2)
2	4 (6.2)
3	15 (23.1)
4	30 (46.2)
5	10 (15.4)
6	0
Kidney disease	
Diabetes	11 (16.9)
Hypertensive	3 (4.6)
Glomerular	16 (24.6)
Cystic	11 (16.9)
Other	24 (36.9)
Immunosuppression	
ATG	7 (10.8)
BX	58 (89.2)
CS	65 (100)
CyA	1 (1.5)
Tac	64 (98.5)
MMF/MPA	64 (98.5)
AZA	1 (1.5)

Data are presented as median and IQR or absolute values and percentages, depending on the variable; BMI, body mass index; HD, hemodialysis; PD, peritoneal dialysis; ECD, extended criteria donor; ATG, anti-thymocyte globulin; BX, basiliximab; CS, corticosteroids; CyA, cyclosporin A; Tac, tacrolimus; MMF, mycophenolate mofetil; MPA, mycophenolic acid; AZA, azathioprine.

Statistical Analysis

Statistical analysis and graphical representations were done using Statistical Package for Social Sciences (SPSS v27, SPSS Inc., Chicago, IL, United States), GraphPad Prism 8.0.1 (GraphPad Software Inc., San Diego, CA, United States), and R Studio (Version 4.2.2, PBC, Boston, MA, United States). Normality was assessed by Kolmogorov-Smirnov test. Flow cytometry data are shown in violin plots and median and interquartile range (IQR) are indicated. For categorical data, absolute values and relative frequencies (%) are given. Differences between two independent groups were calculated with t-tests, Mann-Whitney U-tests, and χ^2-tests, as appropriate. Paired groups were compared using dependent t-test or Wilcoxon signed-rank test for normal and non-normal variables.

Receiver operating characteristics (ROC) curves and area under the receiver operating characteristic curves (area under the curve, AUC) were derived using *pROC* (v. 1.18.4) for R studio [22]. Youden indices were determined for each predictor variable, aiming to identify optimal cutoff points that maximize sensitivity and specificity. Positive predictive values (PPV) and negative predictive values (NPV) were calculated to assess the performance of each variable. DeLong method was used to calculate 95% confidence intervals for AUCs. Probability of CMV DNAemia was calculated with *survminer* (v. 0.4.9). Differences in CMV DNAemia free survival probability were assessed using log-rank test [23].

p-values below 0.05 were defined as significant without adjustment for multiple testing.

RESULTS

Study Population

One hundred and five prospective kidney transplant recipients met our inclusion criteria. Due to loss of follow-up, unavailable flow cytometric data, graft loss, and death, 40 patients had to be excluded, and 65 patients remained for the final analysis (**Figure 1**). Loss of follow-up was primarily due to patients leaving our center, thus not adhering to local standard-of-care including frequency of visits as well as flow cytometry evaluation 1 year after transplantation. Reasons for graft loss included severe

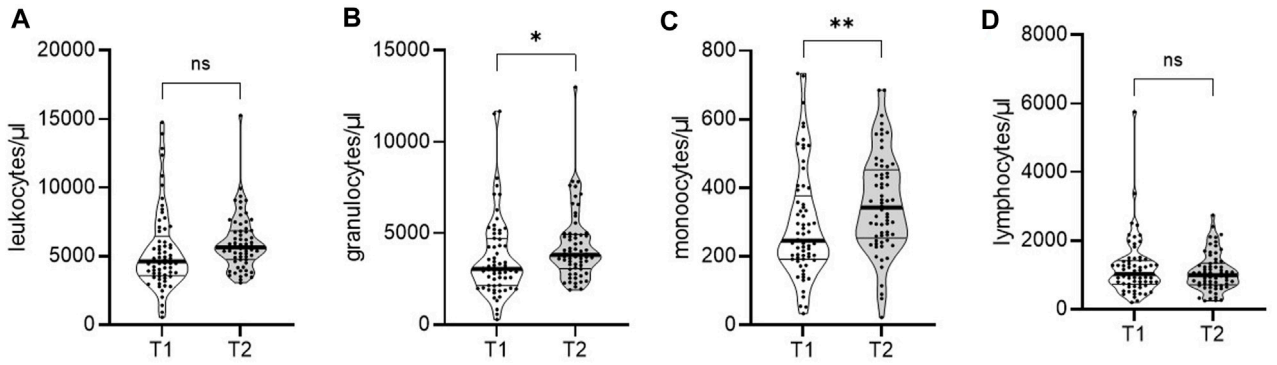

FIGURE 2 | Dynamics of immune cell populations in a cohort of end-stage kidney disease patients to 1-year post-transplant. Whole blood of 65 patients was analyzed by flow cytometry pre- (T1) and 1-year post-transplantation (T2). Violin plots show the data distribution of absolute numbers of **(A)** leukocytes, **(B)** granulocytes, **(C)** monocytes, and **(D)** lymphocytes. Each black dot represents data of one patient. All data are represented in median (heavy black line) and IQR (thin black line). Statistical analysis was calculated with Wilcoxon signed-rank test (*$p < 0.05$; **$p < 0.01$).

transplant rejection ($N = 4$), polyoma nephropathy ($N = 1$) and surgical complications ($N = 1$).

Demographic and baseline clinical data are summarized in **Table 1**. Induction therapy consisted of anti-thymocyte globulin (ATG) or basiliximab (BX), depending on the immunological risk [21]. This was followed by standard triple immunosuppression with tacrolimus (TAC), mycophenolate mofetil (MMF) or mycophenolic acid (MPA) and corticosteroids, apart from one individual who received cyclosporin A (CyA) instead of TAC, and another recipient, who did not tolerate MMF/MPA and was switched to azathioprine (AZA).

For CMV serostatus, 9 high-risk (R-/D+, 13.8%), 11 low-risk (R-/D-, 16.9%), and 45 intermediate risk (R+, 69.2%) patients were included.

Dynamics of Immune Cell Populations and CD8 Subpopulations in Pre- and 1-Year Post-Transplant Recipients

To study the effect of kidney transplantation on immune cell populations, we analyzed a cohort of CKD G5 patients before and 1-year after transplantation. Absolute leukocyte numbers were unchanged 1 year after transplantation (**Figure 2A**). However, absolute numbers of granulocytes and monocytes were significantly increased compared to pre-transplant (**Figures 2B, C**). Overall lymphocyte numbers were comparable at both time points (**Figure 2D**).

Next, we investigated the absolute $CD8^+$ T cell numbers and relative percentages of $CD8^+$ T cell subpopulations in kidney transplant recipients before and 1 year after transplantation. Overall, absolute numbers and percentages of $CD8^+$ T cells were increased 1 year after kidney transplantation (**Figures 3A, B**). Additionally, the composition in the $CD8^+$ T cell population changed after transplantation. Frequencies of $FoxP3^+CD25^+$ were decreased (**Figure 3C**), while frequencies of $CD28^-$ cells were increased (**Figure 3D**). Both the LAG-3^+ and PD-1^+ subpopulations were significantly decreased compared to pre-transplantation (**Figures 3E, F**).

Graft Function Is Reduced in Kidney Transplant Recipients After CMV Infection

We retrospectively investigated the incidence of CMV within our study cohort and found CMV replication defined as CMV PCR ≥ 100 IU/mL in 33 patients (50.7%) during the first year. Juxtaposition of CMV− and CMV+ individuals showed no difference in age, BMI, underlying kidney disease, or immunosuppressive treatment (**Table 2**). We observed a non-significant trend for women and non-Caucasians to be more frequently affected by CMV. Most strikingly, intermediate risk patients were particularly affected by CMV (87.9% intermediate risk patients in overall CMV+), while high-risk patients and prophylaxis were evenly distributed between both groups. Of note, rejection episodes were seen at similarly low frequencies in the CMV− and CMV+ groups (**Table 2**). Furthermore, donor age and extended criteria donors (ECD), as defined by Port et al. [24], were comparable between groups (**Table 2**).

Upon closer investigation of CMV positivity, we found that the median time to positivity was 57 days (28–82 days) after transplantation, and the median duration of CMV DNAemia was 6 days (1–23 days). Median CMV peak was 1500 IU/mL (490–4,950 IU/mL). Only 11 patients were symptomatic, while the majority remained asymptomatic. CMV treatment consisted of valganciclovir in 24 cases (72.7%). Concomitantly with antiviral treatment, antimetabolite dose was reduced in 18 patients (54.5%), or antimetabolite treatment was paused in three patients (9.1%) (**Table 3**). Nine patients (27.3%) were managed without antiviral treatment. CMV DNAemia in these patients was asymptomatic and was cleared either spontaneously ($N = 4$, 12.1%) or by reduction of immunosuppression alone ($N = 5$, 15.2%). CMV positivity in the setting of valganciclovir prophylaxis was observed in nine patients (27.3%). Four of those patients were at high-risk for CMV (12.1%). The other five KTRs received valganciclovir prophylaxis following treatment for acute rejection (15.2%). In four of these patients (12.1%) CMV developed as a breakthrough

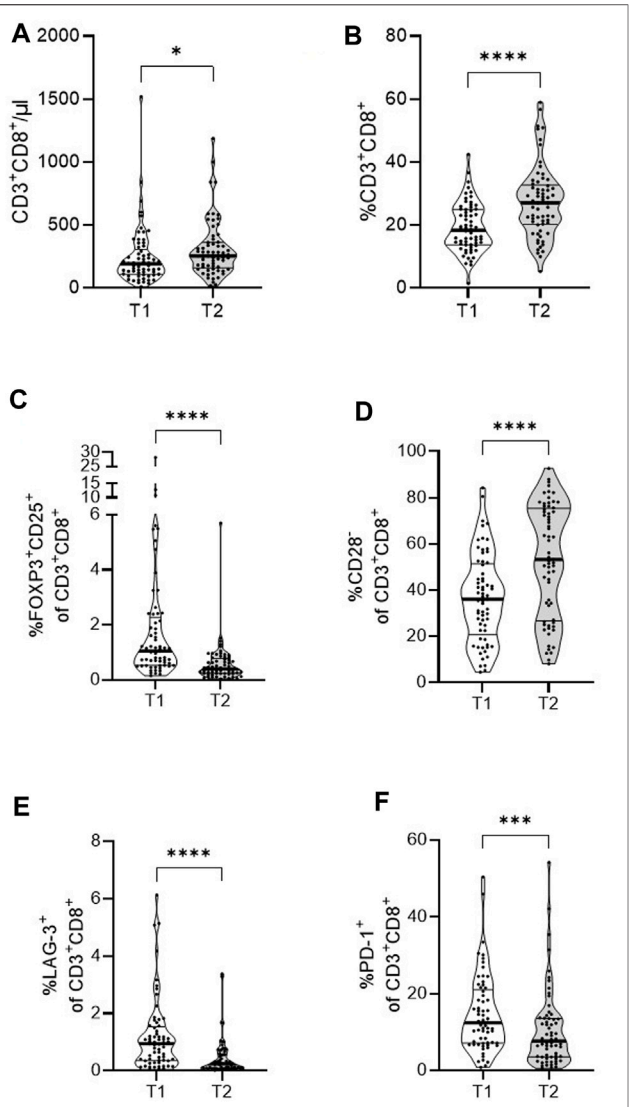

FIGURE 3 | Dynamics of $CD8^+$ T cells and subsets in a cohort of end-stage kidney disease patients to 1-year post-transplant. PBMCs of 65 patients were analyzed by flow cytometry pre- (T1) and 1-year post-transplantation (T2). Violin plots show the data distribution of absolute numbers of **(A)** $CD8^+$ T cells and frequencies of **(B)** $CD8^+$ T cells, **(C)** $FoxP3^+CD25^+$, **(D)** $CD28^-$, **(E)** LAG-3^+, and **(F)** PD-1^+ $CD8^+$ T cells. Each black dot represents data of one patient. All data are represented in median (heavy black line) and IQR (thin black line). Statistical analysis was calculated with Wilcoxon signed-rank test (*$p < 0.05$; ***$p < 0.001$; ****$p < 0.0001$).

infection within 90 days of treatment, and one patient became CMV positive 194 days after diagnosis of rejection (**Table 3**).

Despite the low threshold for the definition of CMV infection, kidney function was reduced in CMV+ after 1 year as evidenced by serum urea, serum creatinine, and creatinine-based estimated glomerular filtration rate (eGFR) (**Table 2**).

TABLE 2 | Comparison of KTRs who remained CMV– and those who become CMV+ within the first year of transplantation.

N	CMV–	CMV+	*p*-value
	32	33	
Age (years)	57.5 (49.5–63.75)	53 (46–63.5)	0.295
Caucasian Ethnicity	31 (96.9)	28 (84.8)	0.094
Male gender	23 (71.9)	17 (51.5)	0.092
BMI (kg/m^2)	26.4 (22.6–31.2)	25.5 (21.6–27.6)	0.200
Preemptive	2 (6.3)	2 (6.1)	0.975
HD/PD	22/8 (68.8/25)	28/3 (84.8/9.1)	0.124/0.087
Diabetes mellitus	7 (21.9)	5 (15.2)	0.485
Donor Age (years)	54.5 (44.3–69.8)	59 (49–71)	0.478
ECD	16 (50)	19 (57.6)	0.540
BK-Polyoma viremia	8 (25)	5 (15.2)	0.321
CMV constellation			<0.001
R–/D–	11 (34.4)	0	
R+/D–	9 (28.1)	4 (12.1)	
R+/D+	7 (21.9)	23 (69.7)	
R+/D?	0	2 (6.1)	
R–/D+	5 (15.6)	4 (12.1)	
CMV prophylaxis	7 (21.9)	9 (27.3)	0.614
Kidney disease			
Diabetes	7 (21.9)	4 (12.1)	0.294
Hypertensive	1 (3.1)	2 (6.1)	0.573
Glomerular	7 (21.9)	9 (27.3)	0.614
Cystic	6 (18.8)	5 (15.2)	0.699
Other	11 (34.4)	13 (39.4)	0.675
Immunosuppression			
ATG	3 (9.4)	4 (12.1)	0.721
BX	29 (90.6)	29 (87.9)	0.721
CS	32 (100)	33 (100)	1.000
CyA	0	1 (3)	0.321
Tac	32 (100)	32 (97)	0.321
MMF/MPA	31 (96.9)	33 (100)	0.306
AZA	1 (3.1)	0	0.306
Rejection within first year	6 (18.8)	6 (18.2)	0.953
Kidney function after 1 year			
Serum-urea (mg/dL)	49.5 (37.5–55)	54 (45–79.5)	0.009
Serum-creatinine (mg/dL)	1.25 (1.08–1.57)	1.66 (1.39–2.06)	<0.001
eGFR (ml/min/1.73m^2)	56.5 (45.8–70.7)	43.4 (28.9–50.7)	<0.001

Continuous variables are depicted as mean and IQR, categorical variable as absolute and relative frequencies; BMI, body mass index; HD, hemodialysis; PD, peritoneal dialysis; ECD, extended criteria donor; ATG, anti-thymocyte globulin; BX, basiliximab; CS, corticosteroids; CyA, cyclosporin A; Tac, tacrolimus; MMF, mycophenolate mofetil; MPA, mycophenolic acid; AZA, azathioprin; eGFR, estimated glomerular filtration rate.

Circulating Leukocyte Numbers as Potential Predictors of CMV in Intermediate Risk Individuals Before Kidney Transplantation

Recognizing the pronounced risk of R+ for CMV and the reduced graft function after CMV (**Supplementary Table S2**), we aimed to estimate the potential of circulating leukocyte numbers as predictors of CMV infection in these patients (16 CMV– and 29 CMV+), specifically. We compared the abundance of leukocyte subpopulations before transplantation of intermediate risk individuals not affected and affected by CMV DNAemia post-transplantation. Individuals who tested CMV+ during the first

TABLE 3 | Characteristics of CMV infection in all 33 CMV+ KTRs.

N	33
Time to positivity (d)	57 (28–81.5)
CMV high risk constellation (%)	4 (12.1)
Valganciclovir prophylaxis (%)	9 (27.3)
Valganciclovir prophylaxis dose (mg/d)	225 (225–450)
Rejection prior CMV (%)	5 (15.2)
ATG rejection treatment ≤90 days prior CMV (%)	4 (12.1)
CMV peak (IU/mL)	1,500 (490–4,950)
Symptomatic CMV disease (%)	11 (33.3)
Duration of positivity (d)	6 (1–23)
Recipients with relapses (%)	10 (30.3)
Watch and wait (%)	4 (12.1)
MMF/MPA dose reduction without antiviral therapy (%)	4 (12.1)
MMF/MPA pause without antiviral therapy (%)	1 (3)
Valganciclovir therapy without MMF/MPA dose reduction/ pause (%)	3 (9.1)
Valganciclovir therapy with MMF/MPA dose reduction (%)	18 (54.5)
Valganciclovir therapy with MMF/MPA pause (%)	3 (9.1)
Valganciclovir dose (mg/d)	450 (281–450)
Letermovir therapy (%)	1 (3)
Letermovir dose (mg/d)	480

Median and IQR are given for continuous and absolute values and relative frequencies for categorical variables, respectively. ATG, anti-thymocyte globulin; MMF, mycophenolate mofetil; MPA, mycophenolic acid.

year of transplantation had significantly lower numbers of overall leukocytes, granulocytes, and monocytes (**Figures 4A–C**). The abundance of overall lymphocytes was comparable pre-transplant regardless of later CMV DNAemia (**Figure 4D**).

Pre-Transplant FoxP3$^+$CD25$^+$ in CD3$^+$CD8$^+$ T Cells as Potential Predictors of CMV in Intermediate Risk Transplant Recipients

Before transplantation, intermediate risk individuals had comparable numbers and frequencies of CD8$^+$ T cells (**Figures 5A, B**). In individuals with intermediate risk who tested positive for CMV within 12 months post-transplantation, the percentage of FoxP3$^+$CD25$^+$ was significantly increased before transplantation (**Figure 5C**), while frequencies of CD28$^-$, LAG-3$^+$, and PD-1$^+$ among CD3$^+$CD8$^+$ T cells were not different pre-transplantation (**Figures 5D–F**) compared to those who remained negative for CMV.

Next, we compared potential pre-transplant predictors, namely, leukocytes, granulocytes, monocytes, and FoxP3$^+$CD25$^+$CD3$^+$CD8$^+$ T cells. Utilizing Youden indices, we aimed to estimate sensitivity and specificity. Our findings revealed comparable areas under the curve (AUC) for all subsets. While Youden-derived thresholds for leucocytes and monocytes offered great sensitivity, 93% and 96%, respectively, specificities with either marker were low (43.8% and 43.8%, respectively). The cutoff for granulocytes, on the contrary, showed good specificity (87.5%) but poor sensitivity (51.7%) for CMV DNAemia. A cutoff of 1.03% for FoxP3$^+$ CD25$^+$ in CD3$^+$ CD8$^+$ T cells, allowed for the best discrimination between those who would become CMV positive and those who would remain CMV negative with a balanced sensitivity and specificity of 72.4% and 75%, respectively (**Table 4**; **Figure 6**).

Further exploration involved the stratification of intermediate risk patients based on the frequency of FoxP3$^+$CD25$^+$ in CD3$^+$CD8$^+$ T cells, employing the established 1.03% cutoff. Results indicated a consistent distribution across demographic factors (age, donor age, BMI), with notably higher prevalence of CMV infection in the group with higher frequencies (**Supplementary Table S3**). While not achieving statistical significance, variations in the use of ATG as induction treatment were noted between the two groups. Probability of CMV DNAemia was higher in KTRs with pretransplant percentages of FoxP3$^+$CD25$^+$ in CD3$^+$CD8$^+$ T cells above 1.03 (**Figure 7**).

Consequences of CMV DNAemia on Leukocyte and CD8$^+$ T Cell Populations 1-Year Post-Kidney Transplantation

One-year post-transplantation, individuals showed no significant differences in leukocyte, granulocyte, and monocyte numbers

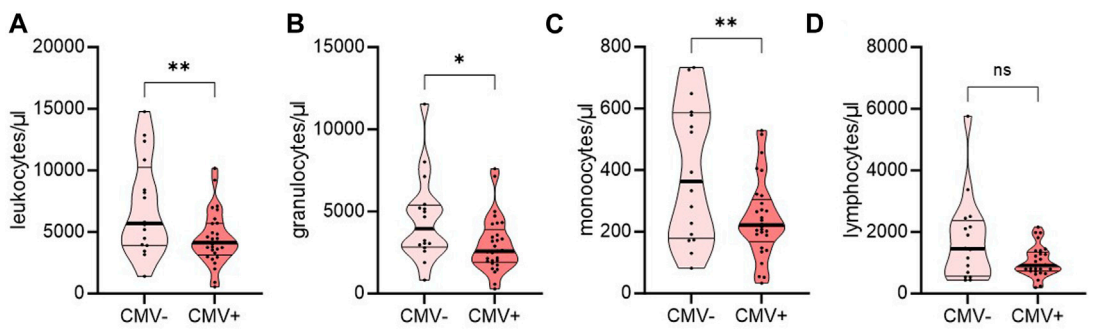

FIGURE 4 | Distribution of immune cell populations in a cohort of end-stage kidney disease patients with intermediate-risk for CMV DNAemia pre-transplant. Intermediate-risk patients were grouped regarding their affection by CMV DNAemia post-transplantation. Whole blood of 16 CMV– and 29 CMV+ patients was analyzed by flow cytometry pre-transplant (T1). Violin plots show the data distribution of absolute numbers of **(A)** leukocytes, **(B)** granulocytes, **(C)** monocytes, and **(D)** lymphocytes. Each black dot represents data of one patient. All data are represented in median (heavy black line) and IQR (thin black line). Statistical analysis was calculated with Student's t-Test or Mann-Whitney-U Test after testing for normal distribution (*$p < 0.05$; **$p < 0.01$).

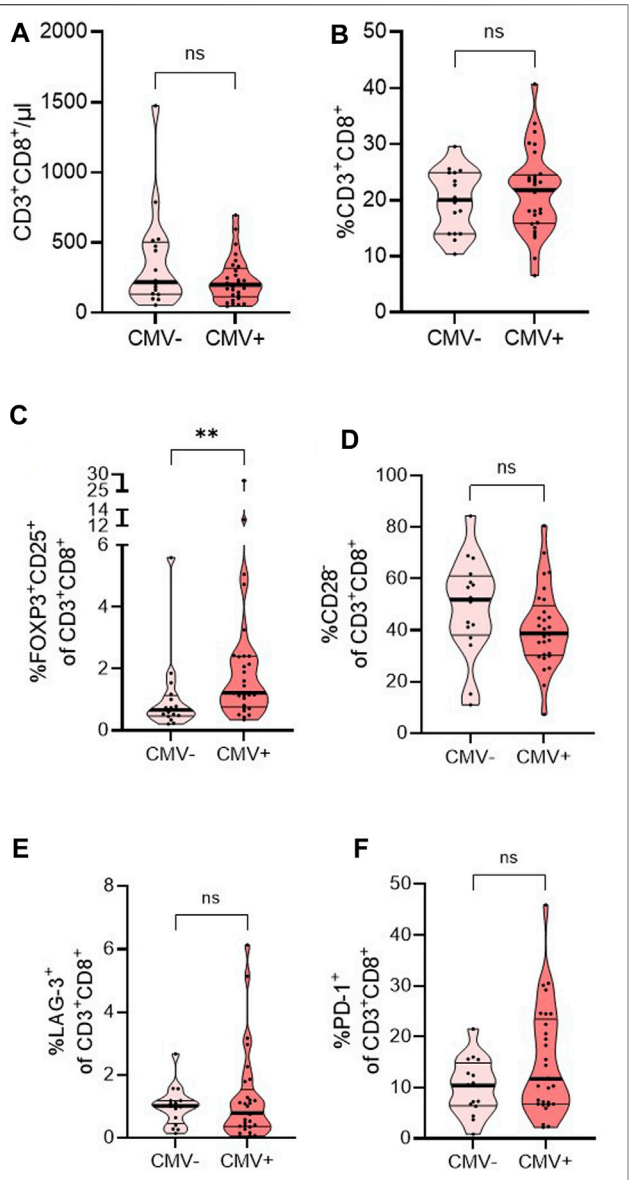

FIGURE 5 | Distribution of $CD8^+$ T cells and subsets in a cohort of end-stage kidney disease patients with intermediate risk for CMV DNAemia pre-transplant. Intermediate-risk patients were grouped regarding their affection by CMV DNAemia post-transplantation. Whole blood of 16 CMV– and 29 CMV+ patients was analyzed by flow cytometry pre-transplant (T1). Violin plots show the data distribution of absolute numbers of **(A)** $CD8^+$ T cells and frequencies of **(B)** $CD8^+$ T cells, **(C)** $FoxP3^+CD25^+$, **(D)** $CD28^-$, **(E)** $LAG\text{-}3^+$, and **(F)** $PD\text{-}1^+$ $CD8^+$ T cells. Each black dot represents data of one patient. All data are represented in median (heavy black line) and IQR (thin black line). Statistical analysis was calculated Mann-Whitney-U Test after testing for normal distribution ($^{**}p < 0.01$).

regardless of CMV infection status (**Supplementary Figures S3A–S3C**). However, individuals who tested positive for CMV post-transplant had a higher number of lymphocytes 1 year after transplantation (**Supplementary Figure S3D**).

CMV DNAemia had lasting effects on the $CD8^+$ T cell compartment 1 year after transplantation. CMV+ individuals showed increased $CD8^+$ T cell numbers and frequencies of $CD3^+CD8^+$ T cells (**Supplementary Figures S4A, B**). While frequencies of $FoxP3^+CD25^+$ cells were comparable to CMV- individuals (**Supplementary Figure S4C**), frequencies of $CD28^-$ cells among $CD3^+CD8^+$ T cells were significantly increased 1-year post-transplant (**Supplementary Figure S4D**). Additionally, in CMV+ individuals, the frequencies of $LAG\text{-}3^+$ among $CD3^+CD8^+$ T cells were elevated (**Supplementary Figure S4E**), while the percentage of $PD\text{-}1^+$ was not changed (**Supplementary Figure S4F**).

DISCUSSION

We studied the dynamics of immune cell composition, focusing on $CD8^+$ T cells before and 1-year after transplantation. The study was based on immune cell phenotyping by flow cytometry to analyze overall leukocyte, granulocyte, monocyte, and $CD8^+$ T cell numbers, as well as frequencies of $CD8^+$ T cell subpopulations associated with immunoregulatory functions (FoxP3), ageing (CD28), and exhaustion (LAG-3, PD-1). Our goal was to find a prognostic phenotypic pattern of post-transplant CMV DNAemia that might be considered to help identify intermediate risk individuals who would benefit from CMV prophylaxis.

Deteriorating kidney function in CKD is associated with decreased T cell numbers, which can be attributed mainly to a reduction of naïve T cells and an increase of $CD8^+$ memory T cells [25]. In line with these results, we show higher overall $CD8^+$ T cell numbers and frequencies 1 year after transplantation compared to pre-transplantation. However, the composition within the $CD8^+$ T cell population is changed. While we did not see an increase in frequencies of $FoxP3^+CD25^+$ regulatory $CD8^+$ T cells, we saw a significant increase of $CD28^-$ $CD8^+$ T cells 1 year after transplantation. This finding confirms previous studies showing that these cells were significantly increased in dialysis patients compared to healthy controls and expanded further after kidney transplantation [26, 27], presumably due to continued antigen exposure [8]. CD28 is a co-stimulatory receptor on T cells mediating activation, proliferation, and longevity. The expression of CD28 declines with age, and these cells are discussed to have impaired effector functions [28].

Inhibitory receptors are negative regulators of immunopathology by counteracting T cell activation and peripheral tolerance [29]. Higher and sustained expression of LAG-3 and PD-1 are associated with T cell exhaustion, which weakens responses to infections. We show that 1-year after transplantation frequencies of LAG-3 and PD-1 in $CD8^+$ T cells are significantly decreased in our cohort. These findings add to previous studies reporting around 1% of exhausted $CD8^+$ T cells after 3 months post-transplantation, with an increase after CMV infection [27]. Moran et al., however, report increased PD-1 expression on $CD8^+$ T cells 1 year after transplantation in a pediatric cohort, which was the opposite in our adult cohort [30]. Among others, loss of co-stimulatory receptors and upregulation of inhibitory receptors associated with exhaustion are hallmarks of T cell ageing [31].

TABLE 4 | Comparison of leucocytes and specific subsets with predictive potential for CMV infection.

Potential predictor	AUC (95% CI)	Youden index	Youden's threshold	Sensitivity	Specificity	PPV	NPV
Leukocytes	0.696 (0.524–0.868)	0.368	7448.744	0.931	0.438	0.75	0.778
Granulocytes	0.703 (0.537–0.868)	0.392	2578.271	0.517	0.875	0.882	0.5
Monocytes	0.681 (0.494–0.868)	0.403	519.655	0.966	0.438	0.757	0.875
FoxP3$^+$CD25$^+$ (% of CD3$^+$CD8$^+$)	0.746 (0.591–0.901	0.474	1.03	0.724	0.75	0.864	0.6

AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

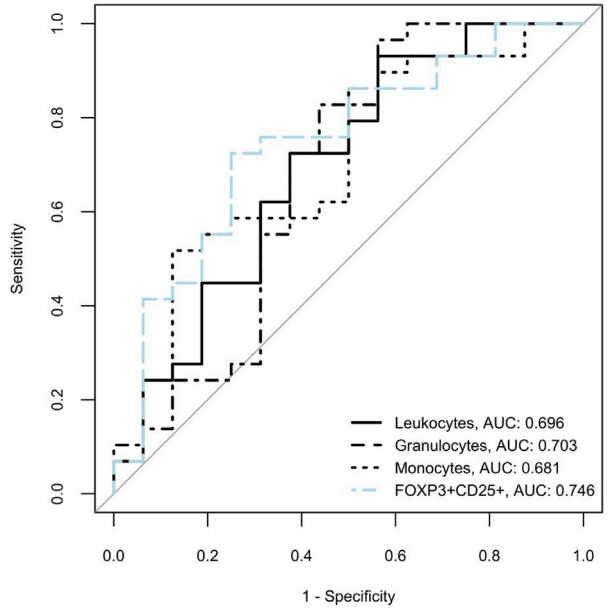

FIGURE 6 | Receiver operating characteristic (ROC) curves for cellular subsets for development of CMV infection in intermediate risk KTRs are shown. Areas under the receiver operating characteristic curves (area under the curve, AUC) are listed next to the variable names in the figure legend.

Premature immune cell ageing has previously been reported in patients with CKD G5 [25]. Our findings suggest a partly reversed CD8$^+$ T cell ageing phenotype due to reduced exhaustion markers after kidney transplantation. On the other hand, an increase in CD28$^-$CD8$^+$ T cells could indicate accelerated CD8$^+$ T cell ageing in transplanted individuals compared to CKD G5.

Apart from the direct effects, CMV infection after transplantation is associated with reduced graft and patient survival [32]. CMV DNAemia was common in our cohort when a cutoff of ≥ 100 IU/mL was applied as the threshold. A major problem in CMV surveillance is the lack of a definitive threshold for significant CMV DNAemia [1, 12]. This issue is aggravated by the low comparability of CMV PCR testing platforms between centers [33]. Thus, determining a CMV PCR threshold for intervention underlies the physician's judgement and depends on the clinical context. Our cutoff aligns with practice at our institution for therapeutic considerations. This comparably low threshold may explain our cohort's low numbers of symptomatic infections and CMV end-organ disease [34]. Nonetheless, kidney function was reduced in those who had experienced CMV positivity by our standard, while other predictors of graft outcome (i.e., donor age and proportion of ECD) were similar between CMV+ and CMV−.

We focused on intermediate risk recipients as they were particularly affected by post-transplant CMV. Additionally, considerable uncertainty regarding the risk-to-benefit ratio of CMV prophylaxis in this subgroup exists. Particularly leukopenia is a common and severe complication with valganciclovir [35–37], and less myelotoxic alternatives have not been tested yet in intermediate risk KTRs [38].

R+ patients affected by CMV DNAemia after transplantation showed lower overall numbers of leukocytes, granulocytes, and monocytes pre-transplantation. Furthermore, these patients displayed higher frequencies of FoxP3$^+$CD25$^+$ CD8$^+$ T cells pre-transplantation. FoxP3$^+$CD25$^+$CD3$^+$CD8$^+$ T cells are proposed to be a regulatory subpopulation within the CD8$^+$ T cell compartment and have been shown to be able to suppress effector CD8$^+$ and CD4$^+$ T cell functions in part by IL-10 production, as well as induce inhibitory receptors on DCs potentially dampening immune responses against infections [39].

Previous studies have investigated the predictive potential of CMV-specific CD8$^+$ T cells for various CMV-related endpoints [40–48]. Addressing the issue of intermediate risk recipients specifically, the absence of a pre-transplant CD8$^+$ T cell response to the immediate early (IE)-1 antigen has been shown to predict post-transplant CMV [47, 48]. Furthermore, an increased abundance of CMV-specific IFNγ$^+$ CD8$^+$ T cells reduced the risk of high-level DNAemia and the necessity of treatment in a cohort of R+ solid organ transplant recipients [45].

Although these studies have shown promising results, their generalizability may be limited by small and heterogenous cohorts of different organ transplants and immunosuppressive regimens.

While our cohort is also small, it uniformly consists of kidney transplant recipients with similar immunosuppression. Moreover, monitoring FoxP3$^+$CD25$^+$CD3$^+$CD8$^+$ T cells is appealing, given its ease of implementation without the requirement for assessing CMV-specificity or conducting functional assays.

Interestingly, in our cohort, the increase in CD8$^+$ T cell numbers and frequencies, as well as CD28 loss at year one after transplantation, are driven by CMV DNAemia. Patients testing continuously negative during the course of 1 year after transplantation show comparable numbers of these CD8$^+$ T cell

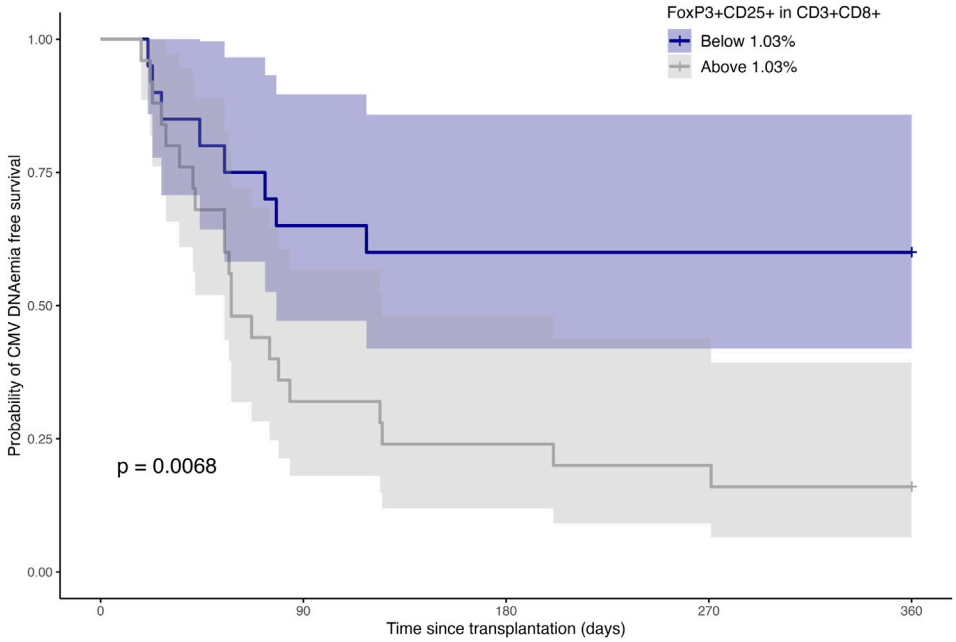

FIGURE 7 | CMV DNAemia-free survival probability over time post-transplantation, stratified by levels of FoxP3$^+$CD25$^+$ within CD3$^+$CD8$^+$ T cells. Shaded areas constitute the 95% confidence intervals. Log-rank test shows a significant difference in probability of CMV DNAemia between groups ("Below 1.03%" vs. "Above 1.03%").

populations to pre-transplantation (data not shown), as also reported by Wang et al. [26].

Beyond the single-center nature and small sample size, several other limitations need to be addressed. We only included patients who underwent their posttransplant follow-up at our center ensuring relatively standardized frequency of visits and PCR testing. We focused on patients with a complete follow-up to allow for an equal time at risk for CMV in all patients. However, generalizability of our results may be compromised by inclusion and exclusion criteria. Similarly, the lack of an external validation cohort is a major limitation, and our findings need to be confirmed in an independent analysis. We specifically focused on CMV intermediate risk kidney transplant recipients, recognizing their susceptibility to frequent CMV infections and the uncertainties surrounding CMV prevention. Due to the already modest number of intermediate risk patients, we refrained from controlling for CMV prophylaxis, prior rejection, and ATG treatment in this subcohort. Although these factors were rare, we acknowledge that these may influence CMV reactivation. One limitation is the fact that, that we did not correct for multiple testing, because of the rather low n-number of flow cytometry analysis performed in this small cohort.

In summary, we found a substantially altered CD8$^+$ T cell pool in kidney transplant recipients compared to the CKD G5 setting prior to transplantation. CD28$^-$CD8$^+$ T cells were expanded especially in patients after CMV DNAemia, while expression of regulatory and exhaustion markers was reduced after 1-year post-transplant. Determination of frequencies of FoxP3$^+$CD25$^+$ in CD3$^+$CD8$^+$ T cells already before transplantation may be a suitable biomarker to assess the CMV risk within the first year after transplantation and might thereby assist in the selection of intermediate risk individuals for CMV prophylaxis. Our findings need to be confirmed in an independent validation cohort. The outlook of CMV prophylaxis approach based on FoxP3$^+$CD25$^+$ assessment warrants consideration for investigation in a prospective trial.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by the Institutional Review Board of the Medical University of Graz, Austria (28-514ex15/16). The study was registered as #DRKS00026238 in the German Register of Clinical Studies. 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

The authors confirm contribution to the paper as follows: Study conception and design: AM, MS, BP, HS, and KE; data collection: AM, MS, VP, and AK; analysis and interpretation of results: AM, MS, VP, KK, BP, AK, PS, RS, AR, and KE; draft manuscript

preparation: AM, MS, and KE. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

Authors VP and BP were employed by CBmed GmbH.

KE received congress-support and speaker fees by Chiesi and Astellas.

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

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.12963/full#supplementary-material

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ORIGINAL RESEARCH
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Pre-Transplant Calcimimetic Use and Dose Information Improves the Accuracy of Prediction of Tertiary Hyperparathyroidism after Kidney Transplantation: A Retrospective Cohort Study

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Tertiary hyperparathyroidism (THPT) is characterized by elevated parathyroid hormone and serum calcium levels after kidney transplantation (KTx). To ascertain whether pre-transplant calcimimetic use and dose information would improve THPT prediction accuracy, this retrospective cohort study evaluated patients who underwent KTx between 2010 and 2022. The primary outcome was the development of clinically relevant THPT. Logistic regression analysis was used to evaluate pre-transplant calcimimetic use as a determinant of THPT development. Participants were categorized into four groups according to calcimimetic dose, developing two THPT prediction models (with or without calcimimetic information). Continuous net reclassification improvement (CNRI) and integrated discrimination improvement (IDI) were calculated to assess ability to reclassify the degree of THPT risk by adding pre-transplant calcimimetic information. Of the 554 patients, 87 (15.7%) developed THPT, whereas 139 (25.1%) received pre-transplant calcimimetic treatment. Multivariate logistic regression analysis revealed that pre-transplant calcimimetic use was significantly associated with THPT development. Pre-transplant calcimimetic information significantly improved the predicted probability accuracy of THPT (CNRI and IDI were 0.91 [$p < 0.001$], and 0.09 [$p < 0.001$], respectively). The THPT prediction model including pre-transplant calcimimetic information as a predictive factor can contribute to the prevention and early treatment of THPT in the era of calcimimetics.

Keywords: calcimimetics, kidney transplantation, parathyroidectomy, tertiary hyperparathyroidism, prediction model

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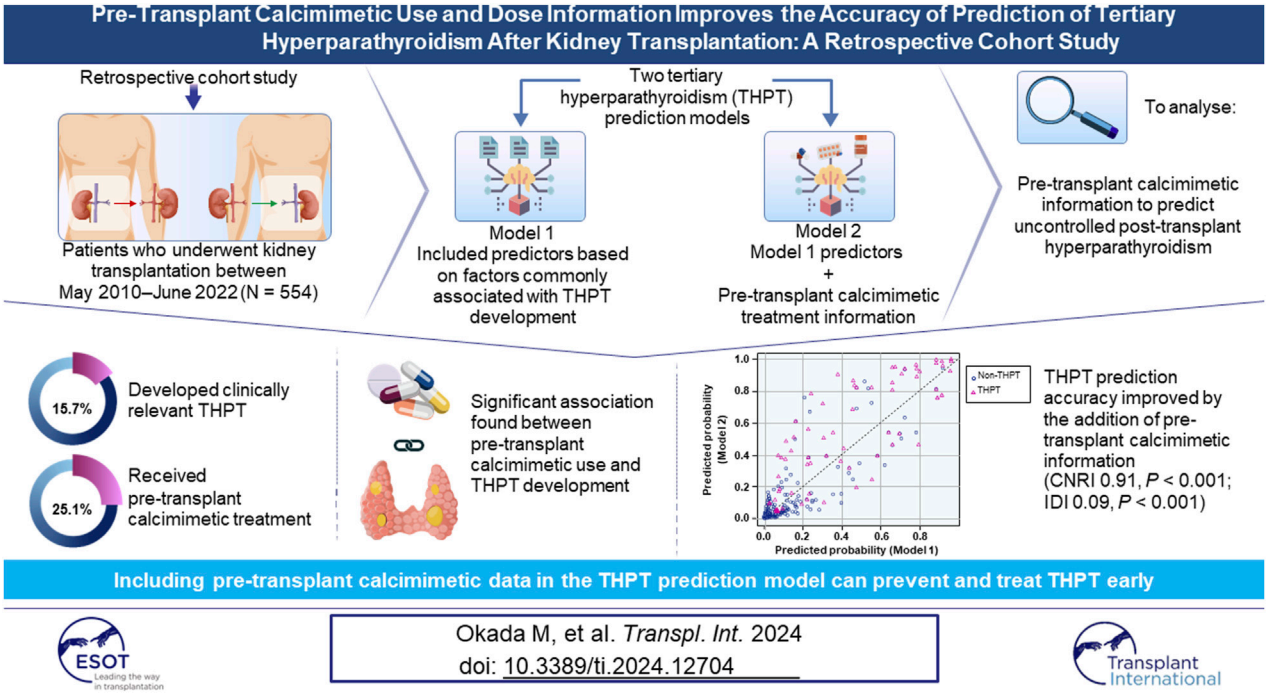

GRAPHICAL ABSTRACT |

INTRODUCTION

Persistent hyperparathyroidism after kidney transplantation (KTx) is associated with unfavorable kidney graft and patient outcomes [1–3]. Tertiary hyperparathyroidism (THPT) is characterized by high parathyroid hormone (PTH) and serum calcium (Ca) levels, even in functioning kidney grafts [4], and often requires therapeutic intervention [5–8]. Common treatment options for THPT include parathyroidectomy (PTx) and calcimimetics [9–11]. However, in KTx patients, PTx can increase serum creatinine levels [12, 13], and the disadvantages of calcimimetics include being off-label in some regions, high medical costs [14], and an increased risk of urinary stones [15, 16]. For patients at high risk of THPT, pre-transplant PTx is appropriate [17, 18].

The predictive factors for THPT include pre-transplant serum Ca and PTH levels, dialysis duration, and parathyroid gland size [19, 20]. Prediction models using only three variables (serum Ca, PTH levels, and dialysis duration) have been shown to accurately predict the risk of THPT [21]. However, recently, pre-transplant calcimimetic administration has also been reported as an additional predictive factor for THPT [22, 23].

The effectiveness of calcimimetics in the treatment of secondary hyperparathyroidism (SHPT) is widely recognized. In vitamin D-resistant SHPT, cinacalcet effectively reduces PTH levels [24, 25]. Several studies have demonstrated that cinacalcet prevents cardiovascular events and patient mortality [26–28]. Following cinacalcet, new calcimimetics have been developed [29, 30], and with an increase in treatment options, the proportion of dialysis patients receiving calcimimetic treatment is likely to increase. In this era of calcimimetics, pre-transplant calcimimetic use and dose information may predict THPT progression after KTx.

THPT risk assessment is complicated by several factors. In patients treated with calcimimetics, the assessment of THPT risk can be challenging because of the drastic decrease in serum Ca and PTH levels [31, 32]. Cianciolo et al. [33] proposed evaluating the need for PTx in KTx candidates receiving calcimimetic treatment after ceasing treatment for 2–4 weeks. However, discontinuation of calcimimetic treatment leads to a rapid increase in PTH levels, which may cause hyperparathyroidism-related adverse events and complicate the optimal timing of KTx. Therefore, assessment of THPT risk without discontinuing calcimimetic treatment is safer. A need for highly accurate prediction of THPT risk arises; this can contribute to the prevention and early treatment of THPT in patients undergoing KTx. Accurate THPT prediction models that include calcimimetic dose information are therefore required.

Hence, in this retrospective study, we aimed to investigate whether the inclusion of calcimimetic use and dose information as predictive factors in a prediction model could improve THPT prediction accuracy.

MATERIALS AND METHODS

Data Source

Consecutive patients who underwent KTx between May 2010 and June 2022 were included. The data were collected on 30 June 2023.

Participants

The exclusion criteria were as follows: 1) PTx before KTx, 2) end-stage kidney disease with an estimated glomerular filtration rate (eGFR) of less than 15 mL/min/1.73 m^2 within a year after KTx, 3) denosumab treatment within a year after KTx, 4) missing data, and 5) preemptive KTx. Data on patient age, sex, body mass index, original disease, dialysis duration, serum Ca and intact PTH levels, kidney graft function, parathyroid gland size (the size of the parathyroid glands of recipients were routinely measured by ultrasound before KTx), ABO blood type incompatibility, positivity for donor-specific human leukocyte antigen antibodies, and PTx and calcimimetic treatment histories, were collected.

All procedures involving participants were approved by the Institutional Review Board (IRB) and performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The IRB waived the requirement to obtain informed consent because of the retrospective nature of the study. Details of the study and its outcomes are available on our institutional website. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Outcome

The primary outcome was the development of clinically relevant THPT, defined as the presence of both hypercalcemia (total serum Ca ≥10.5 mg/dL) and high PTH level (intact PTH >80 pg/mL) 1 year after KTx, based on the guidelines of the Japanese Society for Dialysis Therapy [6, 34]. In addition, post-transplant PTx or calcimimetic therapy to control severe hyperparathyroidism was included in the definition of THPT.

Measurements

Pre-transplant blood sample analyses were performed in all patients within 3 months before KTx. Serum Ca levels were measured using standard methods. Intact PTH levels were measured using the following second-generation immunoassays: an electrochemical luminescence immunoassay (SRL, Tokyo, Japan[1], reference range 10–65 pg/mL) and an enzyme immunoassay (Tosoh, Tokyo, Japan[2], reference range 9–80 pg/mL). For serum albumin levels <4.0 g/dL, all serum Ca levels were corrected [35]. The eGFR was evaluated using the creatinine equation provided by the Japanese Society of Nephrology and the Japanese Society for Pediatric Nephrology [36, 37].

[1]www.srl-group.co.jp

[2]www.tosoh.co.jp

Immunosuppression

Immunosuppressive regimens included calcineurin inhibitors (cyclosporine or tacrolimus), mycophenolic acids, mizoribine, everolimus, and glucocorticoids. Basiliximab was used as induction therapy. In addition, rituximab administration or splenectomy was used as induction therapy in anti-donor antibody-positive patients before KTx, except in those with low antibody titers.

Statistical Analysis

Pearson's chi-squared test was used to analyze nominal variables, and the Mann–Whitney U test or Student's *t*-test was used for continuous variables. The normality of the distribution of the data was assessed using the Shapiro–Wilk normality test and histogram (**Supplementary Table S1**; **Supplementary Figure S1**). Statistical significance was set at $p < 0.05$.

First, logistic regression analysis was performed to confirm that known predictive factors were associated with the development of THPT, even after adjusting for the patient background between the THPT and non-THPT groups. Then, two THPT prediction models were constructed using logistic regression, one with and one without pretransplant calcimimetic use and dose information (Model 1 and Model 2). Owing to the non-linear relationship between serum Ca, intact PTH, dialysis duration, parathyroid gland size, and THPT risk (**Supplementary Figure S1**), these variables were transformed into categorical variables by dividing them into four categories based on the number of cases. The information on pre-transplant calcimimetic treatment was also used to categorize participants into four groups according to the tertile of cinacalcet dose per unit of body weight (mg/kg). Based on previous studies, evocalcet (2.0 mg/day) and etelcalcetide (7.5 mg/week) dosages were considered equivalent to a cinacalcet dosage of 25.0 mg/day [38, 39].

To evaluate the effect of the inclusion of pre-transplant calcimimetic information as a predictive factor for THPT, the accuracy of Models 1 and 2 were compared. First, scatter plots of the predicted probabilities of Models 1 and 2 were created, then continuous net reclassification improvement (CNRI) and integrated discrimination improvement (IDI) were calculated to assess the ability to reclassify the degree of THPT risk by adding pretransplant calcimimetic information [40–42]. To identify the characteristics of THPT patients for whom the addition of the pre-transplant calcimimetic information significantly improved the predictive probability, we stratified THPT cases by a change in predictive probability of 0.1 and compared the characteristics. In addition, receiver operating characteristic (ROC) curves for the predicted THPT probabilities of each model were obtained, and the areas under the curve (AUCs) were compared for the two models using Delong's test [43].

Internal Validation

Internal validation of the prediction models was performed using the bootstrap method [44]. By resampling with replacement, 1,000 pseudo-external datasets were created, and the ROC AUC was obtained. Overfitting was assessed using slope optimism, and calibration was performed.

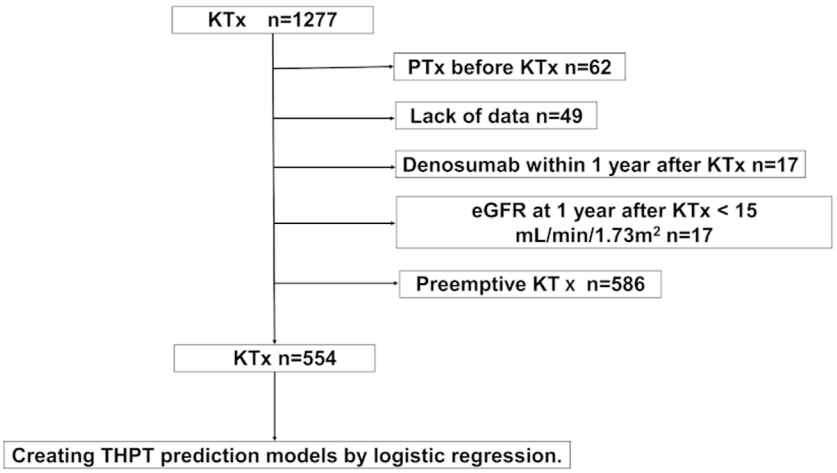

FIGURE 1 | Participant selection flowchart. eGFR, estimated glomerular filtration rate; KTx, kidney transplantation; PTx, parathyroidectomy; THPT, tertiary hyperparathyroidism.

TABLE 1 | Patient characteristics before KTx.

	Total N = 554	Non-THPT N = 467	THPT N = 87	*p*-value
Recipient age (years, IQR)	51 (39–62)	50 (38–62)	53 (46–62)	0.060
Recipient sex (male, %)	352 (63.5)	304 (65.1)	48 (55.2)	0.089
Body mass index (kg/m^2, SD)	22.1 (3.7)	22.1 (3.8)	22.0 (3.3)	0.807
Dialysis vintage (months, IQR)	21 (6–54)	16 (5–38)	112 (48–167)	<0.001*
Previous KTx (%)	22 (4.0)	18 (3.9)	4 (4.6)	0.764
Living donor (%)	506 (91.3)	438 (93.8)	68 (78.2)	<0.001*
Original disease (%)				0.058
Glomerular disease	192 (34.7)	159 (34.0)	33 (37.9)	
Diabetic kidney disease	141 (25.6)	122 (26.1)	19 (21.8)	
Polycystic kidney disease	28 (5.1)	19 (4.1)	9 (10.3)	
Hypertensive kidney disease	38 (6.9)	36 (7.7)	2 (2.3)	
Others	49 (8.8)	39 (8.4)	10 (11.5)	
Unknown	106 (19.1)	92 (19.7)	14 (16.1)	
Preformed DSA (%)	40 (7.2)	38 (8.1)	2 (2.3)	0.068
ABO blood type incompatible kidney transplantation (%)	160 (28.9)	128 (27.4)	32 (36.8)	0.093
Parathyroid gland size (mm, IQR)	7.2 (5.1–9.8)	6.3 (4.7–8.4)	9.4 (7.1–11.6)	<0.001*
VDRA before KTx (%)	352 (63.5)	288 (61.7)	64 (73.5)	0.039*
Alfacalcidol	184 (33.2)	164 (35.1)	20 (23.0)	
Calcitriol	64 (11.5)	47 (10.1)	17 (19.5)	
Maxacalcitol	104 (18.8)	77 (16.5)	27 (31.0)	
Calcimimetics before KTx (%)	139 (25.1)	84 (18.0)	55 (63.2)	<0.001*
Cinacalcet	89 (16.1)	50 (10.7)	39 (44.8)	
Evocalcet	36 (6.5)	25 (5.4)	11 (12.6)	
Etelcalcetide	14 (2.5)	9 (1.9)	5 (2.7)	
Calcimimetic dose per unit of body weight (mg/kg, IQR)	0.4 (0.3–0.7)	0.4 (0.3–0.5)	0.6 (0.4–1.0)	<0.001*
Lab data before KTx				
Corrected calcium (mg/dL, IQR)	9.3 (8.9–9.8)	9.2 (8.9–9.7)	9.8 (9.3–10.3)	<0.001*
Intact PTH (pg/mL, IQR)	157.5 (85.0–248.0)	145.0 (78.0–240.0)	203 (154.5–317.5)	<0.001*

DSA, *donor-specific HLA antibody;* eGFR, *estimated glomerular filtration rate;* IQR, *interquartile range;* KTx, *kidney transplantation;* PTH, *parathyroid hormone;* SD, *standard deviation;* THPT, *tertiary hyperparathyroidism;* VDRA, *vitamin D receptor activator.*

The results of parathyroid gland size excluded patients in whom parathyroid gland was not detected by echography.

Calcimimetic dose was converted into cinacalcet dose and calculated by per unit of body weight, excluding patients who had not received pre-KTx calcimimetic treatment.

*p-*value <0.05.*

Easy R (EZR) version 1.61 (The R Foundation for Statistical Computing) was used for the statistical analyses [45]. The calculations of CNRI and IDI, as well as the internal validation by the bootstrap method, were performed using the R package "rms" (version 6.7–0). Statistical significance was set at $p < 0.05$.

TABLE 2 | Clinical data after KTx.

	Total N = 554	Non-THPT N = 467	THPT N = 87	*p*-value
Lab data 1 year post-KTx				
Corrected calcium (mg/dL, IQR)	9.7 (9.4–10.0)	9.7 (9.4–9.9)	10.6 (9.8–10.8)	<0.001*
Intact PTH (pg/mL, IQR)	91.0 (65.0–130.0)	86.0 (64.2–115.0)	137.0 (88.9–181.0)	<0.001*
Recipient eGFR (mL/min/1.73 m^2, IQR)	44.2 (36.9–51.8)	43.1 (36.4–51.2)	44.2 (36.5–52.1)	0.695
Parathyroidectomy after KTx (%)	43 (4.0)	0 (0.0)	43 (49.4)	<0.001*
Interval between KTx and PTx				NA
<=12 months	NA	NA	25 (58.1%)	
13–24 months	NA	NA	14 (32.6)	
>24 months	NA	NA	4 (9.3)	
Calcimimetics after KTx (%)	36 (3.1)	0 (0.0)	36 (41.4)	<0.001*
Follow up after KTx (months, IQR)	81 (47–122)	81 (47–122)	89 (55–119)	0.371

eGFR, *estimated glomerular filtration rate;* IQR, *interquartile range;* KTx, *kidney transplantation;* NA, *not applicable;* PTH, *parathyroid hormone;* PTx, *parathyroidectomy;* THPT, *tertiary hyperparathyroidism.*
*p-*value <0.05.*

TABLE 3 | Logistic regression for THPT development.

Factors	Univariate			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Living donor	0.24	0.13–0.45	<0.001*	0.73	0.25–2.14	0.568
Preformed DSA	0.27	0.06–1.12	0.071	0.12	0.01–1.48	0.098
Pretransplant VDRA use	1.73	1.04–2.88	0.036*	1.90	0.87–4.16	0.109
Dialysis duration (months, reference to <6)						
6–20	0.75	0.24–2.28	0.609	0.88	0.24–3.22	0.841
21–53	1.50	0.56–3.99	0.419	0.62	0.18–2.18	0.457
54–	14.30	6.21–32.70	<0.001*	6.99	2.26–21.70	<0.001*
Serum Ca before KTx (mg/dL, reference to <8.9)						
8.9–9.2	0.76	0.29–2.00	0.581	1.39	0.37–5.21	0.627
9.3–9.7	2.67	1.23–5.77	0.013*	4.58	1.51–13.90	0.007*
9.8–	5.35	2.56–11.20	<0.001*	16.90	5.16–55.20	<0.001*
Intact PTH before KTx (pg/mL, reference to <85.0)						
85.0–157.0	3.27	1.26–8.52	0.015*	11.50	2.96–44.70	<0.001*
158.0–247.0	6.29	2.52–15.70	<0.001*	19.30	5.38–69.30	<0.001*
248.0–	6.66	2.69–16.50	<0.001*	28.50	7.65–106.00	<0.001*
Parathyroid gland size before KTx (mm, reference to 0)						
0.1–5.7	2.10	0.90–4.86	0.085	1.34	0.45–3.99	0.602
5.8–8.8	4.79	2.40–9.57	<0.001*	3.53	1.32–9.44	0.012*
8.9–	17.60	9.27–33.40	<0.001*	12.30	4.46–34.00	<0.001*
Pretransplant calcimimetics use	7.84	4.77–12.90	<0.001*	10.80	4.73–24.60	<0.001*

Ca, *Calcium;* 95% CI, *95% confidence interval;* DSA, *donor-specific HLA antibody;* KTx, *kidney transplantation;* OR, *odds ratio;* PTH, *parathyroid hormone;* THPT, *tertiary hyperparathyroidism;* VDRA, *vitamin D receptor activator.*
The parathyroid gland size was defined as 0 when parathyroid gland was not detected by echography.
*p-*value <0.05.*

RESULTS

Participant Characteristics

A total of 554 patients met the inclusion criteria (median observation period, 81 months [interquartile range {IQR}: 47–122 months]; **Figure 1**). Of the 554 patients, 87 (15.7%) developed THPT after KTx, whereas 139 (25.1%) received calcimimetic treatment before KTx (**Table 1**, **Supplementary Table S2**). More than 70% of patients had pre-transplant hyperparathyroidism (i-PTH >80 pg/mL) with or without pre-transplant calcimimetic treatment (**Supplementary Table S3**). Significant differences were observed between the THPT and non-THPT groups in terms of dialysis duration, living donor, parathyroid gland size, pre-transplant calcimimetic use, and serum Ca and intact PTH levels (**Table 1**). In addition, serum Ca and intact PTH levels 1 year after KTx also significantly differed between the two groups (**Table 2**). In the THPT group (n = 87), 43 (49.4%) received PTx, and 36 (41.4%) received calcimimetic treatment after KTx (**Table 2**). Most PTx were done within 2 years after

TABLE 4 | Logistic regression THPT prediction models.

Variable	Model 1			Model 2		
	RC (SE)	OR (95% CI)	*p*-value	RC (SE)	OR (95% CI)	*p*-value
(Intercept)	−6.26 (0.79)			−7.57 (0.94)		
Dialysis duration (months, reference to < 6)						
6–20	−0.07 (0.62)	0.94 (0.28–3.13)	0.913	−0.19 (0.67)	0.83 (0.87–3.05)	0.775
21–53	0.11 (0.57)	1.11 (0.36–3.41)	0.852	−0.52 (0.65)	0.59 (0.17–2.13)	0.423
54–	2.40 (0.50)	11.0 (4.12–29.60)	<0.001	1.84 (0.56)	6.27 (2.10–18.70)	0.001
Serum Ca (mg/dL, reference to < 8.9)						
8.9–9.2	−0.42 (0.58)	0.66 (0.21–2.06)	0.470	0.23 (0.68)	1.26 (0.33–4.80)	0.736
9.3–9.7	1.07 (0.57)	2.91 (1.11–7.58)	0.029	1.43 (0.56)	4.18 (1.38–12.60)	0.011
9.8–	1.82 (0.50)	6.20 (2.33–16.50)	<0.001	2.70 (0.59)	15.00 (4.72–47.40)	<0.001
Intact PTH (pg/mL, reference to < 85.0)						
85.0–157.0	1.55 (0.58)	4.71 (1.51–14.70)	0.008	2.27 (0.66)	9.69 (2.65–35.40)	0.001
158.0–247.0	2.70 (0.58)	14.90 (4.80–46.50)	<0.001	2.85 (0.63)	17.40 (5.00–60.20)	<0.001
248.0–	2.63 (0.58)	13.8 (4.44–43.20)	<0.001	3.17 (0.64)	23.80 (6.73–83.90)	<0.001
Parathyroid gland size (mm, reference to 0)						
0.1–5.7	0.83 (0.50)	2.29 (0.86–6.08)	0.096	0.30 (0.55)	1.35 (0.46–3.97)	0.579
5.8–8.8	1.45 (0.46)	4.27 (1.74–10.50)	0.002	1.28 (0.49)	3.61 (1.37–9.50)	0.009
8.9–	2.54 (0.44)	12.60 (5.31–30.00)	<0.001	2.33 (0.53)	10.20 (3.65–28.80)	<0.001
Calcimimetic dose per unit of body weight (mg/kg, reference to 0)						
0.1–0.2	NA	NA	NA	1.88 (0.60)	6.54 (2.04–21.00)	0.002
0.3–0.4	NA	NA	NA	2.23 (0.58)	9.32 (3.02–28.80)	<0.001
0.5–	NA	NA	NA	2.95 (0.55)	19.10 (6.55–55.70)	<0.001

Ca, calcium; 95% CI, 95% confidence interval; NA, not applicable; OR, odds ratio; PTH, parathyroid hormone; RC, regression coefficient; SE, standard error.
The parathyroid gland size was defined as 0 when parathyroid gland was not detected by echography.
Calcimimetic dose was converted into cinacalcet dose and calculated by per unit of body weight and is only adopted as a predictive factor in Model 2.

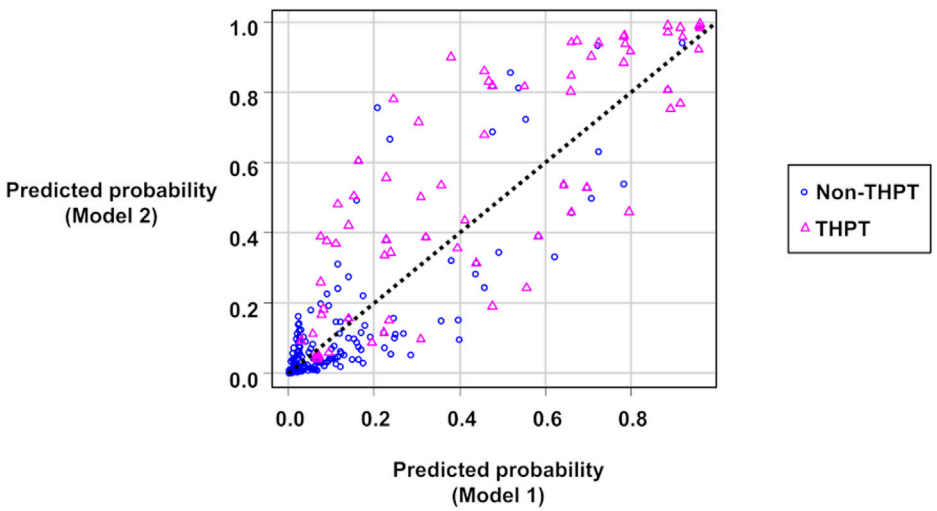

FIGURE 2 | Scatter plots of the predicted probabilities of Model 1 and Model 2. The circles represent non-THPT cases, and the triangles represent THPT cases. The black dashed line represents the coordinates where the predictions of Model 1 and Model 2 match. The circles below the black dashed line or the triangles above it indicate that the THPT predictions have improved in Model 2 compared with Model 1. THPT, tertiary hyperparathyroidism.

KTx (the median interval from KTx to PTx was 10.0 months [IQR: 7–17 months]), and post-transplant calcimimetic treatment was initiated within 1 year after KTx in all cases (**Table 2**).

THPT Predictive Factors

Multivariate logistic regression analysis of predictive factors for THPT development revealed that dialysis duration, pre-transplant serum Ca levels, intact PTH levels, parathyroid

TABLE 5 | Summary of the calculation for CNRI and IDI for Model 2 compared to Model 1.

Proportions of positive and negative changes in predicted probabilities
(1) Increase of predicted probability for THPT group: 0.655 (57/87)
(2) Increase of predicted probability for non-THPT group: 0.199 (93/467)
(3) Decrease of predicted probability for THPT group: 0.345 (30/87)
(4) Decrease of predicted probability for non-THPT group: 0.801 (374/467)

CNRI	Index (SE)	Z value	*p*-value	95% CI
CNRI for THPT group (1–3)	0.31 (0.10)	3.05	0.002*	0.11–0.51
CNRI for non-THPT group (4–2)	0.60 (0.04)	16.28	<0.001*	0.53–0.67
CNRI for entire cohort (1–3+4–2)	**0.91 (0.11)**	8.4	< 0.001*	0.70–1.13
Mean change in predicted probability				
Increase for THPT group (sensitivity): 0.08				
Decrease for non-THPT group (specificity): 0.01				
IDI	**Index (SE)**	**Z value**	***p*-value**	**95% CI**
	0.09 (0.02)	4.35	<0.001*	0.05–0.13

95% CI, *95% confidential interval;* CNRI, *continuous net reclassification improvement;* IDI, *integrated discrimination improvement;* THPT, *tertiary hyperparathyroidism;* SE, *standard error.*
*p-*value <0.05.*
The bold values represent the final results of the analysis.

TABLE 6 | Characteristics of THPT patients classified by degree of improvement in predicted probability.

	PP improvement <0.1 *n* = 48	PP improvement >=0.1 *n* = 39	*p*-value
Dialysis duration (months, IQR)	95 (45–146)	123 (67–171)	0.294
Serum Ca before KTx (mg/dL, IQR)	9.9 (9.50–10.4)	9.6 (9.0–10.0)	0.059
Serum intact PTH before KTx (pg/mL, IQR)	239.5 (177.3–341.8)	190.0 (122.0–286.5)	0.067
Parathyroid gland size (mm, IQR)	9.0 (0.0–11.0)	5.5 (0.0–8.80)	0.05
Pre-transplant calcimimetic treatment (%)	16 (33.3)	39 (100.0)	<0.001*
Pre-transplant calcimimetic dose per unit of body weight (mg/kg, IQR)	0.0 (0.0–0.3)	0.7 (0.4–1.1)	<0.001*

Ca, *calcium;* IQR, *interquartile range;* KTx, *kidney transplantation;* PTH, *parathyroid hormone;* PP, *predicted probability;* THPT, *tertiary hyperparathyroidism.*
Calcimimetic dose was converted into cinacalcet dose and calculated by per unit of body weight.
*p-*value <0.05.*

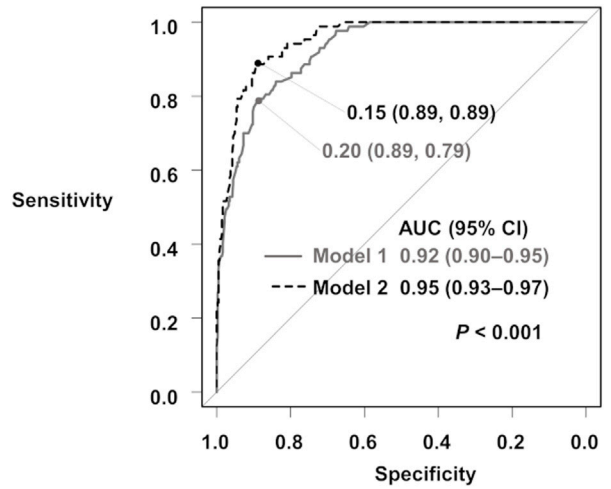

FIGURE 3 | ROC curves for the prediction of THPT from Model 1 and Model 2. The gray curve is the ROC curve for Model 1, and the black dashed curve is the ROC curve for Model 2. The ROC AUCs and 95% CIs are shown. AUC, area under the curve; 95% CI, 95% confidence interval; ROC, receiver operating characteristic; THPT, tertiary hyperparathyroidism.

TABLE 7 | Internal validation using the bootstrap method for the THPT prediction models.

	Model 1	Model 2
ROC AUC obtained through bootstrap resampling	0.91	0.94
Slope (BOC)	0.11	0.16
Mean absolute error	0.03	0.03
Mean squared error	0.00	0.00
0.9 Quantile of absolute error	0.06	0.08

BOC, *bootstrap optimism corrected*; ROC AUC, *receiver operating characteristic area under the curve.*

gland size, and pre-transplant calcimimetic use were significantly associated with THPT (**Table 3**).

THPT Prediction Models

Two THPT prediction models were created based on the logistic regression analysis. Model 1 was created from four predictors: dialysis duration, serum Ca level, intact PTH level, and parathyroid gland size, whereas Model 2 was created by adding the calcimimetic dose per unit of body weight to the predictors used in Model 1 (**Table 4**).

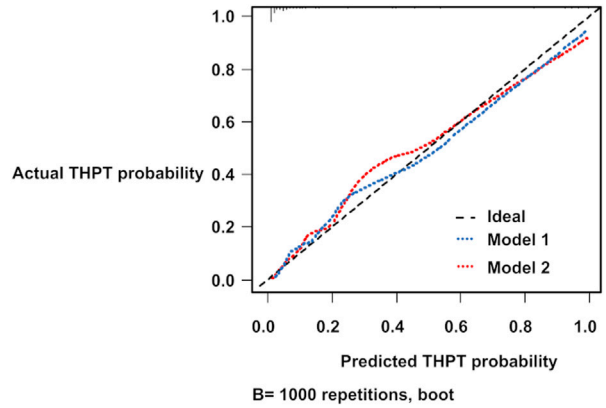

FIGURE 4 | Calibration diagrams for THPT prediction models using the bootstrap method. The blue and red dashed lines represent the calibration diagrams for Model 1 and Model 2, respectively. THPT, tertiary hyperparathyroidism.

Effect of the Pre-Transplant Calcimimetic Information on THPT Prediction

Figure 2 shows scatter plots of the predicted probabilities of Models 1 and 2. When comparing the predicted probabilities of the two THPT prediction models, the addition of the pre-transplant calcimimetic information improved the predicted probabilities in 65.5% (57/87) of the THPT group and 80.1% (374/467) of the non-THPT group, respectively (**Figure 2**; **Table 5**). The CNRI calculated from the sum of the proportion of improvement/worsening of the predicted probabilities was 0.91 (95% CI: 0.70–1.13, $p < 0.001$) (**Figure 2**; **Table 5**). In contrast, the mean changes in predicted probabilities were 0.08 in the THPT group and 0.01 in the non-THPT group, resulting in an IDI of 0.09 (95% CI: 0.05–0.13, $p < 0.001$) (**Figure 2**; **Table 5**). In the subgroup of THPT with an improvement of 0.1 or more in predictive probabilities by adding the pre-transplant calcimimetic information, both the proportion of patients receiving pretransplant calcimimetics and the doses of pre-transplant calcimimetics were significantly higher (**Table 6**).

When comparing the ROC AUCs of the two THPT prediction models, the inclusion of the pretransplant calcimimetic information significantly improved the AUC from 0.92 (95% CI: 0.90–0.95, cut-off value: 0.20, specificity: 0.89, sensitivity: 0.79) to 0.95 (95% CI: 0.93–0.97, cut off value: 0.15, specificity: 0.89, sensitivity: 0.89) ($p < 0.001$) (**Figure 3**; **Supplementary Table S4**).

Internal Validation of THPT Prediction Models

The bootstrapped ROC AUCs for Models 1 and 2 were 0.91 and 0.94, respectively (**Table 7**). The slope optimism values of the two models were 0.11 and 0.16, respectively (**Table 7**). From the calibration diagrams based on the bootstrap validation results, although Model 1 outperformed Model 2 in the 0.3–0.5 probability range, Model 2 outperformed Model 1 in the 0.5–0.8 probability range. Both prediction models slightly underestimated THPT risk at low-risk levels and slightly overestimated it at high-risk levels (**Figure 4**).

DISCUSSION

THPT is a complication often observed after KTx, and post-transplant PTx or calcimimetic induction is often necessary [10, 11]. In this study, including the pre-transplant calcimimetic use and dose information as a predictive factor improved the accuracy of THPT prediction. From the scatter plot of the predicted probabilities of Model 1 and Model 2, the addition of pre-transplant calcimimetic information enhanced the accuracy of prediction of THPT risk in most cases in both the THPT and non-THPT groups, leading to high CNRI values. However, although the ROC AUC of Model 2 was significantly better than that of Model 1, the degree of improvement was relatively modest, contrary to the high CNRI value. In other words, Model 1 was able to predict THPT reasonably well even without pre-transplant calcimimetic information. This is probably because the proportion of patients who had received pre-transplant calcimimetic treatment was not as high, at 25% of the entire cohort. However, the subgroup analysis showed that patients treated with pre-transplant calcimimetics and at higher doses had greatly improved predictive probability. Thus, the larger the proportion of patients receiving pre-transplant calcimimetics and the calcimimetic dose in a cohort, the greater the contribution of calcimimetic information to THPT prediction improvement.

From the kidney graft function and prognosis perspective, pre-transplant PTx may be considered for cases with high THPT risk. For pre-transplant PTx to be properly performed, accurate THPT prediction is indispensable; however, research on THPT prediction models remains limited. Hong et al. [21] developed an excellent predictive model for THPT based on Ca, PTH, and dialysis duration. That study was a pioneering one on THPT prediction and holds significant importance for the prevention and early treatment of THPT. Yet, in that report, there was no mention of a relationship between calcimimetic use and THPT risk. In Japan, since the introduction of cinacalcet in 2008, the number of PTx in dialysis patients has drastically decreased [46]; however, the proportion of post-transplant hyperparathyroidism has not seen a corresponding decrease [3]. Calcimimetics are highly effective against SHPT; however, significant reductions in both PTH and calcium levels may lead to consequent underestimation of THPT risk for patients who should ideally undergo pre-transplant PTx. Therefore, in regions where calcimimetics are widely used, there is a potential risk of misestimating THPT risk.

To the best of our knowledge, this study represents the first report to validate a THPT prediction model that includes pre-transplant use and dose information of calcimimetics. By incorporating pre-transplant calcimimetic information into the predictive model, it becomes possible to properly assign

high-THPT risk cases with suppressed PTH and Ca levels under calcimimetic treatment to the high-risk group. This contributes to pre-transplant PTx decision-making without discontinuing calcimimetics. In the context of widespread calcimimetic treatment, information on calcimimetic use and dose would be important for accurate THPT risk prediction.

As THPT prediction advances, candidates for pre-transplant PTx may be identified more frequently. However, the validity of postponing already scheduled KTx for the purpose of pre-transplant PTx remains uncertain. This is because the extension of dialysis duration is associated with poor patient and graft outcomes [47, 48]. The lack of evidence on whether the benefits of pre-transplant PTx outweigh those of shorter dialysis duration is a factor in this uncertainty. Therefore, the timing of PTx should be carefully considered on a case-by-case basis.

This study had some limitations. First, this was a single-center, retrospective study. Second, serum phosphorus data were lacking to evaluate its clinical relevance as a key factor influencing PTH levels [49]. Third, assessment of parathyroid gland size is another challenge as noted in a previous study [50]. There is a certain concern in reproducibility of ultrasound-guided parathyroid gland size measurement. Fourth, the prediction models were not externally validated. Fifth, our cohort was predominantly composed of patients receiving KTx from living donors, a scenario unique to Japan and distinct from Western countries. In addition, the prevalence of calcimimetic use and dialysis practices may differ between countries. Therefore, the prediction models used in this study may not be effective in predicting THPT in KTx candidates from other countries. However, the strengths of this study include the simplicity of the development methods for the prediction models and the use of analytical techniques with free statistical software. Thus, replicating the methods of this study in various cohorts from different regions using patient data would enable the convenient and cost-effective creation of an accurate predictive model.

In conclusion, information on pre-transplant calcimimetic use and dose improved the accuracy of post-KTx THPT prediction. The THPT prediction model that included pre-transplant calcimimetic use and dose information as a predictive factor can contribute to the prevention and early treatment of THPT in the era of calcimimetics. Future studies should perform external validations using new cohorts or cohorts from other institutions.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by the Institutional Review Board of the Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because of the retrospective nature of the study.

AUTHOR CONTRIBUTIONS

MO: conceptualization, methodology, writing–original draft. TS: writing–original draft. TaH: conceptualization, methodology, writing–review and editing. ToH, YH, KF, TI, and NG: investigation, formal analysis, visualization. SN: writing–review and editing. YW: supervision, writing–review and editing. Each author has reviewed the manuscript, believes it represents valid work, and approves it for submission. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.12704/full#supplementary-material

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ORIGINAL RESEARCH
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Elements of Weight Management Among Pre-Kidney Transplant Candidates: The Patient Perspective

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Obesity and related comorbidities heighten risks for complications in kidney transplant settings. While pre-transplant patients often have access to nutrition counseling and health support, literature is limited on patients' perceptions of weight and motivation to lose weight prior to transplantation. We conducted a survey among ≥18-year-old patients on the kidney transplant waitlist at a single center. Questions addressed weight perception, motivation for weight loss, available resources, and engagement in physical activity. Medical records provided demographic and clinical data. Statistical tests analyzed quantitative data, while free-text responses were thematically grouped and described. Of 1055 patients, 291 responded and were matched with demographic data. Perceived weight changes correlated with actual changes in body mass index (BMI) (<24.9) were more receptive to weight center resources (<30 kg/m^2) are most interested in weight loss resources and demonstrate motivation. Furthermore, pre-transplant nutrition counseling correlates with healthier behaviors. Integrating patients' perspectives enhances pre-transplant protocols by encouraging active involvement in health decisions.

Keywords: kidney transplant, waiting list, obesity, weight perception, weight loss

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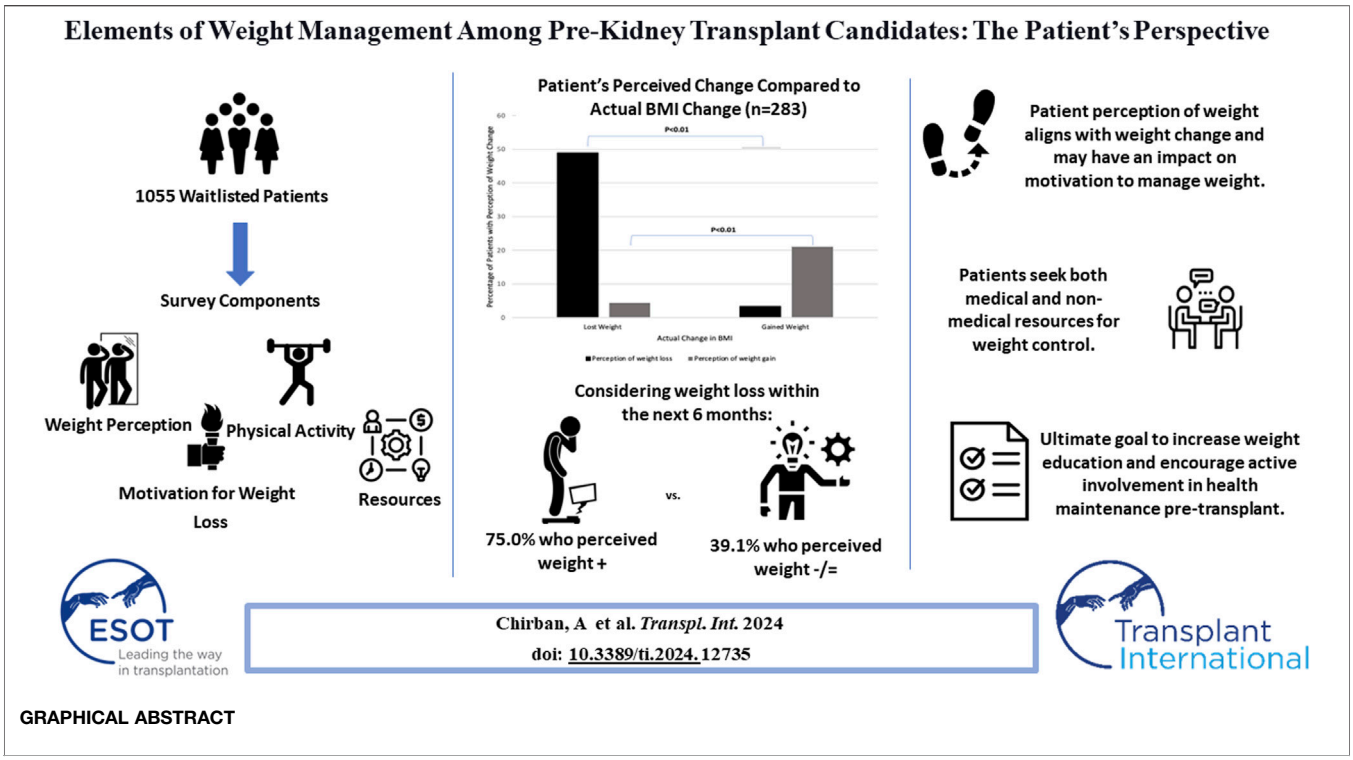
INTRODUCTION

Obesity in the U.S. has been increasing steadily, with a prevalence of 41.9% among all adults [1]. In particular, obesity poses several risks and consequences for patients contributing to chronic kidney disease (CKD) and eventually end-stage renal disease (ESRD) [2–4]. In the U.S., the prevalence of CKD among adults is just under 15%, while the prevalence of ESRD remains among one of the highest in the world, with 2,242 cases per million population in 2018 [5]. Obesity prevalence among kidney transplant patients is even higher that then general population at 60% [6], and leads to an increased risk of complications across all stages of care including pre-, peri- and post-operatively. For patients on the kidney transplant wait list, obesity increases the risk of morbidity and metabolic disturbances, and is associated with longer wait times [2, 7, 8]. Moreover, obesity has implications peri- and post-transplant with increased incidence of wound complications, prolonged length of stay, increased morbidity, and delayed graft function [2, 7–9].

Abbreviations: CKD: chronic kidney disease; ESRD: end stage renal disease; BMI, body mass index.



GRAPHICAL ABSTRACT

Current strategies to address weight loss for kidney transplant patients include lifestyle modifications (diet and exercise), bariatric surgery, and pharmacotherapy [3, 10]. For patients with a body mass index (BMI) > 35, transplant nutrition consult and lifestyle modifications are recommended [3, 10]. However, pre-kidney transplant patient perspectives of these interventions, perceptions of their own weight change, and their willingness and motivations to lose weight, is not well understood.

We sought to identify pre-kidney patient perspectives on weight, weight loss or weight maintenance motivations, resources used for weight loss, and barriers to reaching their weight goal. Understanding patient perspectives of their weight and motivations to lose weight will provide a basis for designing an effective patient-centered weight management protocol for those on the kidney transplant waiting list.

METHODS

A survey was distributed via email to patients on the kidney transplant waitlist at Massachusetts General Hospital. The survey was open for completion for 2 months. Automated reminders to complete the survey were sent through REDCap every 2 weeks. This study was approved by the Mass General Brigham IRB as an exempt study, number 2020P003378.

Inclusion Criteria

Patients who were 18 years and older on the kidney transplant waitlist were eligible to participate in the study.

Exclusion Criteria

At the time of data analysis, patients whose survey responses could not be linked by email address to their demographic data, were not included in the study. There were 17 patients who did not have email addresses associated with their survey responses and hence, were excluded. Among non-responders, 71 patients with incomplete data were not included.

Survey Development

A quantitative and qualitative survey was developed by a multidisciplinary team of healthcare professionals including members of the transplant team, dieticians, and an obesity medicine physician. The survey was designed to address patients' perceptions of weight and motivation to lose weight, factors contributing to weight change while on the waitlist, barriers hindering weight loss, interest in and utilization of medical and non-medical weight loss resources, and impact of COVID-19 on weight and physical activity. The survey was tested by research personnel prior to administration.

Data Collection

Automated reminders to complete the survey were sent through REDCap every 2 weeks. Clinical data including weight, height, most recent BMI and BMI at evaluation, days on the waitlist, current medications, organ transplant status and history of previous transplant, etiology of kidney disease, as well as demographic data including race, gender, and age were collected from each patient's electronic medical record. The survey results were matched to their demographic and clinical data by email address.

Data Analysis

Statistical analyses were conducted with StataMP14.0, College Station, Texas. Patients were divided into three groups according to their body mass index (BMI): 1) Normal weight: $\leq$ 24.9 kg/m^2; 2) overweight: 24.9–30 kg/m^2; 3) obese: $\geq$ 30 kg/m^2. Differences between groups were tested using Mann-Whitney U test and logistic regression analyses for continuous variables. Categorical variables were evaluated utilizing Fisher's exact or Pearson's chi-squared tests as appropriate. Probabilities of less than 0.05 were accepted as significant. Free-text responses were reviewed and grouped according to recurring themes and summarized with descriptive statistics.

Current Transplant Center Practice

Patients on the kidney transplant waitlist undergo an initial transplant evaluation, during which a comprehensive nutrition assessment is conducted. This assessment includes a review of their medical history, current medications, laboratory results, dietary intake, diet history, physical activity level, frailty assessment, and weight history. If patients have a BMI >38 kg/m^2, they are provided with guidance based on their responses to the nutrition assessment to help them achieve a weight loss goal of 5% within 6 months. For weight loss education, these patients receive informative pamphlets that define and explain BMI calculation, discuss why weight loss and achieving a lower BMI are recommended for transplantation, and include information about the Mass General Hospital Weight Center, including details on how to initiate their weight loss journey.

Interaction with the nutrition team is generally limited for patients on the waitlist unless weight loss is necessary for them to meet the criteria for activation on the wait-list. In such cases, patients are periodically contacted for support and guidance by the transplant dietician. During the readiness visit, which occurs when transplant is estimated to occur within the next 1 year based on waiting-time or sensitization, a follow-up nutrition assessment is conducted, and patients receive guidance on dietary protocols to follow after transplant.

RESULTS

Among 1,055 patients who were emailed to participate in the survey, 291 patients responded and could be matched with corresponding demographic data (27.6%). There was a significant different in age, sex, and race among included survey responders versus those invited to participate who did not complete the survey. Participants were more likely to be older, male and white (all $p \leq 0.01$). There were no significant differences in mean BMI ($p = 0.2$), mean days on the waitlist ($p = 0.7$), or etiology of ESRD ($p = 0.1$) (**Table 1**).

Perception of Weight and Motivation for Weight Loss

Among all patients, actual weight change was correlated with patient's perception of weight change while being on the waitlist ($p < 0.01$, **Figure 1**). While 24.91% ($n = 70$) of patients expressed weighing less than what they described as their normal baseline, 14.59% ($n = 41$) expressed weighing more than their normal baseline. Among all survey respondents, 47.1% self-reported that they had lost weight since being waitlisted, whereas 32.6% reported gaining weight since being waitlisted. Of patients who noted weight gain since being waitlisted, 75% ($n = 21$) and 36% ($n = 10$) were seriously considering weight loss and weight maintenance in comparison to those who reported weight loss, no change in weight, or weight fluctuation ($p < 0.001$). Patients with a most recent BMI $\geq$ 30 kg/m^2 were more likely to try to not gain weight, seriously consider weight loss, and less likely to seek weight maintenance in comparison to patients with a BMI<30 kg/m^2 ($p < 0.01$). Further, patients with a BMI $\geq$ 30 kg/m^2 were less likely to attribute their weight to their kidney disease compared to normal and overweight ($p = 0.042$).

Factors Contributing to Weight Change While on the Waitlist

One hundred seventy-eight (66.4%) patients stated they received nutrition counseling prior to responding to the survey. Receiving nutrition counseling was significantly associated with an increase in daily servings of vegetables consumed ($p = 0.024$) and a significantly reduced number of eating meals out ($p = 0.041$). Nutrition counseling was not significantly associated with BMI or weight change.

Barriers for Weight Loss

Among patients with a BMI exceeding 25 kg/m^2, 53.5% identified experiencing barriers to weight loss. Among all respondents, regardless of BMI, 10.3% reported difficulty in maintaining a specific or restrictive diet, while 12.4% mentioned intolerance or a reduced ability to engage in physical activity, often associated with fatigue symptoms. Furthermore, 15.1% of patients cited comorbidities and treatment side effects as factors hindering their ability to lose weight (**Figure 2**).

Interest and Utilization of Medical and Non-Medical Resources

Patients most frequently listed utilization of dietary modifications to maintain weight (68%, $n = 198$) followed by using home exercise programs (39%, $n = 113$), calorie tracking (20%, $n = 59$), other strategies most commonly including aerobic activity and dietary changes (20%, $n = 58$), a gym membership (13%, $n = 38$), and a personal trainer (3%, $n = 9$) (**Table 2**). When asked about the potential future use of weight loss or maintenance strategies, patients were equally interested in utilizing home exercise programs or a personal trainer (23%, $n = 68$), followed by a gym membership (21%, $n = 62$), calorie tracking (15%, $n = 44$), dietary modifications (12%, $n = 36$), and others (8%, $n = 22$).

When stratified by BMI, patients with a higher BMI were significantly more likely to utilize a gym membership ($p = 0.028$). In comparison to participants with a BMI $\leq$24.9 kg/m^2 participants with a BMI 24.9–30 kg/m^2 had a odds ratio of 0.026, (95% CI: 0.073–0.125), and participants with a BMI $\geq$ 30 kg/m^2 had an odds ratio of 0.109 (95% CI 0.009–0.21). Also,

TABLE 1 | Demographics.

	Responders (%)	Non-responders (%)	*p*-value
All patients (N)	291	676	
Age, *mean (SD)*	59.6 (12.4)	56.6 (13.3)	*<0.01*
Sex, *n (%)*			*<0.01*
Male	186 (64)	413 (61)	
Female	105 (36)	263 (39)	
Race/Ethnicity, *n (%)*			*0.01*
White	230 (79)	447 (66)	
Asian	20 (7)	54 (8)	
Hispanic/Latino			
Black or African American	22 (8)	106 (16)	
American Indian/Alaska Native	1 (0)	4 (1)	
Other/Declined/Unavailable	18 (6)	65 (10)	
BMI, *mean (SD)*	28.6 (5.5)	29.1 (6.0)	0.21
BMI <24.9 kg/m^2 *n (%)*	74 (25.5)	178 (26.3)	
BMI = 25–29.9 kg/m^2 *n (%)*	112 (38.5)	235 (34.8)	
BMI >30 kg/m^2 *n (%)*	105 (36.1)	263 (38.9)	
Days on waitlist, *mean (SD)*	1,071.4 (2,207.8)	1,118.5 (1,361.5)	0.74
Etiology of Kidney Disease (Primary and Secondary Diagnosis), *n (%)*			0.85
Glomerular Diseases	25 (8)	60 (9)	
Diabetes Nephropathy	81 (25)	203 (29)	
Hypertension	62 (19)	115 (16)	
Polycystic kidney disease	23 (7)	60 (9)	
Congenital	2 (1)	26 (4)	
IgA nephropathy	25 (8)	54 (8)	
Kidney Toxicity + AKI	30 (9)	32 (5)	
Unknown/Other*	75 (23)	149 (21)	

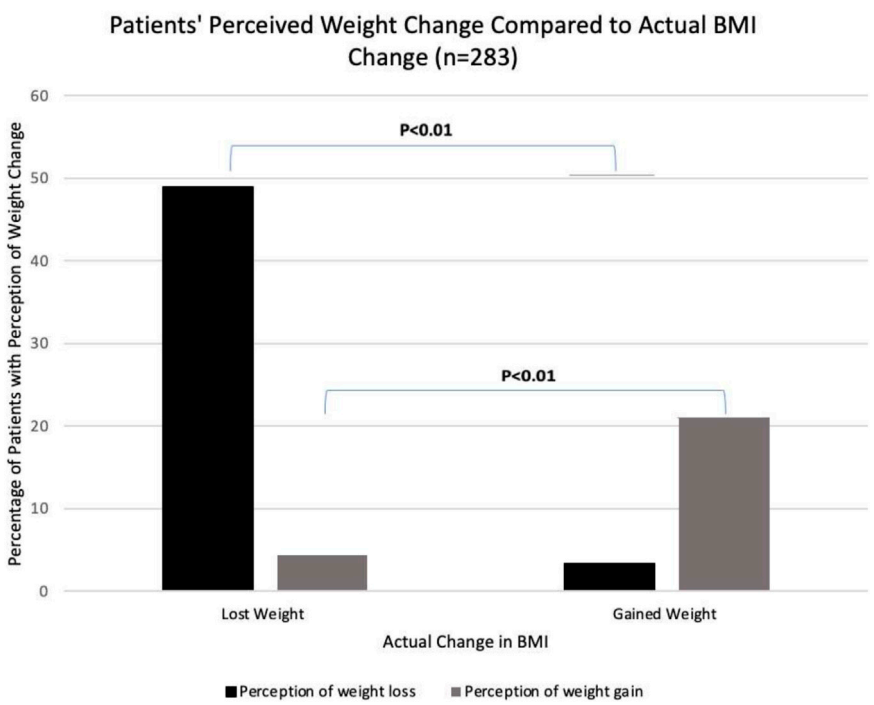


FIGURE 1 | Perception of weight change while on the waitlist was stratified by actual weight change while on the waitlist. The percentage of patients with perception of weight gain or loss (y-axis) accurately reflected actual change in BMI (x-axis) ($p < 0.01$).

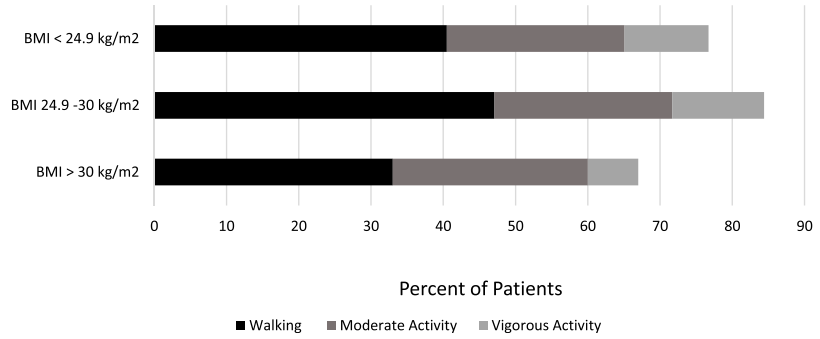


FIGURE 2 | Engagement in physical activity was quantified and stratified by BMI. Individuals categorized as "overweight" demonstrated the highest engagement, with more than 30 minutes of physical activity.

TABLE 2 | Current and future utilization of weight management resources.

Weight management strategies	Current use			Future use		
	N (%)	Or (95% CI)	*p*-value	N (%)	Or (95% CI)	*p*-value
Dietary Modifications	198 (68)	1.17 (0.85–1.60)	0.34	36 (12)	1.32 (0.83–2.10)	0.24
Home Exercise Program	113 (39)	0.87 (0.64–1.17)	0.35	68 (23)	1.17 (0.82–1.66)	0.40
Calorie Tracking	59 (20)	1.37 (0.94–1.99)	0.14	44 (15)	1.62 (1.04–2.51)	0.03
Others	58 (20)	0.96 (0.66–1.39)	0.82	22 (8)	0.97 (0.56–1.70)	0.92
Gym Membership	38 (13)	1.7 (1.06–2.72)	***0.03***	62 (21)	0.98 (0.68–1.41)	0.91
Personal Trainer	9 (3)	1.88 (0.72–4.91)	0.20	68 (23)	1.20 (0.85–1.71)	0.31
Weight management devices	**N (%)**	**Or (95% CI)**		**N (%)**	**Or (95% CI)**	***p*-value**
I don't wish to track my weight	161 (55)	0.85 (0.63–1.14)	0.28	100 (34)	0.75 (0.55–1.02)	0.07
Smart Phone	52 (18)	0.98 (0.67–1.44)	0.92	42 (14)	1.51 (0.97–2.34)	0.07
Smart Watch	49 (17)	1.17 (0.78–1.74)	0.45	52 (18)	0.81 (0.55–1.19)	0.28
Fitbit	28 (10)	0.94 (0.57–1.55)	0.80	48 (16)	1.46 (0.97–2.21)	0.07
Others	13 (4)	1.67 (0.77–3.64)	0.19	12 (4)	1.29 (0.60–2.77)	0.52
Social Media Fitness App	9 (3)	2.44 (0.86–6.90)	0.09	30 (10)	1.36 (0.82–2.24)	0.24
Pedometer	9 (3)	1.01 (0.43–4.37)	0.99	45 (15)	1.32 (0.87–2.01)	0.20
GPS Enabled Watch	5 (2)	1.17 (0.37–3.73)	0.79	21 (7)	1.27 (0.71–2.28)	0.42

regarding future weight loss strategies, participants with a BMI 24.9–30 kg/m^2 and a BMI $\geq$ 30 kg/m^2 were more interested (p = 0.032) in calorie tracking in in comparison to patients with a BMI $\leq$ 24.9 kg/m^2. Otherwise, there was no difference in patient's future strategies for weight loss/maintenance based on BMI category.

When discussing weight management devices, the majority of patients indicated that they do not currently track their weight (55%, n = 161). Among those who currently track their weight, the most common method of weight tracking was a smart phone (18%, n = 52). This was followed by a smart watch (17%, n = 49), Fitbit (10%, n = 28), social media fitness application or a pedometer (3%, n = 9), a GPS enabled watch (2%, n = 5), and others (4%, n = 13). While most patients (34%, n = 100) selected that they are not interested in tracking their weight in the future, 18% (n = 52) expressed interest in a smart watch, followed by a Fitbit (16%, n = 48), pedometer (15%, n = 45), smartphone (14%, n = 42), GPS enabled watch (7%, n = 21), and others (4%, n = 12) (**Table 2**). There were no significant differences in current weight management device utilization or interest in future utilization of weight management resources when stratified by BMI.

Interest in Weight Center Resources and Medically Assisted Weight Loss

While the majority of patients were not interested in a referral to the weight center, weight loss medication, or weight surgery (71%, n = 206), there was a significant correlation between higher BMI and patient interest in these resources (**Table 3**). While weight loss surgery was of least interest to patients with a BMI $\geq$ 30 kg/m^2 (11%, n = 12), it was appropriately significantly greater among higher BMI patients in comparison to normal or overweight.

TABLE 3 | Patient interest in medical resources for weight loss.

	BMI N (%)			Or (95% CI)	*p*-value
	<24.9	24.9–29.99	>30		
Weight center referral	4 (5)	12 (11)	28 (27)	2.68 (1.63–4.42)	*<0.01*
Weight loss medication	0 (0)	6 (5)	28 (27)	7.79 (3.35–18.13)	*<0.01*
Weight loss surgery	1 (1)	1 (1)	12 (11)	5.48 (1.72–17.50)	*0.01*
Not interested	65 (88)	87 (78)	54 (51)	0.36 (0.25–0.53)	*<0.01*

Physical Activity and Impact of COVID-19

There were no significant differences in physical activity as identified by engaging in walking, moderate exercise, or vigorous exercise among patients when stratified by BMI (**Figure 2**). Among all patients, more patients engaged in less than 30 min of physical activity than more than 30 min of activity.

Participants were asked about both activity change and weight change during the COVID-19 pandemic. Regarding activity during COVID, 46.1% reported decreased activity during the pandemic, whereas 43.1% reported no change in physical activity. Furthermore, patient reporting of activity change during COVID-19 did not differ among patients when stratified by BMI ($p = 0.548$).

While the majority of patients, regardless of BMI, indicated no COVID-associated weight change, overall patients were more likely to indicate weight loss than gain during COVID-19. Additionally, there was a significant difference in weight change during the pandemic when stratified by BMI ($p = 0.025$). Among those who indicated more than 10 pounds of weight loss, patients with BMI $\geq$ 30 kg/m^2 had the highest proportion of weight loss during COVID-19, followed by patients with a BMI between 24.9–30 kg/m^2, and patients with BMI. Similarly, a higher proportion of obese patients lost <10 pounds, in comparison to overweight and normal weight patients. Among those who indicated weight gain greater than and less than 10 pounds, there was a higher proportion of patients with a BMI $\geq$ 30 kg/m^2 in comparison to those BMI 24.9–29.9 kg/m^2 and BMI $\leq$ 24.9 kg/m^2.

DISCUSSION

This study surveyed patients currently on the kidney transplant waitlist at a single institution and examined their interest in and utilization of resources for weight maintenance, physical activity, perception and understanding of weight, and motivation to lose weight. Patients with a higher BMI expressed greater interest in use of weight loss resources in the future, such as utilizing a gym membership ($p = 0.028$), and calorie tracking ($p = 0.104$). Patients with a higher BMI were more likely to express openness to weight center referral ($p < 0.001$), weight loss medication ($p < 0.001$), and weight loss surgery ($p = 0.004$). Nutrition counseling was associated with a significant increase in vegetable consumption ($p = 0.024$) but no difference in BMI or weight loss. There were no significant differences in physical activity when stratified by BMI or impact of COVID-19. Obese patients, however, expressed greater fluctuation in weight during the pandemic (both weight loss and weight gain).

Regarding actual weigh change, over time, patient reported weight change accurately reflected weight change by change in BMI at listing and most recent ($p < 0.01$). Patients with a higher BMI were more motivated to lose weight and try not to gain weight ($p < 0.01$). Such findings suggest that patients whose weight is of greatest concern prior to kidney transplant are most interested in seeking resources for weight loss, both medical/surgical and non-medical, and motivated to lose weight. At our single center study, nutrition counseling was associated with an increase in healthy dietary behaviors, as defined as vegetable consumption and not eating out.

As obesity rates increase and result in reduced kidney graft survival and increased patient complications [11], methods to educate patients and help manage weight loss in the context of transplant surgery is of increasing significance. Approximately 60% of patients undergoing a kidney transplant have a BMI>30 kg/m^2 with frequent additional weight gain post-transplant [12]. One study demonstrated that patients with a BMI>30 kg/m^2 experience longer procedure times and warm ischemia, though there was no difference associated with BMI 24.9–30 kg/m^2. Furthermore, kidney graft function post-operatively was reduced after a 1-month among patients who were BMI>30 kg/m^2 [11].

Many transplant centers are adjusting for the increase in obesity and raising the limits of accepted pre-transplant BMI, but ongoing work to improve the safety and efficacy for obese patients receiving a kidney transplant is still underway [13]. According to the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines, patients should not be not excluded from transplantation due to BMI or waist-to-hip ratio status, but patients with obesity should be offered weight loss interventions prior to transplantation [14]. The American Society of Transplantation noted that low-calorie diet, behavioral therapy, and a physical activity program to achieve a BMI<30 kg/m^2 is recommended as a goal for pre-transplant patients [12].

Regarding weight loss strategies, Yemini et al., demonstrated successful bariatric surgery prior to kidney transplant for morbidly obese patients resulting in reduced obesity related comorbidities peri-transplant [12]. Kukla et al., performed a clinical cohort study that compared weight loss pre-kidney transplant for patients with diabetes receiving a conservative

approach to weight loss including individualized nutrition and physical activity regimens as well as specialist consultations, in comparison to patients who received bariatric surgery [15]. It was found that patients who opted for the conservative approach lost 3% of their body weight at 1-year post-weight consultation, whereas patients who underwent a bariatric surgery lost 19% of their body weight [15].

In our study, patients who were at greatest risk for kidney transplant complications (BMI ≥ 30), were most motivated to lose weight and receive resources, both through support from the weight center and personal fitness devices and activities. Given that weight can be a barrier to receiving a transplant and impacts patient and graft survival after transplant, further work is needed to address access to and utilization of weight loss resources and education, as well as to understand how self-perception and cultural values may impact weight loss for pre-kidney transplant patients.

Limitations

There are noteworthy limitations to be mentioned regarding the generalizability of the study findings. First, the primary method of stratifying patients was by BMI, which does not differentiate tissue type and fluid retention. It is recommended that waist circumference be used as an additional method to measure abdominal adiposity, but this was not feasible as it is not routinely collected in our transplant center and therefore is not available from chart review [16]. Additionally, we did not have patients self-report their weight. Weight and BMI were attained from the medical record. With the increase in telehealth visits due to the COVID pandemic, the patients may have been in clinic less frequently which may affect the accuracy of the recorded weight in the medical record. Second, deconditioning because of dialysis and kidney disease may limit pre-transplant patients' physical activity and increase weight fluctuation. While frailty scores are currently collected at our evaluation clinic, this is a change in practice, and they are not available from the chart review we performed.

Third, by nature of this survey study, limited email or internet access may affect response rate, and participation bias may impact the results. Fourth, the data presented is from a single center, and there were statistically significant differences in some demographic features between respondents and non-respondents, limiting the generalizability of the findings. Fifth, we chose to not include questions assessing patients' knowledge of their disease and healthy weight in order to keep the survey brief to optimize response rates; however, further studies could assess patient knowledge as that may impact their behavior regarding weight loss and weight maintenance. Despite these limitations, the findings demonstrate valuable insights regarding the patient's perspective on pre-kidney transplant weight reduction, interest in weight loss resources, impact of weight center interventions on health behaviors, and perception of weight change that reflects weight maintenance motivation.

CONCLUSION

To our knowledge, this is the first study published on patients' perspectives and willingness to lose weight while on the kidney transplant wait list. The findings from this survey will be the basis of the development of focus group guides to further explore patient perceptions of pre-transplant weight loss. Through this research and the planned future studies, weight management protocols may be optimized to best address the current increasing trend of obesity in -pre kidney transplant patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, upon completion of a formal Data Use Agreement process.

ETHICS STATEMENT

The studies involving humans were approved by Mass General Brigham IRB, number 2020P003378. The studies were conducted in accordance with the local legislation and institutional requirements. The study was deemed exempt by the IRB and participant completion of the survey was considered consent to the study.

AUTHOR CONTRIBUTIONS

AC: survey design, data analysis, manuscript development. DV: data analysis, manuscript development. TC: data analysis, manuscript development. MCo: data analysis, manuscript development. MCh: data analysis, manuscript development. JC: survey development. NE: survey design, manuscript development. AS: survey development. LD: survey design, data analysis, manuscript development. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

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ORIGINAL RESEARCH
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Pitfalls in Valganciclovir Prophylaxis Dose Adjustment Based on Renal Function in Kidney Transplant Recipients

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Valganciclovir (VGC) is administered as prophylaxis to kidney transplant recipients (KTR) CMV donor (D)+/recipient (R)– and CMV R+ after thymoglobulin-induction (R+/TG). Although VGC dose adjustments based on renal function are recommended, there is paucity of real-life data on VGC dosing and associations with clinical outcomes. This is a retrospective Swiss Transplant Cohort Study-embedded observational study, including all adult D+/R– and R+/TG KTR between 2010 and 2020, who received prophylaxis with VGC. The primary objective was to describe the proportion of inappropriately (under- or over-) dosed VGC week-entries. Secondary objectives included breakthrough clinically significant CMV infection (csCMVi) and potential associations between breakthrough-csCMVi and cytopenias with VGC dosing. Among 178 KTR, 131 (73.6%) patients had ≥2 week-entries for the longitudinal data of interest and were included in the outcome analysis, with 1,032 VGC dose week-entries. Overall, 460/1,032 (44.6%) were appropriately dosed, while 234/1,032 (22.7%) and 338/1,032 (32.8%) were under- and over-dosed, respectively. Nineteen (14.5%) patients had a breakthrough-csCMVi, without any associations identified with VCG dosing ($p = 0.44$). Unlike other cytopenias, a significant association between VGC overdosing and lymphopenia (OR 5.27, 95% CI 1.71–16.22, $p = 0.004$) was shown. VGC prophylaxis in KTR is frequently inappropriately dosed, albeit without meaningful clinical associations, neither in terms of efficacy nor safety.

Keywords: cytomegalovirus, valganciclovir, renal function, kidney transplantation, dosing

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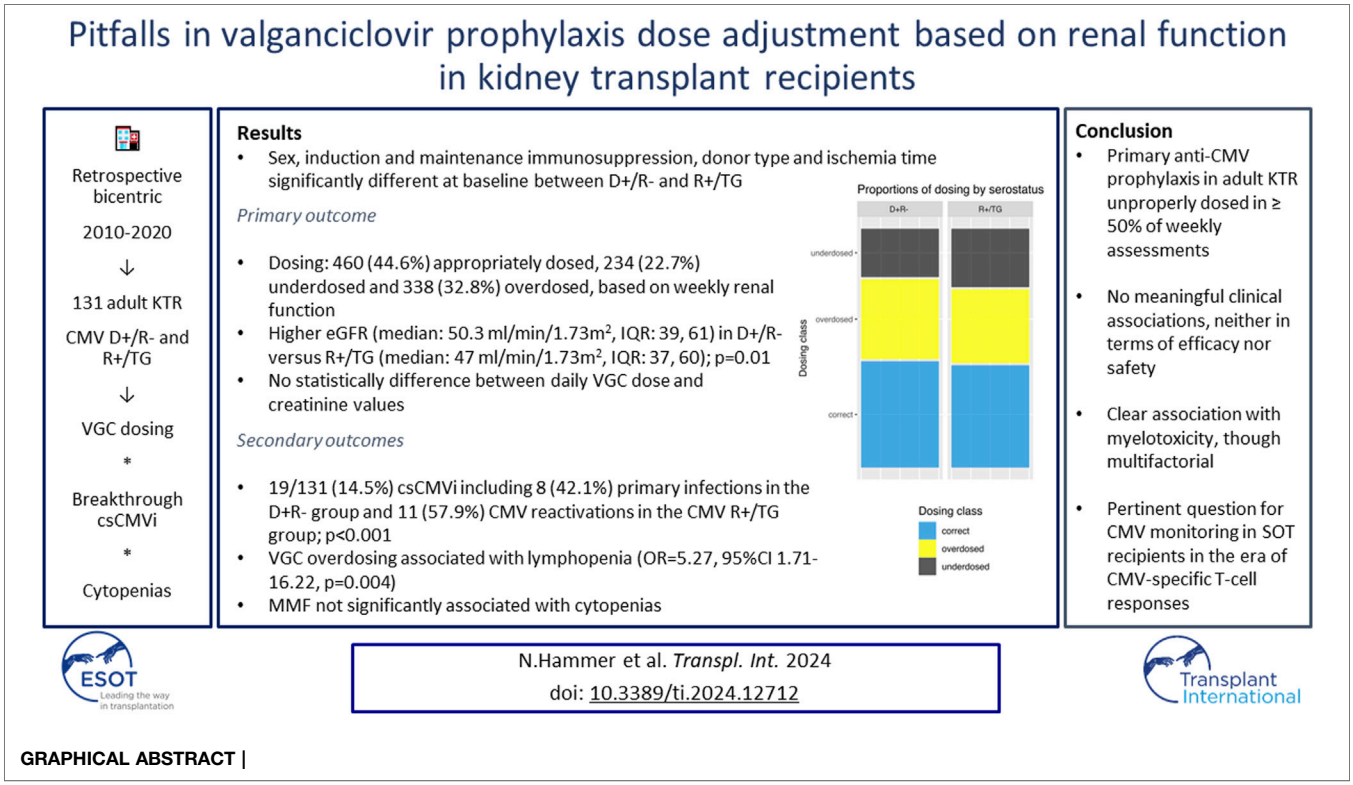
Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CMV, cytomegalovirus; csCMVi, clinically significant CMV infection; DBD, donor after brain death; DCD, donor after cardiac death; DGF, delayed graft function; HSC, hematopoietic stem cells; KPD, kidney paired donation; KTR, kidney transplant recipients; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; PAP, primary antiviral prophylaxis; PCR, polymerase chain reaction; PNF, primary non function; SOT, solid organ transplantation; STCS, Swiss Transplant Cohort Study; TG, thymoglobulin; TDM, therapeutic drug monitoring; VGC, valganciclovir.



GRAPHICAL ABSTRACT |

INTRODUCTION

Clinically significant cytomegalovirus infections (csCMVi) are one of the most common complications after a solid organ transplant (SOT), depending primarily on the donor/recipient (D/R) CMV serology status and the net state of immunosuppression [1]. Prophylactic strategies have included the administration of (val)ganciclovir in high-risk patient populations, for 3 months in CMV R+ receiving induction immunosuppression with thymoglobulin (R+/TG) or 6 months in CMV D+R- [2–6]. Orally administered VGC is administered at a dose of 900 mg daily for prophylaxis in patients with normal renal function [3]. Due to low protein binding, VGC is renally eliminated via both glomerular filtration and active tubular secretion and requires dose adjustment based on renal function [7]. Adjusted VGC dosing has been proposed, although there are no good data to adequately correlate VGC dose with plasma concentrations and therapeutic drug monitoring (TDM) is rarely available and not well validated [8]. Lack of evidence is even more problematic in patients requiring continuous renal replacement therapy or hemodialysis for delayed graft function (DGF) [9]. Despite lack of adequate evidence, VGC dose adjustments based on renal dysfunction are made in most transplant centers worldwide, predominately to prevent neutropenia [10]. However, lower dose administration may lead to decreased drug concentrations, resulting in breakthrough csCMVi and/or (val)ganciclovir resistance selection [8]. Furthermore, in kidney transplant recipients (KTR) renal function may change over time, particularly early post-transplantation, necessitating frequent monitoring and adjustment of VGC dosing [11]. The latter may be particularly cumbersome and prone to mistakes, for those KTR discharged with still impaired renal function and renally dosed VGC requiring close and frequent ambulatory follow-up.

We hypothesized that VGC dosing is not properly adjusted to renal function based on established recommendations, due to lack of patient monitoring particularly on an outpatient basis, potentially leading to higher rates of breakthrough csCMVi or VGC associated toxicities during the first 3–6 months post-transplant. We aim to describe the proportion of VGC primary CMV prophylaxis weekly doses, that are either under- or over-dosed according to renal function.

MATERIALS AND METHODS

This was a two-center retrospective observational study conducted at the University Hospitals of Geneva and Bern, in Switzerland. All adult (>18-year-old) CMV D+R- or CMV R+/TG KTR, who received a kidney transplant between 1st January 2010 and 31st December 2019, had a follow-up of 1-year post-transplant, and who had signed an informed consent form to participate in the Swiss Transplant Cohort Study (STCS) were included. The study was approved by the responsible Ethics Committees (2022-00959) and the STCS (FUP 197/2022).

Objectives

The primary objective was to describe the proportion of inappropriately dosed VGC primary CMV prophylaxis weekly entries. The following secondary objectives were studied: 1) the incidence of breakthrough csCMVi, 2) potential associations between breakthrough csCMVi and VGC dosing, and 3) the incidence of cytopenias and potential associations with VGC dosing considering the potential myelosuppressive effect of VGC. All objectives were assessed during the first 3 and 6 months in CMV R+/TG and CMV D+R− KTR, respectively.

Definitions

Valganciclovir dosing was based on published guidelines [3, 12]. Briefly, VGC prophylaxis was considered appropriate if dosed at 900 mg daily in patients with an estimated glomerular filtration rate (eGFR) ≥60 mL/min/m^2, and reduced to 450 mg daily, every 48 h, and twice weekly in patients with eGFR at 40–59 mL/min/m^2, 25–39 mL/min/m^2, and 10–24 mL/min/m^2, respectively (**Supplementary Dosing Schema**) [11]. There is no recommendation for an eGFR <10 mL/min/m^2. Inappropriate VGC dosing included underdosing and overdosing, defined as any dose below and above the predetermined eGFR ranges, respectively. Inappropriate dosing can be influenced by an early graft dysfunction, such as a delayed graft function (DGF), defined as an acute kidney injury (AKI) which occurs in the first week after transplantation or a primary non function (PNF), defined as permanent lack of graft function from the time of transplantation, both requiring a dialysis treatment [13, 14]. CMV infection and disease were defined based on international guidelines [15]. csCMV infection (csCMVi) was defined as any CMV infection (asymptomatic CMV DNAemia, CMV viral syndrome, probable or proven CMV disease) for which anti-CMV preemptive or targeted treatment was initiated. Breakthrough csCMVi was defined as any CMV infection/disease diagnosed while patients were receiving prophylaxis with VGC [16]. Cytopenias were defined based on laboratory thresholds used in both centers, which defined leucopenia as a leucocyte count <3 G/L, neutropenia as an absolute neutrophil count (ANC) < 1.5 G/L, lymphopenia as an absolute lymphocyte count (ALC) <1 G/L, and thrombocytopenia as platelet count <150 G/L.

Institutional Practices

Primary CMV prophylaxis with VGC was administered for 6 and 3 months post-transplant in CMV D+R− and CMV R+/TG KTR, respectively, in both centers. Plasma measured CMV DNAemia was monitored by quantitative polymerase chain reaction (qPCR). To facilitate prescription and avoid potential mistakes, it has been established based on institutional protocol to perform weekly CMV DNAemia in all CMV D+R− and CMV R+ patients, despite or not primary anti-CMV prophylaxis is administered. In Geneva, CMV PCR was performed on plasma with the COBAS® 6800 test (Roche Diagnostics, Indianopolis, United States), with a level of detection (LOD) and quantification (LOQ) of 21 IU/mL and 25 IU/mL, respectively. In Bern, CMV PCR was performed on plasma by an in-house test (Roche Diagnostics, LightCycler z480 II, Indianopolis, United States) using copies/mL with a LOQ starting from 500 copies/mL. Results in copies/mL at one center were converted to IU/mL, using the 1 IU/mL = 0.91 copies/mL equivalence formula [17, 18]. The primers and probes were synthesized by Eurofins. The accepted threshold to initiate therapy was >1,000 IU/mL in both centres.

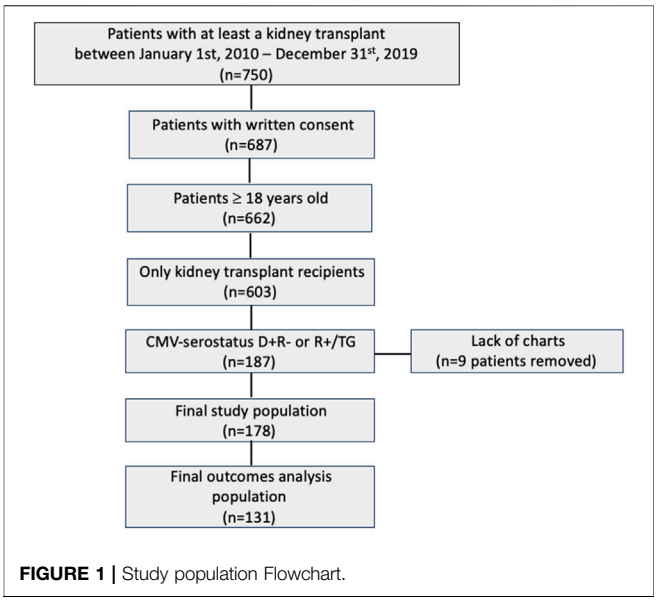


FIGURE 1 | Study population Flowchart.

Data Collection

The following data were retrieved from the STCS database, including demographics (age, sex, and body mass index), baseline comorbidities (diabetes mellitus, hypertension, coronary heart disease and smoking), hemodialysis requirement and transplantation-related variables, such as induction and maintenance immunosuppressive regimens, donor type, and cold ischemia time. Renal function, assessed as creatinine and eGFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation from 2012 (CKD-EPI 2012), and other laboratory values such as leucocytes, ANC, ALC, and platelet count were collected through patient electronic charts. VGC dosing, renal function and blood cell count variables, and CMV DNAemia were collected weekly until the end of VCG prophylaxis administration. For patients with breakthrough csCMVi data collection was stopped on the day of the infection diagnosis. Hence, results are presented per patient for the baseline patient characteristics and per weekly entries for VGC dosing and csCMVi. Project data collected based on the Case Report Form (CRF) were transferred to electronical records in Redcap® prior to analysis. For the Bern population, source documents of laboratory analyses were stored on SharePoint and individual values were automatically imported to Redcap®. All weekly data entries were restricted to entries where the VGC dosing was defined, and further restricted to follow-up week 12 and 24 for CMV R+/TG and CMV D+R− KTR, respectively.

Statistical Analysis

Quantitative variables are presented as medians (with interquartile ranges, IQR). Qualitative variables are presented

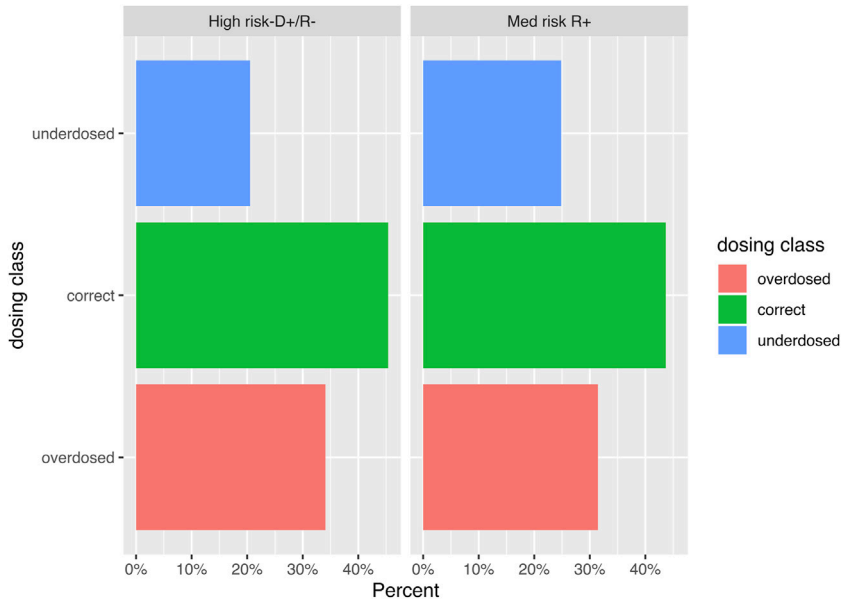


FIGURE 2 | Bar graph visualizing the distribution of the weekly valganciclovir dosing entries (n = 1,032) according to the CMV serostatus of donors and recipients. The difference in proportion of entries was highest for underdosed entries, where 20.7% of the weekly entries of CMV donor (D)+ recipient (R)- kidney transplant recipients were underdosed versus 24.8% of the entries of CMV R+ patients.

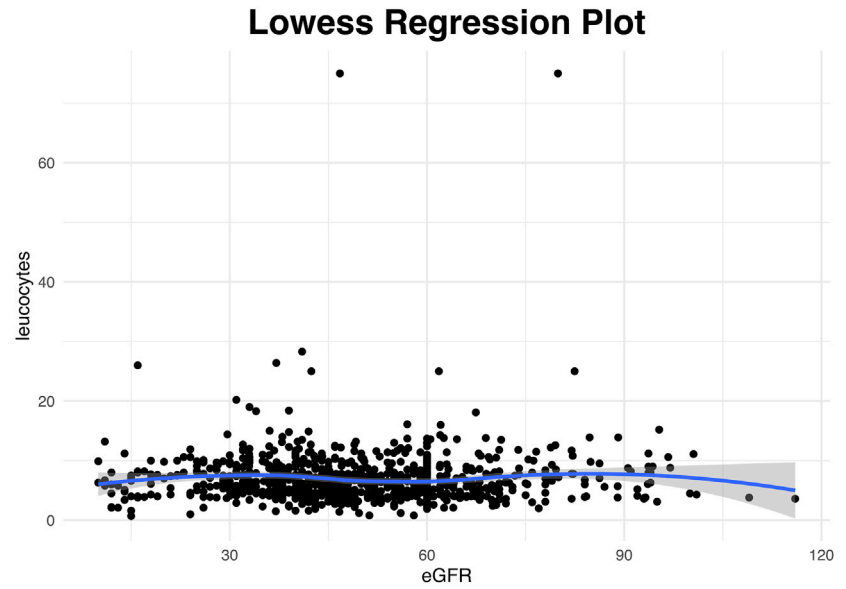


FIGURE 3 | Scatterplot for the available weekly entries demonstrating the association between renal function presented as glomlular filtration rate (eGFR) and leucocyte counts trough a lowess smoother. (Analysis restricted to entries from the second follow-up week onwards with four extreme values that had eGFR above 180 or leucocytes above 200 manually removed). The rather horizontal nonlinear line indicates that there was no association between eGFR and leucocytes.

as numbers and percentages. To compare patients across the serostatus group, we used the Student's t-test (or Mann-Whitney-U test) and for more than two groups, we used ANOVA (or Kruskal–Wallis test). For categorical variables Fisher's exact test was used. Statistical significance was assumed for $p < 0.05$ and all tests were two-tailed. Longitudinal data were reported in week-entries, according to the follow-up of patients. In order to ensure a minimal number of weekly entries of VGC prophylaxis dosing classification, patients had to have at least 2 weekly entries with VGC dosing and eGFR in the first 3 and 6 months for R+/TG and D+R−, respectively. Patients with insufficient week entries were excluded from outcome analysis. To investigate the effect of CMV serostatus on csCMV, we performed a cause-specific Cox proportional hazards model. Competing events were a new

TABLE 1 | Baseline patient characteristics.

	D+/R- *n* = 100 (%)	R+/TG *n* = 78 (%)	Total *n* = 178 (%)	*p*-value
Demographics				
Sex, Male	76 (76)	46 (59)	122 (68.5)	0.02
Age (years) median (IQR)	56.4 (42.2, 66.5)	54.6 (43.1, 61.7)	55.3 (42.7, 63.7)	0.51
BMI (kg/m^2) median (IQR)	25.5 (23.2, 28.1)	25.9 (23.5, 29.5)	25.5 (23.4, 29.3)	0.55
Weight (kg) median (IQR)	77 (65.4, 89.8)	74.1 (61, 87.4)	76 (63.3, 88.8)	0.19
Comorbidities				
Hypertension	82 (82)	71 (91)	153 (86)	0.13
Diabetes	14 (14)	14 (17.9)	28 (15.7)	0.54
Coronary heart disease	16 (16)	20 (25.6)	36 (20.2)	0.13
Smoking[a]	15 (15.5)	7 (9.2)	22 (12.7)	0.26
Etiologies of kidney disease				0.18
Glomerulonephritis	25 (25)	14 (17.9)	39 (21.9)	
Glomerulosclerosis	15 (15)	23 (29.5)	38 (21.3)	
ADPKD	21 (21)	13 (16.7)	34 (19.1)	
Diabetes	9 (9)	10 (12.8)	19 (10.7)	
Previous graft failure	6 (6)	6 (7.7)	12 (6.7)	
Reflux/pyelonephritis	3 (3)	4 (5.1)	7 (3.9)	
Congenital	4 (4)	1 (1.3)	5 (2.8)	
Interstitial nephritis	4 (4)	0	4 (2.2)	
Other[b]	13 (13)	9 (11.5)	22 (12.4)	
Induction immunosuppression				
Basiliximab[c]	82 (82)	12 (15.4)	94 (52.8)	<0.001
Thymoglobulin	16 (16)	78 (100)	94 (52.8)	<0.001
Maintenance immunosuppression				<0.001
Ciclosporine	37 (37)	11 (14.1)	48 (27)	<0.001
Tacrolimus	46 (46)	58 (74.4)	104 (58.4)	<0.001
MMF	69 (69)	33 (42.3)	102 (57.3)	<0.001
mTOR	3 (3)	1 (1.3)	4 (2.2)	0.63
Cold ischemia time (min) median (IQR)	346 (100.8, 580.3)	552 (96.8, 787.5)	391 (100.3, 665.5)	0.03
Previous renal graft	12 (12)	11 (14.1)	23 (12.9)	0.68
Number of previous grafts				0.93
1	88 (88)	67 (85.9)	155 (87.1)	
2	10 (10)	9 (11.5)	19 (10.7)	
>2	2 (2)	2 (2.6)	4 (2.2)	
Dialysis prior to transplant	64 (64)	47 (60.3)	111 (62.4)	0.61
Dialysis type prior to transplant				0.48
HD	49 (76.6)	39 (83)	88 (79.3)	
PD	15 (15.5)	8 (17)	22 (12.7)	
Donor type				<0.001
DBD	52 (52)	35 (44.9)	87 (48.9)	
Living	43 (43)	24 (30.8)	67 (37.6)	
DCD	5 (5)	19 (24.4)	24 (13.5)	
Donor				
Sex, Female	58 (58)	43 (55.1)	101 (56.7)	0.76
Age (Years) Median (IQR)	57 (47.8, 64.3)	53.5 (44.3, 61)	55 (46, 63)	0.12
Kidney dysfunction post-transplant				0.29
DGF	21 (21)	24 (30.8)	45 (25.3)	
PNF	3 (3)	1 (1.3)	4 (2.2)	

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; DBD, donor after brain death; DCD, donor after cardiac death; DGF, delayed graft function; HD, hemodialysis; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; PD, peritoneal dialysis; PNF, primary non function.

[a]*There were five missing values.*

[b]*Other etiologies included nephrocalcinosis, thrombotic microangiopathy, acute kidney injury post sepsis, eclampsia, cortical necrosis or unknown.*

[c]*Some patients induced with basiliximab could receive a supplemental treatment with thymoglobulins due to DGF or acute rejection.*

transplantation, death, or loss to follow-up. Fisher's exact test was used to compare cumulative incidence of breakthrough csCMVi for associations between VGC dosing and breakthrough csCMVi and myelotoxicity. To explore the effect of overdosing on cytopenia, we used mixed effects logistic regression models, i.e., *generalized linear mixed models*. The *random intercept* included in the model varied among patients, accounting for the variation in measurements for subjects due to multiple measurements over time. We additionally accounted for follow-up week and weekly MMF medication in the models. The analyses were limited to the weeks with complete entries for cytopenia. As the time trend might not be identical for each patient, we did a sensitivity analysis with the same models, but additionally with a random slope for time. All statistical analysis

TABLE 2 | Valganciclovir dose assessment as appropriate, under- or over-dosing based on the CMV donor/recipient status.

	Valganciclovir dose assessment			
	D+/R- *n* = 532 (%)	R+/TG *n* = 500 (%)	Total *n* = 1,032 (%)	*p*-value
Appropriately dosed	241 (45.3)	219 (43.8)	460 (44.6)	0.28
Overdosed	181 (34)	157 (31.4)	338 (32.8)	
Underdosed	110 (20.7)	124 (24.8)	234 (22.7)	
Daily VGC dose in mg, median (IQR)	450 (450, 900)	450 (450, 450)	450 (450, 900)	0.09
Creatinine (umol/L), median (IQR)	133 (108, 160)	130.5 (106, 160)	131 (107, 160)	0.56
eGFR (ml/min/1.73 m^2) median (IQR)	50.3 (39, 61)	47 (37, 60)	49 (38, 60)	0.01

D Donor, R Recipient, IQR, interquartile range; VGC, valganciclovir.

were performed on R Version 4.3.2. Generalized mixed models were fitted using the R package "Ime4". The package "ggplot2" was used for visualization.

RESULTS

Characteristics of the Study Population

From 750 KTR, 178 patients fulfilled the inclusion criteria and were included in the study (**Figure 1**). There were 114 patients (64%) recruited in Geneva and 64 (36%) in Bern. The median age was 55.3 years (IQR 42.7, 63.7), most patients were male (n = 122, 68.5%), with a median BMI of 25.5 kg/m^2 (IQR 23.4, 29.3). Baseline patient characteristics were comparable between CMV R+/TG and CMV D+R− patients, except for sex (male n = 46, 59% versus n = 76, 76%; p = 0.02), cold ischemia time (346 min versus 552 min; p = 0.03), immunosuppressive induction treatment by thymoglobulin (n = 78, 100% versus n = 16, 16%; p < 0.001), immunosuppressive maintenance by ciclosporine (n = 48, 27%; p < 0.001), tacrolimus (n = 46, 46%; p < 0.001) and MMF (n = 102, 57.3%; p < 0.001), and the type of donor (n = 87, 48.9% DBD versus n = 67, 37.6% living versus n = 24, 13.5% DCD); p < 0.001; **Table 1**).

Valganciclovir Dosing

Among 178 patients, 131 patients (73.6%) had at least 2 week entries for the longitudinal data of interest and were included in the outcome analysis (**Figure 1**). Their baseline characteristics are reported in **Supplementary Table S1**. There were 1,032 weekly VGC dose entries for 131 patients, for a median of 6 (IQR 3, 9) entries per patient over the entire prophylaxis period. Overall, 460 (44.6%) were appropriately dosed, while 234 (22.7%) and 338 (32.8%) were under- and over-dosed, respectively, based on the recorded weekly renal function values (**Figure 2**). Daily VGC dose (p = 0.09) and creatinine value (p = 0.56) were not significantly different among D+/R− and R+/TG. However, eGFR was higher (median: 50.3 mL/min/1.73 m^2, IQR: 39, 61) in D+/R− versus R+/TG (median: 47 mL/min/1.73 m^2, IQR: 37, 60; p = 0.01) patients (**Table 2**). Overall, inappropriate dosing was similar during the first 4 weeks (225/390, 57.7%) with later (>4 weeks, 347/642, 54%, p = 0.27) post-transplant. In contrast, inappropriate dosing was more frequent among R+/TG (133/214, 62.1%) than D+/R− (92/176, 52.3%, p = 0.05) during the first 4 weeks post-transplant compared to later. Weekly VGC prophylaxis dosing according to renal function is described in detail in **Supplementary Table S2**. Dose appropriateness did not significantly differ between D+R− (241/532, 45.3%) and R+/TG (219/500, 43.8%; p = 0.66). In contrast, VGC was less likely to be appropriately dosed in Geneva (329/767, 42.9%) compared to Bern (131/265, 49.4%; p < 0.001).

Breakthrough csCMV Infections

Of the 131 patients, 19/131 (14.5%) had breakthrough csCMVi. By comparing among serostatus, there were 8 (42.1%) primary infections in the D+R− group and 11 (57.9%) CMV reactivations in the CMV R+/TG group (p < 0.001), but no statistically difference in term of symptomatology presentation, p = 0.06; (**Supplementary Table S3**). Comparisons of the weekly VGC dose performed between patients with and without a breakthrough csCMVi, taking into consideration the appropriateness of all weekly VGC doses for the former and those during the 2 weeks prior to the breakthrough csCMVi in the latter group, respectively, did not show any difference between the two groups. Similarly, there was no statistically significant difference in the rate of breakthrough csCMVi between patients with underdosed weekly VGC doses (3/20, 15%) compared to those patients without VGC underdosing (226/952, 23.7%; p = 0.44). In multivariable Cox analysis, CMV R+/TG KTR had essentially the same risk to develop a csCMVi compared to D+R− [HR 1.02, 95% CI (0.32–3.30), p = 0.97], even when adjusting for maintenance immunosuppression[1].

Cytopenia

Leucopenia, neutropenia and thrombocytopenia was reported in a small proportion of tested samples (48/928, 5.2%, 23/735, 3.1%, and 58/880, 6.6%, respectively). In contrast, lymphopenia was observed in more than 2/3 of specimens tested (566/742, 76.3%). There was no statistically significant difference in the proportion of weekly leucopenia, neutropenia, or thrombocytopenia values based on whether VGC was overdosed or not (p = 0.63, p = 0.48, and p = 0.65), respectively. In contrast, lymphopenia was more frequently observed when VGC was overdosed (p = 0.01; **Table 3** and **Figure 3**). Considering the potential myelosuppressive effect of VGC and MMF, mixed effects logistic regression models were developed (**Table 4**). While a significant association between

[1]Considering the low number of events, we only assessed association with maintenance immunosuppression and serostatus.

TABLE 3 | Cytopenias in association with valganciclovir dosing.

	Not overdosed *n* = 694 (%)	Overdosed *n* = 338 (%)	Total *n* = 1,032 (%)	*p*-value
Leucopenia[a]	35/644 (5.4)	13/284 (4.6)	48/928 (5.2)	0.63
Neutropenia[a]	15/528 (2.8)	8/207 (3.9)	23/735 (3.1)	0.48
Lymphopenia[a]	393/534 (73.6)	173/208 (83.2)	566/742 (76.3)	0.01
Thrombocytopenia[a]	39/617 (6.3)	19/263 (7.2)	58/880 (6.6)	0.65

[a]*Available values for leucocyte, neutrophil, lymphocyte, and platelet counts were 48, 23, 566, and 58, respectively for: 644, 528, 534 and 617 not overdosed valgancoclovir; 284, 207, 208, and 263 overdosed valganciclovir.*

TABLE 4 | Predictors of cytopenias on multivariable analysis.

Lymphopenia	OR	95% CI	*p*-value
VGC overdosing	5.27	1.71–16.22	0.004
MMF[a]	1.79	0.21–15.37	0.60
FUP	1.16	1.01–1.26	<0.001
Leucopenia			
VGC overdosing	2.28	0.49–10.48	0.29
MMF[a]	2.83	0.34–23.34	0.33
FUP	1.54	1.32–1.81	<0.001
Neutropenia			
VGC overdosing	2.45	0.27–21.99	0.42
MMF[a]	0.22	0.003–15.78	0.49
FUP	1.38	1.16–1.64	<0.001
Thrombocytopenia			
VGC overdosing	0.74	0.21–2.65	0.64
MMF[a]	1.40	0.03–57.5	0.86
FUP	1.03	0.95–1.13	0.44

FUP, follow up weeks; MMF, mycophenolate mofetil; OR, odds ratio; VGC, valganciclovir, 95% CI, 95% confidence interval.
[a]*Overall, 19/105 MMF treatment durations had a missing stopdate, and the duration was imputed via median.*

VGC overdosing and lymphopenia (OR = 5.27, 95% CI 1.71–16.22, $p = 0.004$) was shown, there were no significant associations between VGC overdosing and leucopenia (OR = 2.28, 95% CI 0.49–10.48, $p = 0.29$), neutropenia (OR = 2.45, 95% CI 0.28–21.62, $p = 0.42$), and thrombocytopenia (OR = 0.74, 95% CI 0.21–2.65 $p = 0.64$). Similarly, there were no significant associations of MMF with lymphopenia (OR = 1.78, 95% CI 0.21–15.37, $p = 0.6$), leucopenia (OR = 2.83, 95% CI 0.34–23.35, $p = 0.33$), neutropenia (OR = 0.22, 95% CI 0.003–15.10, $p = 0.48$), or thrombocytopenia (OR = 1.40, 95% CI 0.03–57.51, $p = 0.86$). We hypothesized the longer the VGC of MMF administration, the more potent their effect on bone marrow suppression. Hence, we included time post-transplant in follow-up weeks in the model, showing a significant association of follow-up weeks on lymphopenia (OR = 1.16, 95% CI 1.07–1.26, $p < 0.001$), leukopenia (OR = 1.54, 95% CI 1.31–1.80, $p < 0.001$), and neutropenia (OR = 1.38, 95% CI 1.18–1.61, $p < 0.001$). As an identical time trend could not be assumed for every patient, we added a sensitivity analysis with additional random slope for FUP weeks (**Supplementary Table S4**). It confirmed the significant association of VGC overdosing with lymphopenia (OR = 6.65, 95% CI 1.55–28.56, $p = 0.011$), such as the significant association of follow-up weeks on neutropenia (OR = 1.23, 95% CI 1.11–1.37, $p < 0.001$), while only retaining point effects of the OR above for lymphopenia (OR = 2.35, 95% CI 0.72–7.67, $p = 0.16$) and leukopenia (OR = 1.19, 95% CI 0.87–1.61, $p = 0.28$).

DISCUSSION

In this two-center observational study we report that VGC administered as primary anti-CMV prophylaxis in adult KTR is not properly dosed in more than half of weekly assessments during the first months post-transplant, albeit without significant efficacy and safety associations.

Data on the most effective and safest VGC prophylaxis dosing are lacking. Previous studies reported not properly dosed VGC in association with CMV infection and breakthrough csCMVi [19, 20]. Dose adjustments have been proposed to ascertain efficacy, while limiting the potential toxicities associated with higher VCG concentrations, namely, its effect on the bone marrow and associated cytopenias. A lower VGC dosing (450 mg daily for an eGFR ≥60 mL/min/m^2) has been shown to significantly reduce the incidence of leucopenia and to be cost-effective [21, 22]. For this study, we followed the proposed dose adjustments as shown in the Compendium®, an open-access Swiss medication database operated by HCI Solutions SA and regularly updated, which provides short monographs, clear clinical decision support and interaction profiles, and dose adjustments based on renal function of the drugs [23]. Although not identical, the adjustments proposed by the Swiss Compendium are quite similar with other dose adjustment guidelines and recommendations [3]. Rapid changes of renal function are frequent events over the first weeks post-kidney transplantation, ranging from dialysis or pre-dialysis creatinine values to normal values in a few weeks, or the presence of an early graft dysfunction such as DGF or PNF, directly impacting on the dose of multiple medications, including that of VGC, and prompting frequent dose adaptations. In our cohort, 25.3% patients had a DGF while 2.2% had a PNF, which is consistent with the existing literature and could explain why inappropriate VGC dosing was more frequent during the first 4 weeks after transplantation compared to later. That entails close and frequent monitoring of those patients and their renal function, which needs to be assured and organized, particularly once patients are discharged from the hospital and monitored on an outpatient basis. Notably,

following a detailed review of weekly renal function and VGC dose assessments during the early period post-KT, our data suggest that VGC is very frequently either over- or under-dosed considering the associated weekly renal function measurement. Although this finding may merely reflect lagging results between bloodwork performed and review by the treating physician and VGC dose adjustment, the number of weekly dissociations between VGC dose and renal function remains quite considerable. Despite an outpatient assessment of KTR once weekly or every other week, it is likely considering the complexity of care of KTR that VGC dosing is not always addressed and hence occasional pitfalls may occur. In fact our data suggest that inappropriate dosing may be even more frequent that we thought, pointing out the need for more careful and intensive monitoring of the patient medication list and doses. The burden and outpatient organization of dose adjustment of medications, including antiinfective agents, in the early post-transplant period in KTR is an area requiring more and consistent studying in the future.

Comparisons of the weekly VGC dose between patients with and without a breakthrough csCMVi was not different between the two groups. Consequently, our hypothesis that VCG under-dosing could have been associated with higher rates of breakthrough csCMVi was not retained despite a global incidence of 14.5%, higher than an incidence between 2.5% and 6.5% reported in the literature [24]. Comparisons of the weekly VGC dose between patients with and without a breakthrough csCMVi was not different between the two groups. Our findings are similar to data reported by Stevens *et al* on the incidence of breakthrough csCMVi among 90 transplant recipients receiving standard (900 mg daily) versus lower (450 mg daily) doses of VGC prophylaxis. There was no significant difference between the two groups with breakthrough csCMVi occurring in a single patient receiving standard VGC dosing and in six patients in the lower VGC dosing group (2.2% versus 13.3%; $p = 0.11$) [16]. Although not definitive, those findings do not call into question the actual VGC dosing recommendations. However, they suggest that an intensive VCG dose monitoring and prompt dose adjustment based on the associated renal function may not be the only and primary determinant of breakthrough csCMVi in KTR during the early post-transplant period, allowing a certain margin of miscalculation without significant clinical efficacy pitfalls. This is an important observation that requires additional research, considering the time and cost investment in renal function and dose adjustment monitoring applied in most transplant centers worldwide. This observation applies in both CMV R+/TG and D+R− patients, as results did not significantly differ based on the D/R serostatus constellation. There was a trend for more csCMVi in patients enrolled in one center, although this could be attributed to different strategies applied in the two centers, including frequency and type of CMV DNAemia monitoring and threshold for preemptive treatment initiation.

Cytopenia is part of the numerous complications occurring post-transplantation and is known to complicate treatment administration in up to 60% of KTR who will experience at least one episode of leucopenia or neutropenia [25]. A meta-analysis found that VGC 900 mg daily was associated with a 3.3 times greater risk of leucopenia [26]. Considering the potential myelosuppressive effect of VGC, its dose requires further adjustments based on renal function results, especially in patients receiving TG for induction after a deceased-donor or in presence of DGF [27]. In our study we found an association between VGC dosing and lymphopenia, which was higher among overdosed patients. Whether lymphopenia could be related to VCG dosing and/or a number of other potential variables, including induction and maintenance immunosuppression, breakthrough csCMVi, or concomitant administration of other medications with potential myelotoxic effect (e.g., MMF, thymoglobulins, trimethoprim/sulfamethoxazole, for example) remains to be better defined [28]. Notably, there were no strong associations between leucopenia or neutropenia and neither VGC overdosing nor MMF administration in our study. This is likely due to the high number of missing values, not allowing us to make any additional meaningful observations between the variables tested, despite the well known myelosuppressive effect of both agents. In fact, when looked at the effect of weekly follow-ups on cytopenias, the only significant association after performing a sensitivity analysis was found by neutropenia. This reflects a potential cumulative effect of those treatments on bone marrow suppression and further highlight a certain dose- and time-effect imputed to a combined myelotoxicity effect of VGC, MMF, and other agents, including thymoglobulin.

Our study has numerous limitations, including its retrospective two-center design, limited number of patients, and even lower number of patients with adequate weekly data to allow for meaningful comparisons and powerful conclusions. In addition, differences in data coding, VGC dosing, outpatient visit frequency, and CMV DNAemia measurement and threshold for preemptive treatment initiation between the two centers might have accounted for higher numbers of csCMVi in one center compared to the other. Finally, eGFR measurements used for renal function assessment were based on the CKD-EPI formula, as recommended by the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN), while the pre-cited guidelines measured eGFR by Cockcroft-Gault equation or Modification of Diet in Renal Disease (MDRD) equation [11, 12, 29, 30].

CONCLUSION

Despite its limitations, this bicentric study addresses a pertinent question in the management of post-transplant CMV prophylaxis in the VGC prophylaxis era. Based on our observations, VGC dosing is frequently inappropriate, albeit without meaningful clinical associations, neither in terms of efficacy nor safety. Our findings need to be validated in larger scale studies, in order to better assess the importance of intensive renal function and VGC dose adjustment monitoring in the post-transplant setting. This question remains pertinent, despite the fact that CMV-specific T-cell responses and other agents, such as letermovir, may become more prevalent in the monitoring of CMV in SOT recipients in the near future.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by the responsible Ethics Committees (2022-00959) and the STCS (FUP 197/2022). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

NH, LH, DS, and DN conceived and designed the project, with LH specifically conducting the statistical analysis. NH and DN wrote the manuscript. FH, CH, SdS, BV, and CvD critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.12712/full#supplementary-material

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ORIGINAL RESEARCH
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Donor Blood Tests do Not Predict Pancreas Graft Survival After Simultaneous Pancreas Kidney Transplantation; a National Cohort Study

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Simultaneous pancreas-kidney (SPK) transplantation improves quality of life and limits progression of diabetic complications. There is reluctance to accept pancreata from donors with abnormal blood tests, due to concern of inferior outcomes. We investigated whether donor amylase and liver blood tests (markers of visceral ischaemic injury) predict pancreas graft outcome using the UK Transplant Registry (2016-2021). 857 SPK recipients were included (619 following brainstem death, 238 following circulatory death). Peak donor amylase ranged from 8 to 3300 U/L (median = 70), and this had no impact on pancreas graft survival when adjusting for multiple confounders (aHR = 0.944, 95% CI = 0.754–1.81). Peak alanine transaminases also did not influence pancreas graft survival in multivariable models (aHR = 0.967, 95% CI = 0.848–1.102). Restricted cubic splines were used to assess associations between donor blood tests and pancreas graft survival without assuming linear relationships; these confirmed neither amylase, nor transaminases, significantly impact pancreas transplant outcome. This is the largest, most statistically robust study evaluating donor blood tests and transplant outcome. Provided other factors are acceptable, pancreata from donors with mild or moderately raised amylase and transaminases can be accepted with confidence. The use of pancreas grafts from such donors is therefore a safe, immediate, and simple approach to expand the donor pool to reach increasing demands.

Keywords: pancreas transplantation, SPK transplantation, registry study, donor blood tests, graft surival, organ utilisation

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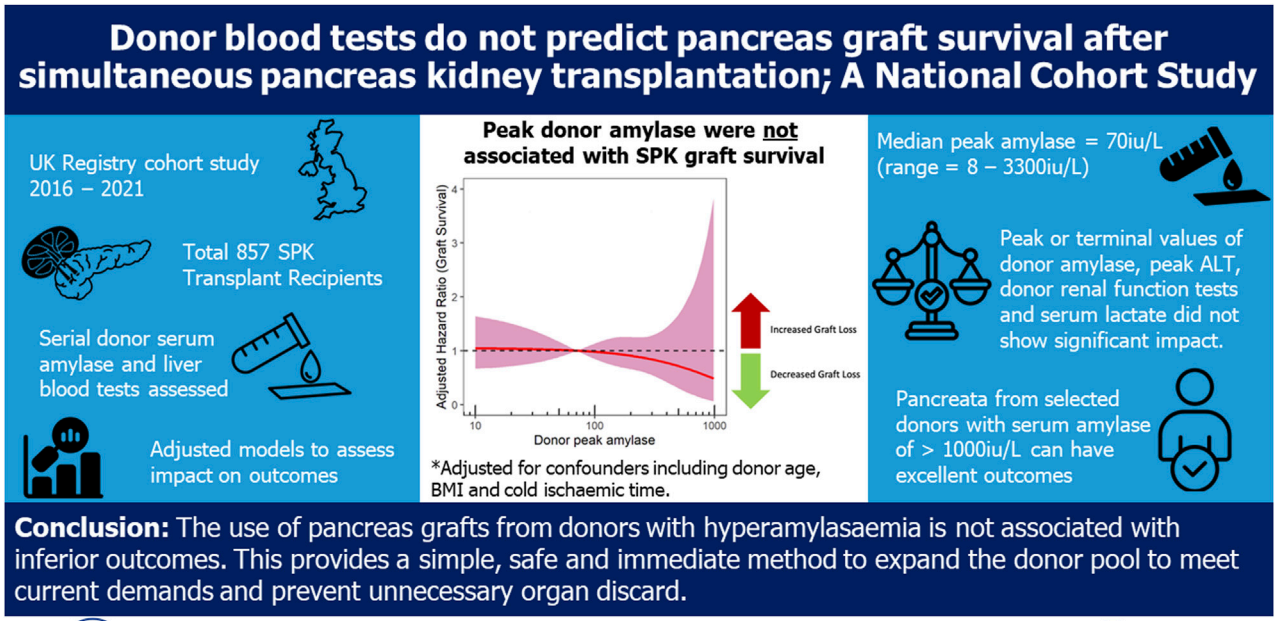
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; CIT, Cold Ischaemic Time; DCD, Donor after Circulatory Death; DBD, Donor after Brainstem Death; DM, Diabetes Mellitus; LBT, Liver Blood Tests; NHS, National Health Service (United Kingdom); NHSBT, National Health Service Blood and Transplant; SPK, Simultaneous Pancreas-Kidney transplantation; WIT, Warm Ischaemic Time.



GRAPHICAL ABSTRACT |

INTRODUCTION

Diabetes Mellitus (DM) is a growing pandemic [1–3] associated with increased risks of developing life-limiting systemic complications. Diabetic patients may experience reduced quality of life and incur high healthcare-associated costs, particularly in patients with poorly controlled disease. Pancreas transplantation significantly improves the quality of life of patients, and can limit the progression of serious medical comorbidities [4–7].

The number of patients on the UK waiting list for pancreas transplantation is at an all-time high, and waiting time has worsened following the COVID-19 pandemic [8]. As of March 2023, 265 patients are actively waiting for a pancreas graft in the United Kingdom, representing a 27% increase from before the pandemic [9]. Taken together, there is a need to optimise decision-making surrounding organ utilisation and expand the donor pool to match the current demands for pancreas transplantation. It is essential to understand factors that predict transplant outcomes. It is equally important to identify factors that do not lead to poor outcomes, preventing the unwarranted rejection of donor organs based on these factors.

Initial screening of donors includes various blood tests, such as serum amylase and liver blood tests. Hyperamylaseamia (defined as serum amylase levels greater than 110 UI/L) can be seen in up to 40% of donors, and a markedly elevated serum amylase (more than three times the upper limit of normal) is generally considered to represent pancreatitis [10]. However, this blood test has low specificity, and can be raised due to a variety of aetiologies [11, 12].

Serum liver blood tests (LBTs) are markers of acute hepatocellular or cholangiocyte injury. The embryological development of the pancreas is closely related to the formation of foregut and midgut structures. The pancreas shares the same vascular supply with other foregut/midgut structures (including liver), receiving blood from both coeliac trunk and superior mesenteric artery. Therefore, markers of acute hypoxic injury to the liver could be a surrogate for hypoxic injury to the pancreas [13, 14].

This study aims to ascertain whether donor amylase and LBTs predict pancreas graft survival in patients undergoing SPK transplantation.

MATERIALS AND METHODS

Data on adult simultaneous pancreas and kidney (SPK) transplants was retrieved from the UK Transplant registry, maintained by the National Health Service Blood and Transplant (NHSBT). Adult recipients (>16 years) from all 8 UK pancreas transplant centres, transplanted between January 2016 and December 2021, were included. These dates were chosen because, before January 2016, serial donor amylase and serial LBTs were not recorded. Recipients of grafts donated following circulatory or brain stem death [donation following brain stem death (DBD)/donation following circulatory death (DCD)] were included.

Data were provided in an anonymized form (patient identifiable information and transplant unit not provided) as per NHSBT approvals, and individual ethical or institutional review board approval was not required for this project. This project was approved by the pancreas advisory board.

Data were extracted from NHSBT in August 2023. Data were cleaned, and values that were deemed impossible were removed. Our primary aim was to compare the impact of donor serum amylase on 3-year pancreas graft survival. Secondary analyses compared the impact of donor alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALT) and bilirubin, as well as renal blood tests and lactate, on 3-year pancreas graft survival.

Graft loss was defined as retransplantation, pancreatectomy or return to insulin therapy due to graft failure and was analysed as time-to-event, death censored, and measured until July 2023 (the common closure date of the study).

Statistical Analysis

Missing data is summarised in **Supplementary Table S1**. Missing data were dealt with by multiple imputation using the fully conditional specification technique applied to generate 5 imputed datasets. Due to significant right skew, peak amylase, LBT, renal function test and serum lactate values were log transformed prior to performing multiple imputation. These imputed datasets were used for all multivariable models.

Our approach for constructing multivariable models matched that described previously [13]. When entering LBT values as predictors in the following models they were kept as continuous variables, rather than splitting into arbitrary categories; this approach improves power and is best practice. The blood tests were kept as continuous variables, which is superior to creating arbitrary categories [15–17]. To combat issues with skew, all blood test values were entered into models as log2 (blood test value).

Cox proportional hazards method was used to build multivariable graft survival models. Donor, graft, recipient and operative factors available from NHSBT registry were initially screened. Variables were selected based on clinical experience, if they had previously been reported to affect graft survival, or if they were significantly correlated with donor amylase and LBTs. **Table 3** lists all considered variables. Automatic variable selection techniques (such as backwards stepwise selection) were avoided as these are recommended against in small datasets [18].

As there was significant correlation between each of the blood tests, there would be significant issues with multi-collinearity if they were entered into the same model. Therefore, separate multivariable models were built for donor amylase and each individual LBT, renal function test and serum lactate values. Results of these models are displayed as adjusted hazard ratios (aHR) with 95% confidence intervals. Interaction terms where introduced into these models to assess whether the impact of donor blood tests on pancreas graft survival differed in older donors or those with prolonged CIT.

Finally, we repeated our main cox regression models for graft survival, using a restricted cubic spline approach (3 knots located at 10/50/90th percentiles) to assess the impact of donor serum amylase and LBTs on outcome without assuming linear relationships [19].

For all tests performed $p < 0.05$ was deemed significant. Analyses were performed in SPSS™ version 26 (IBM Corp, Armonk, New York, United States) or R (R Foundation for Statistical Computing, Vienna, Austria). The latter was used to generate all figures.

RESULTS

857 adult recipients of deceased donor pancreas (619 DBD and 238 DCDs) were included, with median follow up of 37.5 months. Median donor age was 34 (interquartile range 24–46). Cohort demographics are included in **Table 1**, with further details in **Supplementary Table S1**.

Summary of Donor Serum Amylase and Liver Blood Tests

Table 2 provides a summary of donor amylase and liver blood tests across the cohort (see **Supplementary Material S2** for further details). Peak Amylase and ALT values are graphically displayed in **Figure 1**. A wide range of peak donor amylase were identified in our study. 465 donors had a peak amylase of <100 iu/L, 257 donors had a peak amylase of between 100 iu/L and 1000 iu/L, and five donors had peak amylase >1000 iu/L (130 were missing a value for peak amylase). Of all donors, a total of 197 had an amylase value of >130 iu/L (the P-PASS cut-off) [20].

Supplementary Figure S1 provides a graphical display of peak donor AST, ALP and bilirubin values. There were no significant differences in the blood tests between DBD and DCD donors (**Table 2**).

Impact of Amylase and Liver Blood Tests on Pancreas Graft Survival

Table 3 displays the multivariable cox regression model for 3-year pancreas graft survival. Peak donor amylase, peak transaminases (ALT and AST), peak ALP, and peak bilirubin did not predict pancreas graft survival, even when adjusting for a range of factors (**Table 3**).

The impact of blood tests on outcome was then assessed separately in DBD and DCD cohorts. Repeating the model in **Table 3** in the DBD cohort, confirmed that donor amylase did not predict pancreas graft survival in this group (aHR = 0.965, 0.760–1.227, $p = 0.768$). For DCD graft recipients, a further multivariable model was created, with the addition of normothermic regional perfusion (NRP) as a confounder; again, this confirmed no impact of donor amylase on pancreas graft survival (aHR = 0.984, 0.609–1.590, $p = 0.948$). Similar analyses found no impact of peak donor liver blood tests in either the DBD or DCD subgroup.

We have also performed a multivariable analysis on those with amylase values greater than 130 (the cut-off used in the P-PASS score) [20], adjusting for all of the factors in **Table 3**. Pancreases from donors with peak amylase >130 were not at higher risk of graft loss compared with those with amylase ≤130 (aHR = 0.730,

TABLE 1 | Summary of Cohort Demographics (*N* = 857).

	DBD (N = 619)	DCD (N = 238)	Overall (N = 857)
Recipient Age			
Median [Min, Max]	42.0 [21.0, 64.0]	42.0 [20.0, 61.0]	42.0 [20.0, 64.0]
Recipient Sex			
Female	267 (43.1%)	92 (38.7%)	359 (41.9%)
Male	352 (56.9%)	146 (61.3%)	498 (58.1%)
Recipient Ethnicity			
White	515 (83.2%)	205 (86.1%)	720 (84.0%)
Non-White	97 (15.7%)	32 (13.4%)	129 (15.1%)
Recipient BMI			
Median [Min, Max]	24.6 [17.7, 36.5]	25.1 [18.4, 36.9]	24.8 [17.7, 36.9]
Type of Recipient Diabetes			
Type 1 Diabetes Mellitus	488 (78.8%)	179 (75.2%)	667 (77.8%)
Type 2 Diabetes Mellitus	22 (3.6%)	10 (4.2%)	32 (3.7%)
Donor Sex			
Female	316 (51.1%)	96 (40.3%)	412 (48.1%)
Male	303 (49.0%)	142 (59.7%)	445 (51.9%)
Donor Age			
Median [Min, Max]	35.0 [10.0, 63.0]	29.0 [4.00, 54.0]	34.0 [4.00, 63.0]
Donor BMI			
Median [Min, Max]	23.4 [14.5, 38.4]	22.6 [11.3, 36.2]	23.1 [11.3, 38.4]
Donor Ethnicity			
White	554 (89.5%)	216 (90.8%)	770 (89.8%)
Non-White	53 (8.6%)	21 (8.8%)	74 (8.6%)
Donor Cause of Death			
Hypoxic Brain Injury	198 (32.0%)	111 (46.6%)	309 (36.1%)
Intrcranial Haemorrhage	284 (45.9%)	61 (25.6%)	345 (40.3%)
Intrcranial Thrombosis	27 (4.4%)	9 (3.8%)	36 (4.2%)
Trauma	30 (4.8%)	25 (10.5%)	55 (6.4%)
Other	55 (8.9%)	17 (7.1%)	72 (8.4%)
Cold Ischaemic Time (minutes)			
Median [Min, Max]	647 [223, 1,320]	611 [339, 1,060]	634 [223, 1,320]
3-year Graft failure			
No	547 (88.4%)	214 (89.9%)	761 (88.8%)
Yes	68 (11.0%)	21 (8.8%)	89 (10.4%)

DBD, donation following brainstem death; DCD, donation following circulatory death.

TABLE 2 | Summary of Peak Donor Serum Amylase and Liver Blood Tests.

	DBD (N = 619)	DCD (N = 238)	Overall (N = 857)
Amylase			
Median [Min, Max]	70 [8, 3,300]	69 [10, 1,310]	70.0 [8, 3,300]
ALT			
Median [Min, Max]	59 [8, 5,090]	89 [9, 5,930]	67.0 [8, 5,930]
AST			
Median [Min, Max]	65 [0, 2040]	94.0 [10, 7,910]	72.0 [0, 7,910]
ALP			
Median [Min, Max]	85 [31, 721]	90.0 [35, 541]	86.0 [31, 721]
Bilirubin			
Median [Min, Max]	12 [3, 124]	11.5 [3, 65]	12.0 [3, 124]

DBD, donation following brainstem death; DCD, donation following circulatory death; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase.

95% CI 0.460–1.733, $p = 0.730$). This is a sensitivity analysis only, as using arbitrary cut-offs for continuous variables significantly reduces the power of analyses.

Donor amylase and transaminases may have a greater impact in older donors and pancreases with prolonged cold ischaemic time. This hypothesis was tested by the addition of interaction terms to the model shown in **Table 3**. There was no evidence that the impact of donor peak amylase or peak ALT on pancreas graft survival differed based on donor age (interaction $p = 0.340$ & $p = 0.890$ respectively), or prolonged cold ischaemic time (interaction $p = 0.699$ & $p = 0.924$ respectively).

The relationship between peak amylase/LBT values and graft survival was also modelled using restricted cubic splines (**Figures 2A, B**). This avoids assumptions about the nature of the relationship between peak blood test values and outcome, whilst also adjusting for all the confounders listed in **Table 3**. As shown in **Figures 2A, B**, this confirms no impact of peak amylase or peak ALT on outcome. By way of counter example, a restricted cubic spline analysis was also performed for recipient age which is a known prognostic factor; this showed that younger recipients have worse outcome (**Figure 2C**).

It may be argued that the terminal value (the value closest to donation) is more predictive of outcome. As serum amylase and LBT levels closest to donation (rather than peak values) may represent the cumulative effect of ischaemic injury during donation, we built further models using terminal values in an identical fashion to **Table 3**. This is shown in **Table 4**, where terminal values of amylase, LBTs, renal function tests and serum lactate were not significant in outcomes.

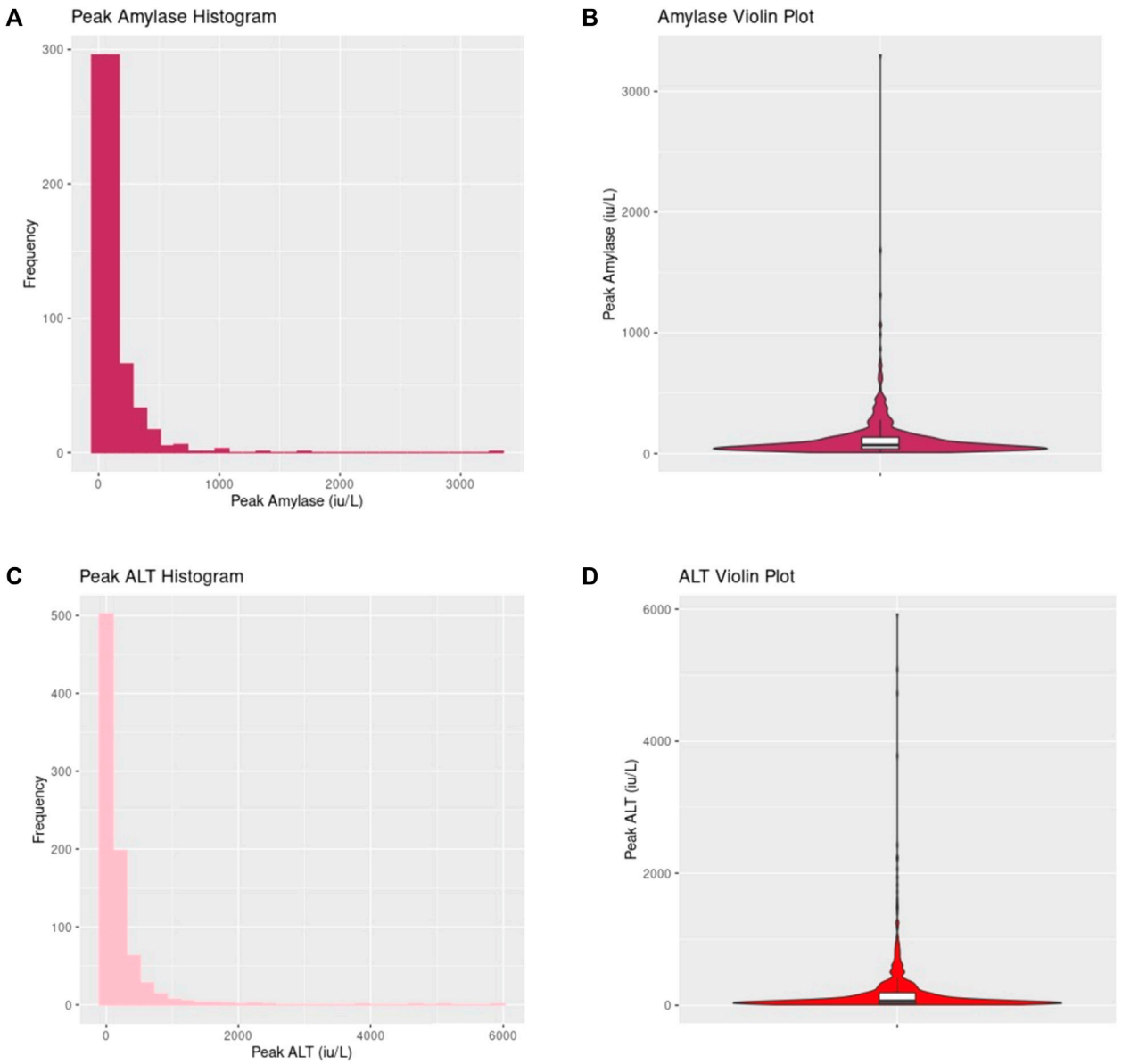


FIGURE 1 | Donor peak amylase and peak alanine transaminase (ALT) distribution. **(A,B)** demonstrates values of peak amylase across the entire cohort displayed in histogram and violin plot respectively. **(C,D)** shows values of peak ALT across the entire cohort displayed in histogram and violin plot respectively.

There may be specific concern where donor amylase values are extremely elevated (>1000 iu/L, 10 times the upper limit of normal). Follow-up data was available for 4 pancreas transplants which used grafts from donors with peak amylase over 1,000; all of these were functioning at last follow-up (**Figure 3**).

Sensitivity analyses were performed where raw amylase and LBT values (rather than log-transformed values) were entered into the cox regression model. Again, peak donor amylase and LBTs did not show significant impact in recipient outcomes.

We also assessed the impact of donor renal function tests and lactate, as the function of the transplanted kidney can impact pancreas graft function. Donor HbA1c was not recorded for more than 90% of the donors and therefore could not be assessed in this study. Donor peak creatinine, peak urea, peak estimated glomerular filtration rate (eGFR), and serum lactate did not predict pancreas graft survival (**Supplementary Table S3**). None of the examined blood tests predicted kidney graft survival in multivariable models. However, kidney graft survival may be better assessed in a study dedicated to kidney grafts, with much larger cohorts of kidney transplants alone.

DISCUSSION

This large, statistically robust cohort study (619 DBD and 238 DCDs) has found no association between donor amylase

TABLE 3 | 3-Year Graft Survival Cox regression using pooled data on peak donor amylase and liver blood tests from imputed datasets.

	Adjusted HR (95% CI)	*p*-value
Blood Tests		
Amylase (Peak)	0.944 (0.754–1.181)	0.602
ALT (Peak)	0.967 (0.848–1.102)	0.616
AST (Peak)	0.908 (0.771–1.070)	0.247
ALP (Peak)	0.865 (0.594–1.261)	0.451
Bilirubin (Peak)	1.229 (0.930–1.624)	0.148
Cold Ischaemic Time (hours)	1.338 (0.611–2.930)	0.467
Donor Age (years)	1.009 (0.992–1.026)	0.322
Donor Type	0.731 (0.430–1.243)	0.247
Donor BMI	1.078 (1.015–1.144)	0.014
Transplant Year	0.948 (0.820–1.096)	0.472
Recipient Age (years)	0.960 (0.935–0.986)	0.003
Recipient BMI	0.992 (0.918–1.073)	0.842

For blood tests, logs were taken before inclusion in this model, due to all blood tests results being right-skewed. The effect estimates relate to a unit increase in log2 (blood tests value). Results from the various LBTs (ALT, AST, ALP, and bilirubin) could not be included in a single model because of multicollinearity; therefore, multivariable results for each LBT are from a separate multivariable model. Multivariable results for variables other than LBTs are from the model including peak Amylase.

ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; CI, confidence interval; LBT, liver blood test; HR, hazard ratio; DBD, donation following brainstem death; DCD, donation following circulatory death.

TABLE 4 | Sensitivity Analyses with terminal values of amylase and liver blood tests.

	Adjusted HR (95% CI)	*p*-value
Blood Tests		
Amylase (Terminal)	0.979 (0.776–1.236)	0.857
ALT (Terminal)	0.965 (0.828–1.124)	0.646
AST (Terminal)	0.895 (0.669–1.198)	0.430
ALP (Terminal)	1.011 (0.713–1.434)	0.950
Bilirubin (Terminal)	1.067 (0.798–1.428)	0.661
Cold Ischaemic Time (hours)	1.348 (0.614–2.957)	0.457
Donor Age (years)	1.009 (0.992–1.026)	0.297
Donor Type	0.736 (0.433–1.251)	0.258
Donor BMI	1.077 (1.015–1.144)	0.015
Transplant Year	0.949 (0.821–1.098)	0.484
Recipient Age (years)	0.960 (0.935–0.986)	0.003
Recipient BMI	0.993 (0.919–1.073)	0.857

For blood tests, logs were taken before inclusion in this model, due to all blood tests results being right-skewed. The effect estimates relate to a unit increase in log2 (blood tests value). Results from the various LBTs (ALT, AST, ALP, and bilirubin) could not be included in a single model because of multicollinearity; therefore, multivariable results for each LBT are from a separate multivariable. Multivariable results for variables other than LBTs are from the model including peak Amylase.

ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; CI, confidence interval; LBT, liver blood test; HR, hazard ratio; DBD, donation following brainstem death; DCD, donation following circulatory death.

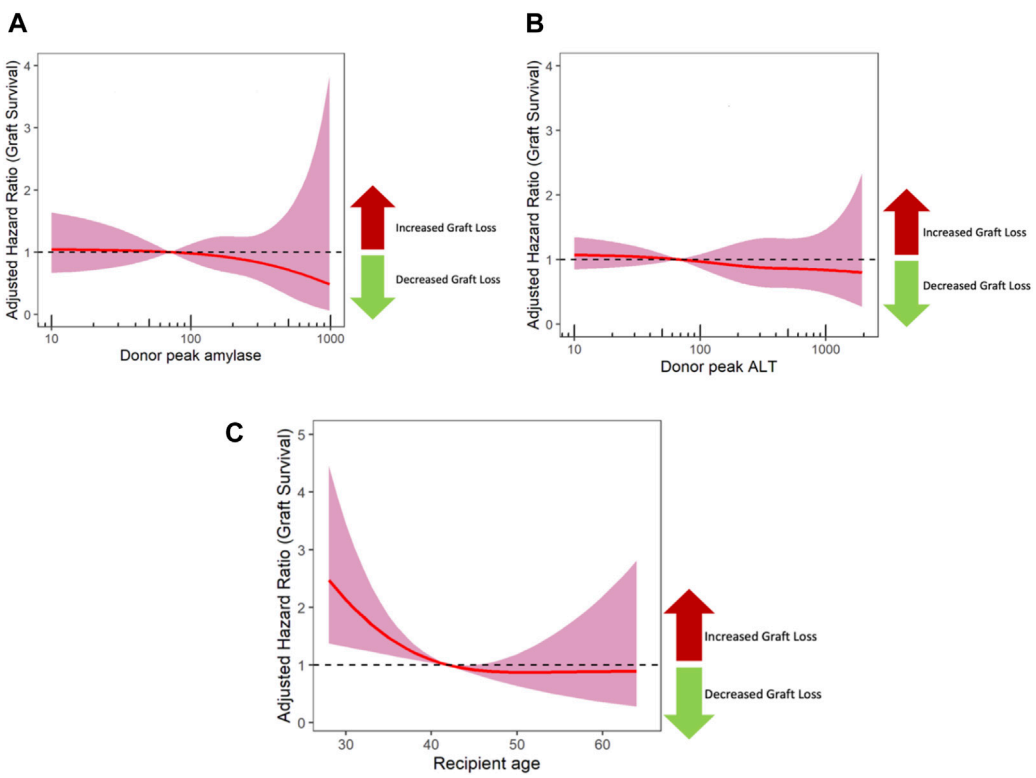


FIGURE 2 | The impact of peak donor Amylase **(A)** and ALT **(B)** on graft survival using cox regression models with restricted cubic splines. The shaded area represents the 95% confidence interval, and a dashed line at 1 represents no impact on outcome. For comparison, a separate model was performed for recipient age **(C)**, which showed that younger recipients have worse outcome. ALT, alanine transaminase.

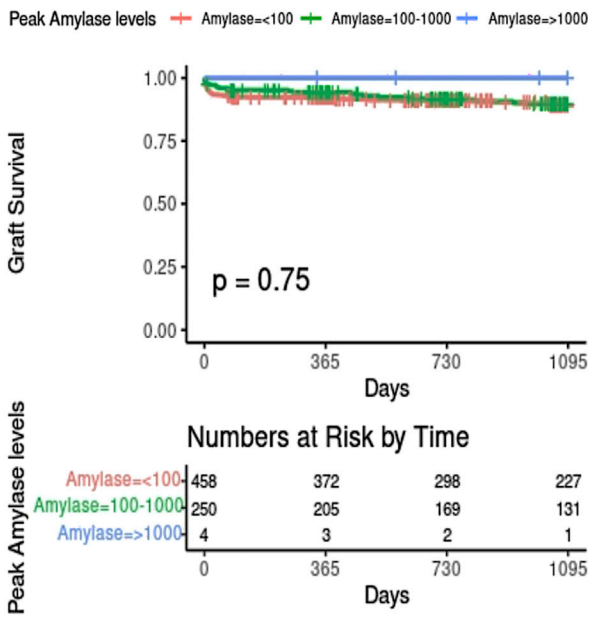


FIGURE 3 | Kaplan-Meier plot showing graft survival based on donor peak amylase level. Only those with complete amylase and graft survival data are shown.

and pancreas graft survival in SPK transplantation, on adjusted analyses. Although there was no evidence of an impact on outcome at any donor amylase level, relatively few pancreases were transplanted from donors with extreme increases in amylase (>1,000). Therefore, the impact of extreme elevations in amylase remain uncertain and such donor should be assessed on a case-by-case basis. It is reassuring that all four pancreases transplanted from donors with amylase >1,000 were functioning well at last follow up.

Additionally, our study has also found no association between donor LBTs and pancreas graft outcome. Hence, donor amylase and LBTs alone should not be a determining factor in organ utilisation in the modern era of pancreas transplantation.

With the rising demand for pancreas transplantation due to the increasing global disease burden of diabetes mellitus [1–3] and longer waiting lists there is a need to widen access to pancreas transplantation through improved utilisation of grafts. Further knowledge and evidence-based organ assessment is crucial in quantifying extended-criteria and marginal donor organs [21]. At the time of organ selection, some serological markers such as amylase levels and liver blood tests can be useful taken together with other markers of increasing risk when deciding the suitability and quality of a pancreas allograft but it is important to note they are non-specific and that there are other donor variables that may affect these blood tests [10–12, 22]. Nonetheless, surgeons remain reluctant to accept pancreas grafts from donor with raised serum amylase due to concerns of inferior outcomes. This becomes more important during an era of DCD transplantation as these are more prone to ischaemic damage but represent an underused resource [23–25].

Vinkers et al established the Pre-procurement Pancreas Allocation Suitability Score (P-PASS) in 2008, where a total of nine clinical parameters were used to predict the odds of a donor allograft being accepted for transplantation. The P-PASS score includes donor body mass index, age, duration of intensive care stay, serum amylase, lipase, sodium, duration of donor cardiac arrest, and whether or not the donor was on vasopressor support. Liver function tests, cold ischaemia time and type of donor, i.e., DCDs vs. DBDs are excluded in P-PASS. A low P-PASS score of 17 and below were three times more likely to be accepted as pancreas donors than donor grafts that scored above 17 [20]. The P-PASS score has been utilised by Eurotransplant since 2009 [26]. Amylase levels were among the nine parameters in this scoring system, where raised Amylase of ≥130 iu/L contributes to a higher P-PASS score, which is associated with high odds of organ discard [20]. It is important to note that the P-PASS score was developed based on chance of organ decline, and not based on outcome in transplanted pancreases. It therefore reflects what clinicians perceive as high risk, rather than factors which actually predict pancreas quality.

Interestingly, two retrospective analyses by Schenker et al and Blok JJ et al [27] revealed that there is no significant difference in long-term patient and graft survivals between donors with low (≤17) and high (≥17) P-PASS scores [28]. This supports our findings and further reiterates that donor pancreas allografts should not be rejected based solely on high P-PASS scores and the parameters that deem a subgroup of donors as marginal donors.

In the US the Pancreas Donor Risk index was developed from data taken from the Scientific Registry of Transplant Recipients database and is linked to graft survival. It has also been validated in the UK cohort [29]. It may offer better predictions for more marginal pancreases and some studies have confirmed it is a better predictor of pancreas graft survival after SPK rather than after solitary pancreas transplantation [30]. It is also a better predictor than the P-PASS for pancreas graft survival [27]. Age, and cold ischaemia are included but amylase and lipase are excluded from the PDRI, as they were not associated with outcome. A recent systematic review conducted by Ling et al have shown that both P-PASS and PDRI are inadequate risk indices for use in solid pancreas transplantation due inadequate reporting of model performance metrics outside of current externally validated cohorts. P-PASS was derived for pancreas graft acceptance and not for prediction of graft survival. PDRI was validated for the outcomes of 1-year pancreas survival, and limited to graft survival for SPK transplants only [31]. These studies also did not focus on donor blood tests, and their impact on outcome, our study fills these gaps.

Liver function tests and amylase are both included in the North American Islet donor score which was developed to guide decision making as to whether to accept a particular pancreas to improve isolation outcomes [32, 33]. However, both amylase and transaminases were shown in the same Wang 2016 paper to have no impact on success of islet isolation from 1,056 donors. This mirrors our results in whole pancreas transplantation.

Additionally, it is worth noting that a previous smaller study by Hesse and Sutherland have demonstrated that an isolated

elevation of amylase is not usually related to the functional status of the pancreas allograft, unless there was overt pancreatic trauma or pancreatitis. Graft function post-transplantation was found to be comparable in the recipients, regardless of whether the donor had normal or elevated amylase levels [34]. Krieger and others further echoes this, as they have shown that SPK graft survival rates in recipients of grafts from donors who had raised serum amylase compared favourably to outcomes in recipients of "ideal" donor grafts [35].

There are some limitations to the studies discussed above; both were performed in the early phases of pancreas transplantation, and only confined to the United States. Furthermore, the sample sizes in both studies were smaller than the present study. Both studies also reviewed graft outcomes based on arbitrary categories of normal and abnormal serum amylase, which reduces the power of the study [15–18]. Despite the limitations, these studies support our findings that hyperamylaseamia in donors is not a contraindication for pancreas organ donation. To our knowledge, our work is the largest cohort study to date, looking at the relationship between serum amylase and liver function tests upon pancreas graft survival in the modern era of pancreas transplantation. We have incorporated prospectively collected data from a large cohort, with robust statistical analysis as detailed above.

With the increased use of DCD grafts, there is an increased vulnerability towards inevitable ischaemic-reperfusion injury during procurement [36, 37]. Due to the close anatomical relationship between the pancreas and its partially shared vascular supply with the foregut, raised donor LBTs may represent ischaemic injury to abdominal viscera [14, 38–42]. Raised liver blood tests (LBTs) in liver donors were frequently used to define extended-criteria donors, in the context of liver transplantation [43, 44]. Due to the partially shared vascular supply [14, 38–42] between liver and pancreas we hypothesised that elevations in LBTs, especially transaminases, reflect hypoxic injury to the liver and are therefore a surrogate for hypoxic injury to the pancreatic allograft. This is supported by work showing that donors dying from hypoxic brain injury have far higher transaminase levels [11, 12].

Parajuli and others have found that delayed kidney graft function represented a significant risk factor for early pancreas graft loss (<90 days post-transplant) in SPK transplant recipients [45]. In view of this, we have therefore separately assessed the impact of peak donor renal function tests in our study, as the function of the transplanted kidney can impact pancreas graft function [45, 46]. We have found that donor renal blood tests did not predict pancreas graft survival (**Supplementary Table S3**). However, transplanted kidney graft survival may be better assessed in a study dedicated to kidney grafts, with much larger cohorts of kidney transplants alone.

More recently, our group explored the significance of deranged LBTs in liver transplantation and found that raised donor transaminases do not predict post-liver transplant outcomes [13]. Our study mirrors these findings in pancreas transplant, as there were no associations between abnormal LBTs and pancreas graft survival. Since routine liver function tests are carried out as part of the work up for a potential transplant donor, our findings reinforces that rises in LBTs should not be considered as a limiting factor in pancreas allograft allocation.

Furthermore, whilst in intensive care units, some donors may be given insulin in response to donor hyperglycaemia of varying aetiologies [47, 48]. A recent, large cohort study by Shapey et al suggests that donor insulin use is associated with a higher risk of graft loss due to islet failure and a lower risk of graft loss due to thrombosis in pancreas transplant recipients [49]. This suggests that actual markers of organ function and pancreas physiology may be more predictive of pancreas transplant outcomes, rather than non-specific enzyme release, such as amylase.

This study is limited by the retrospective design. Specifically, we lack granularity of data regarding imaging and clinical features of acute pancreatitis, or details regarding pancreatic trauma. As we only included donated pancreas grafts which were accepted and used for transplantation, the vast majority will be from donors without clinical or radiological features of pancreatitis or pancreatic trauma. Therefore, we cannot comment on the suitability of pancreases from donors where these features are present. We also lack information on serum lipase. Though we acknowledge it is a more specific marker of pancreatic injury, it is not routinely performed in the UK setting. Further study into the effects of lipase and pancreas graft transplantation outcomes, in a healthcare system that routinely measures donor serum lipase, may be a point in future research.

There is also a degree of selection bias, as various clinicians have different thresholds for donor amylase when it comes to discarding grafts at the time of organ procurement. As described in our results section, there is a wide range of donor amylase values in the pancreas grafts that were transplanted in our study. Hence multivariable analysis was performed to adjust for key confounders.

Finally, the right skewed distribution of serum blood tests translates to smaller number of donors in the extremely elevated results. This is reflected in the marked increase in the confidence intervals of the cox regression model adjusted hazard ratios with restricted cubic splines (**Figure 2**). The low number of donor with high amylase may affect the power of our study, and the most powerful way of assessing this was by using restricted cubic splines (**Figure 2**). The confidence intervals around these splines reveal uncertainty as amylase level increases. These are confidence fairly narrow up to a peak amylase value of 500, and then sharply increase due to the lower numbers of pancreases transplanted from donors with amylase values greater than 500. Although pancreases from donors with severely increased peak amylase (>1,000) all performed well in this study, this is a small group. Therefore it remains uncertain whether large increases in amylase (>1,000) impact on graft survival, and such donors should be assessed, on a case-by-case basis.

In conclusion, our study has demonstrated that the use of pancreas grafts from donors with hyperamylasaemia and raised liver blood tests is not associated with inferior outcomes. Mild or moderately raised donor amylase and liver blood tests should therefore not be considered a barrier to transplantation and organ utilisation when other donor factors are considered acceptable. This knowledge should prevent unnecessary organ discard, and

provides a simple method to expand the donor pool to meet current demands.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

Study concept and design: ST, CW, and SW. Acquisition of data: NH, ST, and SW from the National Health Service Blood and Transplant Registry. Data analysis: ST and NH. Data interpretation: All authors. Drafting of the manuscript: NH and ST. Critical revision of manuscript: All authors. Study Supervision: SW and CW. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

Author ST worked on this project during an MRC Clinical Research Training Fellowship (MR/Y000676/1) at Newcastle University.

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

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.12864/full#supplementary-material

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ORIGINAL RESEARCH
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Minimizing Incision in Living Donor Liver Transplantation: Initial Experience and Comparative Analysis of Upper Midline Incision in 115 Recipients

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Living donor liver transplantation (LDLT) needs "Mercedes Benz" or "J-shaped" incision, causing short and long-term complications. An upper midline incision (UMI) is less invasive alternative but technically challenging. Reporting UMI for recipients in LDLT vs. conventional J-shaped incision. Retrospective analysis, July 2021 to December 2022. Peri-operative details and post-transplant outcomes of 115 consecutive adult LDLT recipients transplanted with UMI compared with 140 recipients with J-shaped incision. Cohorts had similar preoperative and intraoperative variables. The UMI group had significant shorter time to ambulation (3 ± 1.6 vs. 3.6 ± 1.3 days, p = 0.001), ICU stay (3.8 ± 1.3 vs. 4.4 ± 1.5 days, p = 0.001), but a similar hospital stay (15.6±7.6 vs. 16.1±10.9 days, p = 0.677), lower incidence of pleural effusion (11.3% vs. 27.1% p = 0.002), and post-operative ileus (1.7% vs. 9.3% p = 0.011). The rates of graft dysfunction (4.3% vs. 8.5% p = 0.412), biliary complications (6.1% vs. 12.1% p = 0.099), 90-day mortality (7.8% vs. 12.1% p = 0.598) were similar. UMI-LDLT afforded benefits such as reduced pleuropulmonary complications, better early post-operative recovery and reduction in scar-related complaints in the medium-term. This is a safe, non-inferior and reproducible technique for LDLT.

Keywords: living donor liver transplantation, recipient surgery, upper midline incision, wound complications, incision scar

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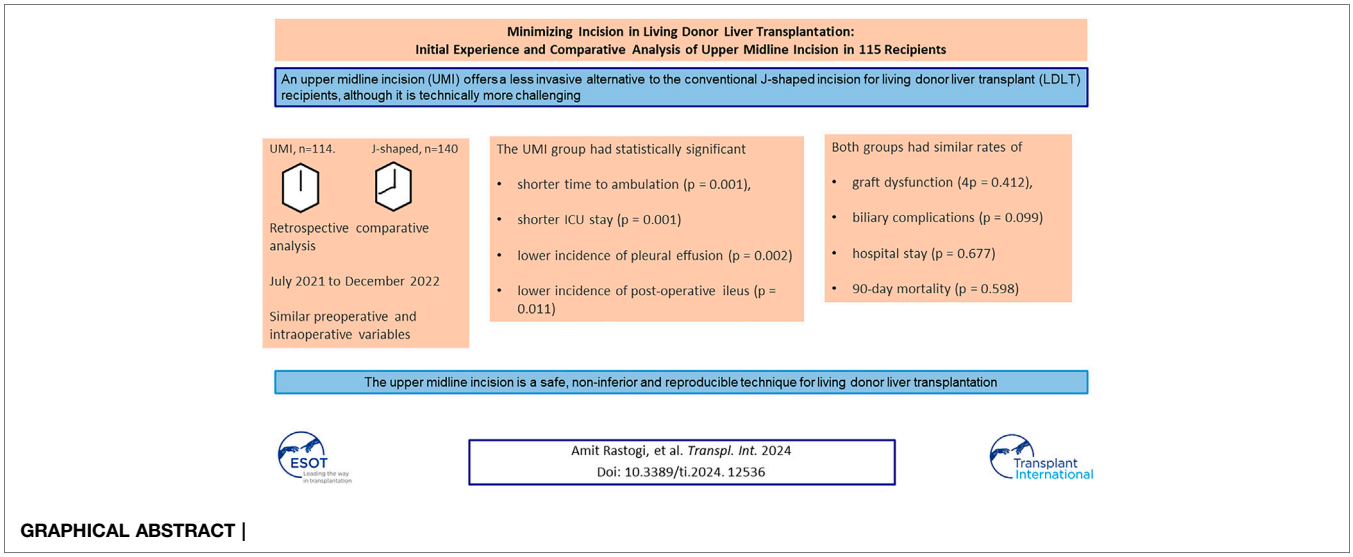
Abbreviations: ALD, Alcoholic liver disease; ATT, Anti-tubercular therapy; BMI, Body Mass Index; CAD, Coronary artery disease; CIT, Cold ischemia time; CTP, Child-Turcotte-Pugh score; GRWR, Graft-to-recipient weight ratio; HbcAb, Hepatitis B core antibody; HCC, Hepatocellular carcinoma; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HEV, Hepatitis E virus; ICU, Intensive care unit; IV, Intravenous; IVC, Inferior vena cava; LDLT, Living donor liver transplantation; LT, Liver transplantation; MELD, Model for End-Stage Liver Disease score; MHV, Middle hepatic vein; n, number; NASH, Non-alcoholic steatohepatitis; PRBC, Packed red blood cells; RHV, Right hepatic vein; RL, Right lobe; SBP, Spontaneous bacterial peritonitis; SLK, Simultaneous liver-kidney; SPSS, Statistical Package for the Social Sciences; WIT, Warm ischemia time.



GRAPHICAL ABSTRACT |

INTRODUCTION

The incision used for liver recipient surgery has evolved over the years from the classic "Mercedes Benz" to the "J shaped" or "Hockey stick" incision [1, 2]. Both incisions can provide sufficient exposure, but they involve extensive cutting of the abdominal muscles, which can pose short-term concerns such as pain, hematoma, poor respiratory compliance, wound infection, dehiscence, and paresthesia over the scar. Long-term complications may include scar formation, hernia, and loss of sensation in the upper abdomen [1].

The midline incision, on the other hand, offers excellent exposure to the surgical field while avoiding muscle cutting [2]. It passes through the avascular rectus sheath, causing minimal damage to the subcutaneous nerves and blood vessels. However, surgeons have often avoided using smaller incisions in recipients due to the risk of bleeding associated with portal hypertension during hepatectomy and the technical challenges of achieving perfect vascular anastomoses with a short warm ischemia time during graft implantation.

After the initial reports of successful utilization of an upper midline incision [2] or laparoscopic assistance with such an incision (hybrid procedure) for recipient surgery [3, 4], Jochmans et al reported the feasibility of a single xipho-pubic laparotomy for hepatectomy, nephrectomy, and transplantation in cases of polycystic disease for simultaneous liver-kidney transplant [5] while Fonseca-Neto et al reported recipient surgery with whole liver cadaveric donor grafts through an upper midline incision [6]. This hybrid procedure continues to be published in the current literature [7–10] and has now been reported in a pediatric recipient [11].

Based on our extensive experience with the use of the midline incision for liver donor surgery, we introduced an upper midline abdominal incision for recipient hepatectomy and liver graft implantation in LDLTs and modified our surgical steps as described. It is noteworthy that the published literature on this topic is so far based on a small number of patients. In this report, we aim to contribute our experience with 115 consecutive cases of recipient surgery performed with an upper midline incision which, to the best of our knowledge, represents the largest reported experience with this technique. The aim of this study was to compare the recipient outcomes of a midline incision versus a conventional "J-shaped" incision in LDLT.

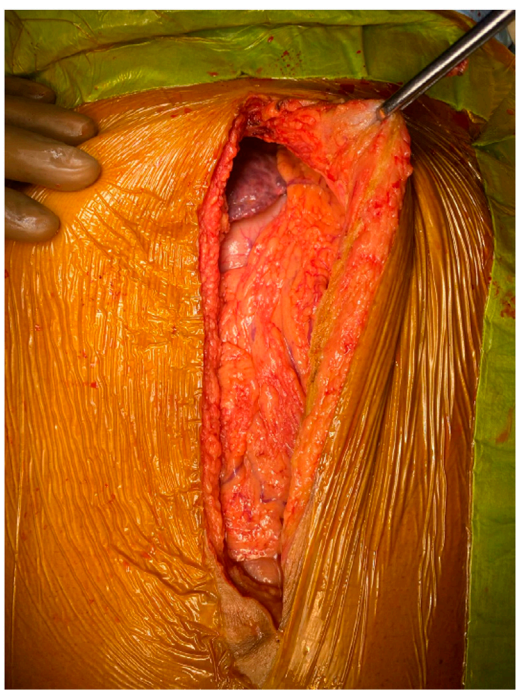


FIGURE 1 | Midline skin incision.

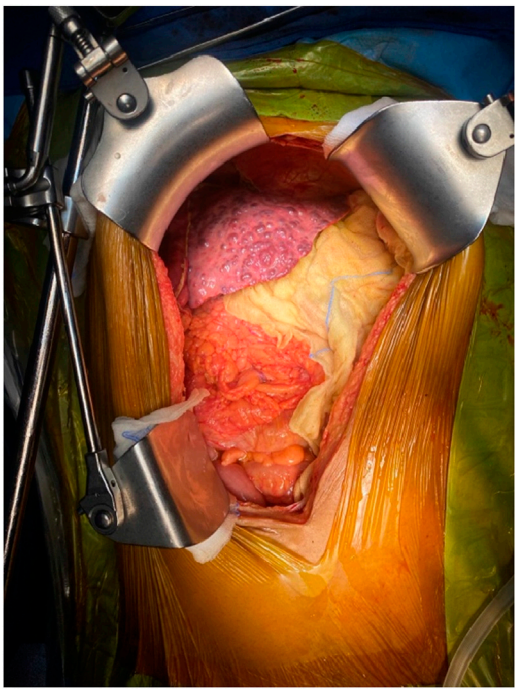


FIGURE 2 | Placement of abdominal retractor blades: two costal margin retractors and one right abdominal wall retractor.

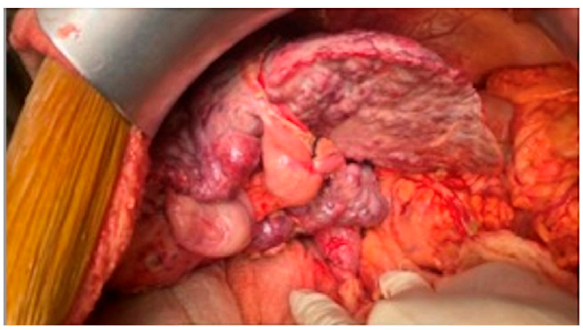


FIGURE 3 | Completion of portal dissection: native liver in the anhepatic phase.

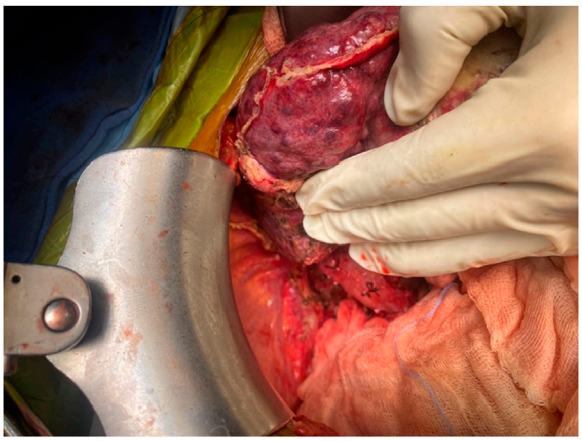


FIGURE 4 | Right lobe mobilization.

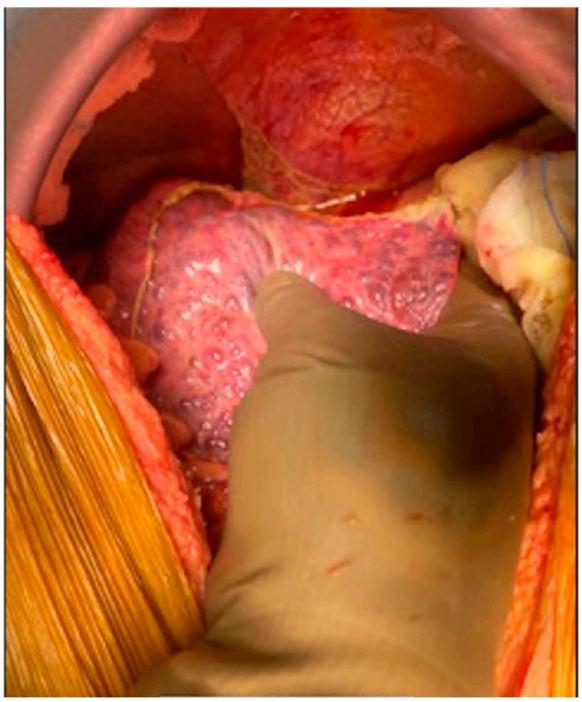


FIGURE 5 | Left lobe mobilization.

MATERIALS AND METHODS

This was a retrospective analysis of a prospectively maintained, comprehensive database of all liver transplants performed at our center. A total of 115 adult recipients underwent LDLT via a midline incision between July 2021 and December 2022. Peri-operative details and post-transplant outcomes of this group were analyzed and compared with those of a group of 140 recipients who underwent LDLT via a J-shaped incision during the same period. The patients were randomly selected to receive either type of incision. The surgical team remained the same in both groups.

This study was approved by the Institutional Review Board of the Hospital.

Selection of Midline Recipients

Pediatric, dual-lobe, re-transplant, and combined liver-kidney transplant recipients were excluded. In the initial part of our experience with the first five midline LDLTs, recipients with a high body mass index (BMI) greater than 35, a history of previous abdominal surgery, or a history of spontaneous bacterial peritonitis (SBP) were also excluded. All excluded cases were not part of the present comparative analysis. Subsequently, all patients were randomized to either group.

Two different incisions were used for donor surgery in the midline cohort. Open donor hepatectomy was performed in

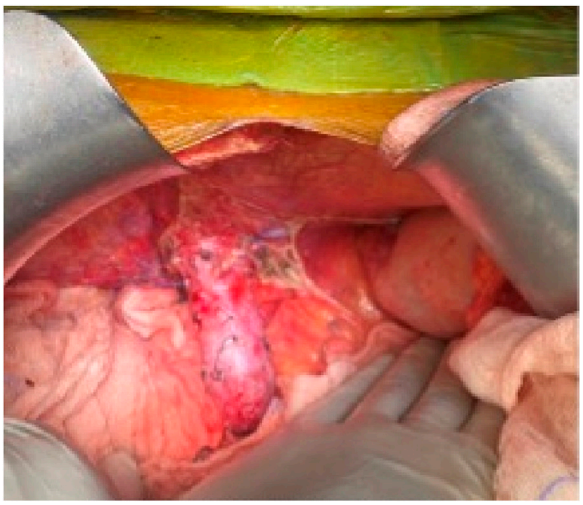


FIGURE 6 | Abdominal cavity after removal of native liver.

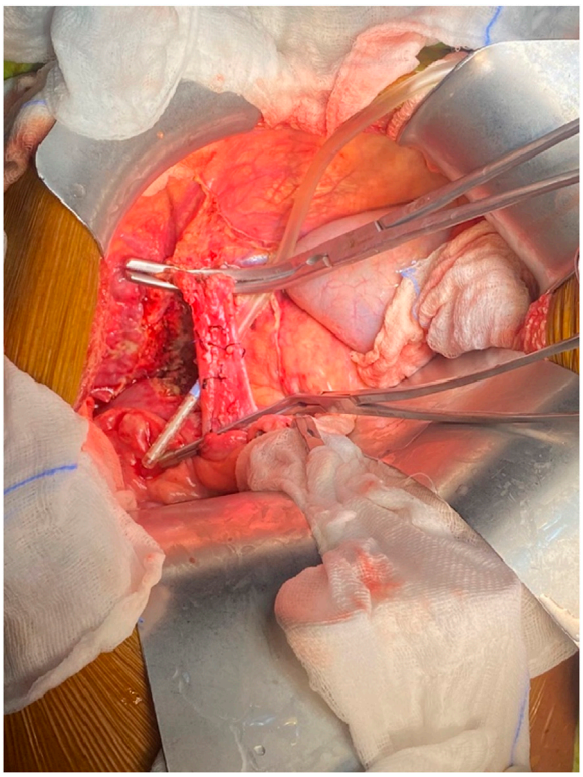


FIGURE 7 | IVC cross-clamping.

91 cases using the upper midline incision, while 24 cases underwent a total robotic donor hepatectomy. For the "J incision" cohort 121 donors underwent open donor hepatectomy (conventional and midline) while 19 donors underwent robotic donor hepatectomy.

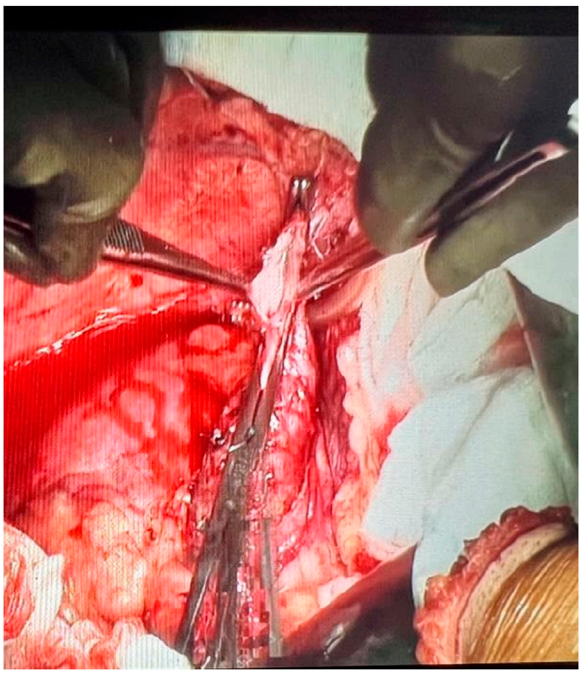


FIGURE 8 | IVC side clamping.

Surgical Technique

The upper midline incision extended from the xiphoid to the umbilicus and curved around it if needed (**Figure 1**). To achieve a wide elliptical exposure, we used Thomson's Retractor™ with conventional bilateral costal retractors. During the hepatectomy, right lateral traction was applied to the right abdominal wall at the lower edge of the incision using a side arm attachment of the Thomson's Retractor™ (**Figure 2**) and later on the left side during implantation. This maneuver increased the space around the porta, and the stomach and colon/bowel were packed down with surgical sponges.

The salient difference from the conventional technique is the early portal dissection and division of the hepatic arteries and bile ducts. If portal hypertension is severe, the portal vein is also divided before right lobe mobilization. This helps to reduce both, the blood loss and the size of the liver for subsequent mobilization of the right lobe (**Figure 3**). This is performed from the inferior to the superior aspect of the liver instead of the conventional lateral to medial mobilization. With increasing experience, we have been able to avoid the division of the portal vein prior to the mobilization of the right lobe in more than 50% of our recipients. Right lobe mobilization was followed by left lobe mobilization (**Figures 4**, **5**), posterior and anterior IVC dissection, ligation of the hepatic veins, and removal of the diseased liver (**Figure 6**).

Bench surgery was performed in the usual manner with respect to the anatomy of the graft. In the majority of recipients, we performed a "plasty" of the end of the MHV extension with the RHV orifice to allow for a single RHV and MHV outflow anastomosis.

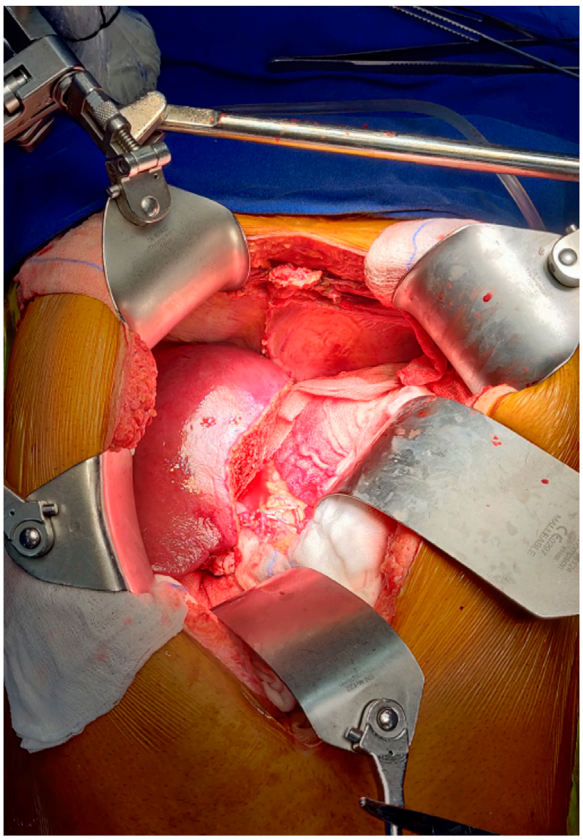


FIGURE 9 | Implanted graft.

TABLE 2 | Categorization and comparison of MELD score of recipients in the midline and conventional incision groups.

MELD	Midline incision (*n* = 115)	J shaped incision (*n* = 140)
<21	88 (76.5%)	96 (68.6%)
21–30	25 (21.7%)	37 (26.4%)
>30	2 (1.7%)	7 (5.0%)

Chi-Square Value = 3.026, p-value = 0.220.

Graft implantation was done by cross-clamping (or side-clamping in cases of renal or cardiac dysfunction) the IVC (**Figures 7**, **8**). The supra-hepatic caval clamp remained the same (Ulrich Swiss™ IVC clamp 280 mm) as in the conventional incision. However, to clamp the lower IVC, a longer clamp (Debakey renal artery clamp) was used from the left side (versus the right side in the conventional technique). Longer clamps were also used for side caval clamping (FB508R Debakey-Satinsky Clamp, Aesculap US).

Implantation of the outflow veins (RHV, MHV, and inferior hepatic veins) and portal vein was followed by graft reperfusion and subsequent hepatic artery and bile duct anastomoses (**Figure 9**).

The bench reconstruction, implantation technique, and postoperative management protocols for all recipients were the same for all recipients irrespective of the incision used. Recipients were nursed in the ICU for 2–4 days and then transferred to the ward.

Statistical Analysis

The analysis involved the profiling of patients based on various demographic, clinical, and laboratory parameters. Descriptive

TABLE 1 | Pre-operative characteristics of recipients in the midline and conventional incision groups.

Pre-operative variables	Midline incision (*n* = 115)	J shaped incision (*n* = 140)	*p*-value
Men (no.)	95 (82.6%)	111 (79.3%)	0.503
Age (years)	49.8 ± 11.6	48 ± 13.5	0.246
BMI (Kg/m^2)	24.7 ± 4.2	24.3 ± 5.1	0.571
Moderate to gross ascites	83 (72.2%)	99 (71.0%)	0.833
Portal vein thrombosis (Yerdel grade 2 or more)	3 (2.6%)	6 (4.3%)	0.464
CTP score	9.1 ± 2.2	8.7 ± 2.2	0.114
Comorbidities			
Diabetes mellitus	46 (40%)	42 (30%)	0.095
CAD	4 (3.5%)	2 (1.4%)	0.283
HCC	23 (20%)	21 (15%)	0.293
Etiology of Liver Disease			
HBV	10 (8.7%)	14 (10%)	0.723
HCV	14 (12.2%)	17 (12.1%)	0.994
ALD	31 (27%)	33 (23.6%)	0.535
Autoimmune	9 (7.8%)	6 (4.3%)	0.232
NASH	18 (15.7%)	15 (10.7%)	0.242
ATT induced	0 (0%)	1 (0.7%)	0.364
HEV	0 (0%)	2 (1.4%)	0.198
Wilson's Disease	3 (2.6%)	2 (1.4%)	0.499
Cryptogenic	12 (10.4%)	24 (17.1%)	0.126

ALD, alcoholic liver disease; ATT, anti-tubercular therapy; CAD, coronary artery disease; CTP, Child-Turcotte-Pugh score; HCC, hepatocellular carcinoma; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HEV, Hepatitis E virus; MELD, Model for End-Stage Liver Disease score; NASH, Non-alcoholic steatohepatitis.

TABLE 3 | Intra-operative characteristics of recipients in the midline and conventional incision groups.

Intraoperative variables	Midline incision (*n* = 115)	J shaped incision (*n* = 140)	*p*-value
Operative Time (minutes)	749.5 ± 248.1	701.4 ± 165.7	0.069
Donors undergoing robotic hepatectomy	24 (20.9%)	18 (12.9%)	0.088
Right-lobe grafts	113 (98.2%)	134 (95.7%)	0.246
Graft weight (grams)	677.9 ± 129.3	652.3 ± 133.1	0.125
GRWR	1.02 ± 0.23	1.0 ± 0.26	0.461
RL recipients with GRWR <0.8 (%)	16 (13.9%)	23 (16.4%)	0.657
>1 graft hepatic duct	65 (56.5%)	68 (48.5%)	0.548
IVC Clamp Time (minutes)	39.9 ± 12.4	42.3 ± 9.8	0.087
Partial/side clamping	63 (54.8%)	73 (52.1%)	0.633
CIT (minutes)	101.2 ± 39.1	112.5 ± 36.8	0.018*
WIT (minutes)	29.7 ± 10.6	31 ± 8.6	0.298
PRBC transfusion (units)	6.3 ± 4.3	5.3 ± 4.1	0.058
Blood loss (mL)	2241.3 ± 1253.8	2101.4 ± 1106.9	0.345
Blood lactate prior to transfer to the ICU (mmol/L)	4.92 ± 2.59	5.2 ± 3.27	0.46

CIT, cold ischemia time; GRWR, graft-to-recipient weight ratio; ICU, intensive care unit; IVC, inferior vena cava; PRBC, packed red blood cells; RL, right lobe; WIT, warm ischemia time. indicate significant* p *value, < 0.05.*

TABLE 4 | Post-operative outcomes of recipients in the midline and conventional incision groups.

Post-operative variables	Midline incision (*n* = 115)	J shaped incision (*n* = 140)	*p*-value
Blood lactate on the first postoperative day (mmol/L)	3.18 ± 2.05	3.79 ± 2.76	0.056
Mechanical Ventilation (days)	1.4 ± 1.1	1.3 ± 0.9	0.188
Time to ambulation (days)	3.0 ± 1.6	3.6 ± 1.3	0.001*
ICU stay (days)	3.8 ± 1.3	4.4 ± 1.5	0.001*
Hospital stay (days)	15.6 ± 7.6	16.1 ± 10.9	0.677
Wound-related complications	12 (10.4%)	18 (12.9%)	0.55
Graft dysfunction	5 (4.3%)	12 (8.5%)	0.412
Biliary complications	7 (6.1%)	17 (12.1%)	0.099
Pleural effusion	13 (11.3%)	38 (27.1%)	0.002*
Transfusion requirement	10 (8.7%)	25 (17.9%)	0.034*
Re-exploration rate for bleeding	3 (2.6%)	2 (1.4%)	0.245
Post-operative ileus	2 (1.7%)	13 (9.3%)	0.011*
Mortality (90 days)	9 (7.8%)	17 (12.1%)	0.598
Incisional hernia	5 (4.3%)	5 (3.6%)	0.774

ICU, intensive care unit. indicate significant* p *value, < 0.05.*

statistics were used to analyze quantitative variables, which were reported as means and standard deviations. Categorical variables were expressed as absolute numbers and percentages. The independent Student's t-test was used to compare the means between independent groups. Cross tables were generated, and the Chi-square test was used to test for associations. A *p*-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software, version 24.0.

RESULTS

The overall and mean follow-up periods for both groups were 6–19 months (mean 8.2 months ± 6.5). **Tables 1–3** show the preoperative and intraoperative characteristics, and postoperative outcomes of the two groups of recipients.

The midline incision and J-shaped incision groups had similar preoperative variables and demographic characteristics, as there were no significant differences in age, gender, BMI, CTP score, MELD score, hepatocellular carcinoma, or underlying etiology (**Table 2**). In addition, the prevalence of diabetes mellitus, and CAD was not significantly different between the two groups.

As shown in **Table 3**, there were no statistically significant differences between the midline incision and J-shaped incision cohorts in terms of operative time, frequency of right lobe grafts, open versus robotic donor hepatectomy, graft weight, graft-to-recipient weight ratio (GRWR), the proportion of patients with low GRWR grafts (<0.8%), number of graft bile ducts, IVC clamping time, the proportion with partial versus total IVC clamping during implantation, warm ischemia time (WIT), blood loss, transfusion requirement, and blood lactate prior to transfer to the ICU. However, cold ischemia time (CIT) was shorter in the midline incision group than in the J-shaped incision group (values 101.2 ± 39.1 vs. 112.5 ± 36.8; $p = 0.018$).

Table 4 shows the post-operative parameters and outcomes between the two groups of recipients. There was no statistically significant difference in blood lactate on the first post-operative day or the duration of the requirement for mechanical ventilation between the two groups. However, the midline incision group had a statistically significant shorter time to ambulation ($p = 0.001$),

a shorter ICU stay ($p = 0.001$), but a similar hospital stay compared to the J-shaped incision group. At the same time, the J-shaped incision cohort had significantly higher rates of pleural effusion, transfusion requirements, and post-operative ileus. While the incidence of wound-related complications such as seroma, wound infection, and dehiscence was higher in the J-shaped incision group, the difference was not statistically significant. The rates of graft dysfunction, re-exploration rate for bleeding, biliary complications, and mortality were similar between the two groups.

In the midline incision cohort, four patients required an extension of the incision, and three needed a muscle-cutting (conventional) incision. These conversions were done in the early part of the experience, and all three were converted after liver explantation. Two of these patients developed bowel edema after the anhepatic phase, and one patient experienced bleeding from the RHV anastomosis just before abdominal closure. A fourth patient required an extension of the midline incision to below the umbilicus due to a thick muscular wall that reduced the working space. With increasing experience, we felt that this extension could potentially mitigate the need for conversion to a muscle incision. Adequate exposure was maintained, and muscle cutting was avoided in these cases.

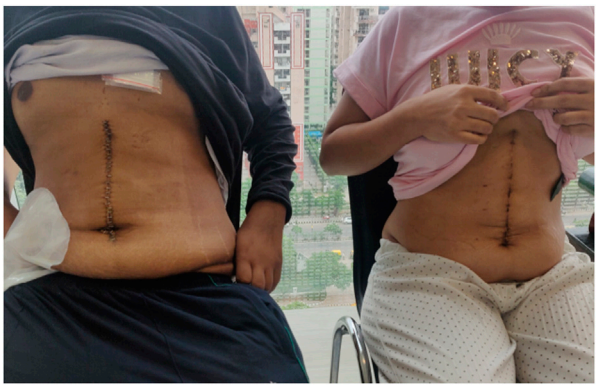


FIGURE 10 | First case, July 2021: recipient on the left and donor on the right.

DISCUSSION

Multiple authors have documented the safety of using the upper midline incision in major hepatectomies, including those in liver donors [12–16] and more recently in patients with chronic liver disease and liver fibrosis [17]. Our team has also incorporated the use of the midline incision in liver recipients, capitalizing on our experience with its application in donors and the recognized benefits of this incision over those that require cutting through muscle tissue. We have successfully performed over 500 donor hepatectomies using the midline incision. In our cohort of midline incision recipients, 91 donor surgeries were done with an open upper midline approach while 24 donors underwent robotic hepatectomy.

We opted for the pure open upper midline incision approach for liver surgery over the totally minimally invasive [8] or laparoscopically assisted midline approaches [3, 4, 9] for several reasons. First, the complete laparoscopic or robotic approach is not suitable for many recipients due to their range of conditions, portal hypertension, technical difficulties in vascular and biliary anastomoses, and graft anatomical variations encountered. Second, the anastomoses for graft implantation are in the plane of the IVC and the hepato-duodenal ligament, which are easily accessible through a midline incision. Third, the use of good retraction, long instruments, and modification of the surgical technique enables easy standardization of the operative steps for use by all surgeons on the team, rather than restricting it only to those with expertise in minimally invasive surgery. We believe that a pure open upper midline laparotomy procedure is also safer than a hybrid approach with its natural benefits in postoperative rehabilitation [3].

The upper midline incision can provide adequate exposure for recipient surgery. Midline incisions allow for easy left lobe mobilization and access to the suprahepatic vena cava and provide good exposure for both the hepatic and portal vein anastomoses [2]. This approach has been safely used in LT recipients receiving whole grafts from deceased donors [6]. Additionally, a midline incision extending from the xiphoid process to the pubis has been reported to be adequate for hepatectomy, native nephrectomy, and simultaneous liver-kidney (SLK) transplantation in patients with polycystic disease [5]. More recently, the upper midline incision was reported to be adequate for graft implantation in a pediatric patient, further highlighting its usefulness in the LT setting [11].

In the initial phase of the study, the exclusion criteria were outlined as previously described. After the first five cases, the team consistently utilized an upper midline incision for all subsequent cases, regardless of recipient characteristics like BMI, height, etc., which may have suggested a limited working field [6]. The incision was extended as needed based on the situation keeping patient safety as our primary objective. As discussed above, with increasing experience, we have not resorted to extending to a muscle-cutting incision and extending along the midline below the umbilicus in occasional patients.

A learning curve for performing donor hepatectomy through an upper midline incision has been reported in the literature [18]. In our group, the initial cases of upper midline recipient surgery were performed by senior surgeons with extensive experience, as recommended in previous studies [2]. As experience was gained, other surgeons within the group also began to perform the procedure.

The amount of blood loss in the two cohorts of patients was found to be comparable in the study, which is consistent with previously published experience [3]. There was no notable distinction between the two groups in terms of immediate post-operative lactate levels before transfer to the ICU, suggesting that both groups exhibited comparable metabolic responses during surgery. CIT is multifactorial and a small difference was observed between the two cohorts in our study, the significance of which remains inconclusive.

The advantages of a midline incision in comparison to transverse incisions are that it preserves the innervation and

avoids muscle disruption, resulting in less postoperative pain [6]. Patients who undergo midline incisions have reported better results in terms of numbness and cutaneous sensation [19, 20]. Midline incisions also offer the benefit of a decreased risk of wound complications, such as infection and dehiscence, in contrast to utilizing a transverse incision [6, 11]. Avoidance of abdominal muscle and nerve disruption also leads to reduced use of analgesics and early ambulation and rehabilitation [19]. Patients also exhibit greater compliance with physiotherapeutic maneuvers such as spirometry, leading to a shorter ICU stay [3, 6, 11]. Our patients in the midline incision group showed a comparable trend, with significantly shorter time to ambulation, a lower incidence of postoperative pleural effusion and ileus, and a shorter ICU stay.

In previous donor studies, a midline incision was found to offer better cosmesis and increased self-confidence, with patients reporting good self-assessment of appearance and daily activities [19, 20]. The majority of our patients have expressed satisfaction with the incision at follow-up clinics (**Figure 10**). However, a formal questionnaire-based analysis has yet to be performed.

Earlier studies have suggested that incisional hernia occurrence after liver transplant is higher in cases with an element of midline incision compared to those without [21, 22]. However, a recent meta-analysis of incisional hernia formation in hepatobiliary surgery found no significant difference in incisional hernia formation between the hybrid (with midline incision) and transverse incision groups [23]. Another recent meta-analysis reported a median incidence of incisional hernia of 15.1%, with a median time of 42.9 months post-liver transplantation [24]. As our study focuses on the initial experience with the midline incision, our follow-up period is relatively short. Five patients in each group have developed incisional hernia so far, but none of them have undergone surgery yet. Hence, comparing the incidence of incisional hernia between the two cohorts may not be meaningful at this stage.

The limitations of the current study include the lack of a randomized controlled trial design and its retrospective nature. Another limitation is the relatively short follow-up period, which precludes an adequate assessment of complications such as incisional hernia. Finally, no objective assessment of patient satisfaction was conducted, which could be addressed through a questionnaire-based study.

To the best of our knowledge, this is the largest series to date, but the sample size could still be considered relatively small, which may limit the generalizability of the results. Furthermore, the study was conducted at a single center, which may limit the external validity of the findings to other centers with different patient populations and surgical teams.

CONCLUSION

Our initial experience with midline LDLT has yielded promising results, with favorable outcomes for the recipients. We have demonstrated that a completely open midline approach is possible without requiring the mobilization of the right lobe using laparoscopic or robotic techniques. With increasing experience, we believe that this approach can be extended to most patients undergoing LDLT.

Our midline incision technique offers a safe, non-inferior, and reproducible procedure with potential benefits such as reduced pleuropulmonary complications and better early post-operative recovery, due to the non-muscle-cutting nature of the incision. We believe that the reduction in incision size and the resulting scar may lead to better acceptance of liver transplant surgery. The continued use of muscle-cutting incisions in recipient surgery is due to the technical complexity involved. Nevertheless, more prospective data are needed to verify these initial findings.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by the Institutional Review Board of Medanta hospital Gurugram. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

AR—corresponding author, conception and design of study, acquisition of data, analysis and interpretation of data, drafting the article, revising it critically. AG—analysis and interpretation of data, drafting the article, revising it critically. RB—acquisition of data, drafting the article, revising it critically. FK—acquisition of data, analysis and interpretation of data. KY—acquisition of data, analysis and interpretation of data. SC—acquisition of data, analysis and interpretation of data. PB—acquisition of data, analysis and interpretation of data. SD—acquisition of data, analysis and interpretation of data. NC—acquisition of data, analysis and interpretation of data. NS—acquisition of data, analysis and interpretation of data. AS—analysis and interpretation of data, revising it critically, final approval of the version.

CONFLICT OF INTEREST

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

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ORIGINAL RESEARCH
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Solid Organ Transplant Litigation at One of Europe's Largest University Hospitals

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Due to its intrinsic complexity and the principle of collective solidarity that governs it, solid organ transplantation (SOT) seems to have been spared from the increase in litigation related to medical activity. Litigation relating to solid organ transplantation that took place in the 29 units of the Assistance Publique-Hôpitaux de Paris and was the subject of a judicial decision between 2015 and 2022 was studied. A total of 52 cases of SOT were recorded, all in adults, representing 1.1% of all cases and increasing from 0.71% to 1.5% over 7 years. The organs transplanted were 25 kidneys (48%), 19 livers (37%), 5 hearts (9%) and 3 lungs (6%). For kidney transplants, 11 complaints (44%) were related to living donor procedures and 6 to donors. The main causes of complaints were early post-operative complications in 31 cases (60%) and late complications in 13 cases (25%). The verdicts were in favour of the institution in 41 cases (79%). Solid organ transplants are increasingly the subject of litigation. Although the medical institution was not held liable in almost 80% of cases, this study makes a strong case for patients, living donors and their relatives to be better informed about SOT.

Keywords: information, solid organ transplantation, complaints, litigation, postoperative complication

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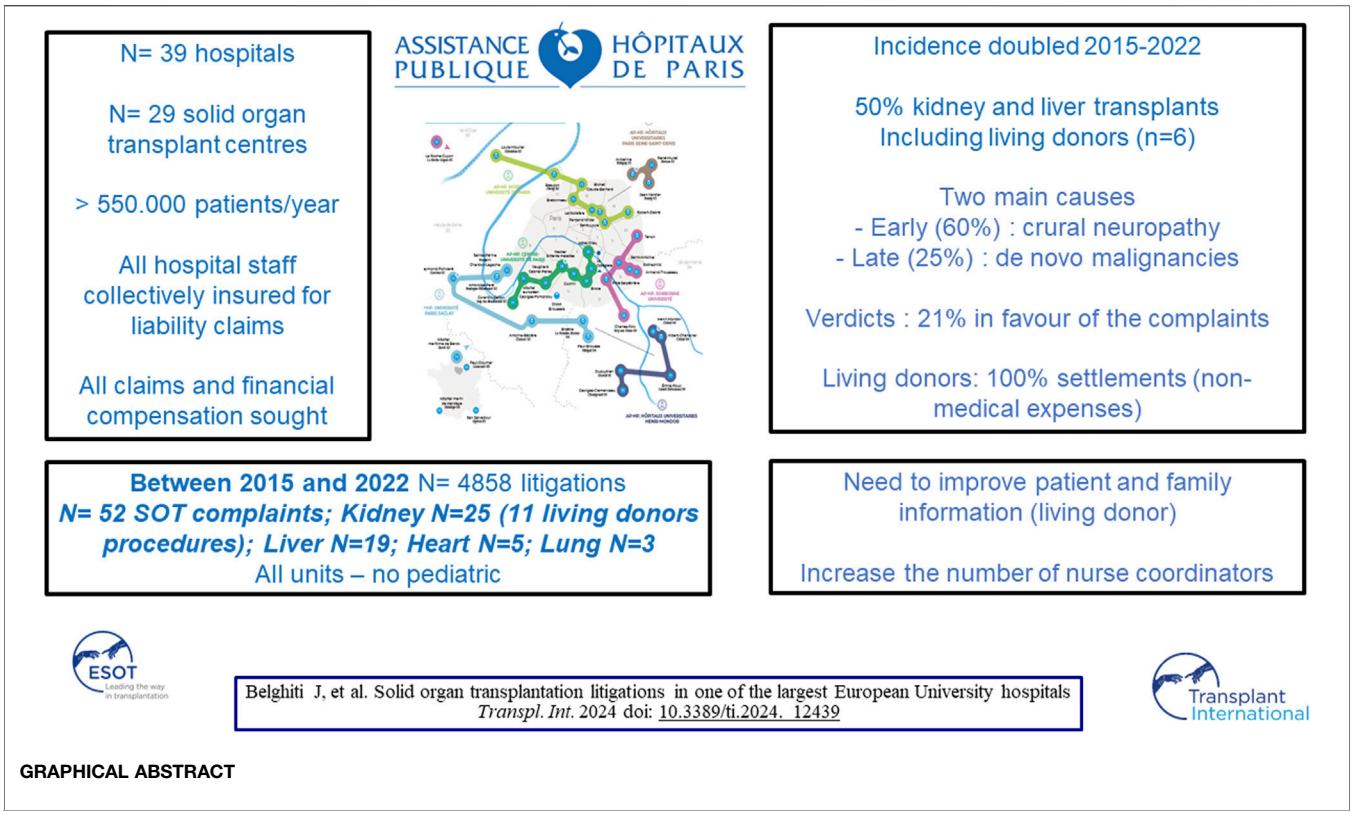
INTRODUCTION

Solid organ transplantation (SOT) combines the best medical care with a high level of expertise involving cutting-edge medical and surgical management. This procedure saves the lives of countless patients suffering from irreversible liver, lung or heart failure, and increases the survival rate of patients suffering from kidney failure every year [1–4]. In European countries, allografts come from anonymous donors who have died without financial compensation. However, the number of candidates for organ transplants exceeds the availability of allografts and is associated with significant post-operative mortality and morbidity. As a result, the allocation rules and the failure of this procedure may be the subject of disappointment, leading patients and families to complain. In Europe, very few legal proceedings have been reported and there is a desire to maintain a positive public image of the hospital. All this has led us to consider that SOTs are not affected by the increasing judicialization of medical activity. In the absence of reliable data to support these views, we conducted a study focusing on legal proceedings following SOT at Assistance Publique Hôpitaux de Paris (AP-HP), the largest teaching hospital in France.



GRAPHICAL ABSTRACT

MATERIALS AND METHODS

Study Sites and Procedure

This study is a quantitative, descriptive and evaluative study within the AP-HP, which is the largest university in France with more than 30 hospitals located in Paris and the suburbs, caring for more than 8 million patients a year.

In AP-HP, all employees of all hospitals, including doctors, nurses and other (paramedical) staff, are collectively insured for civil liability claims. The AP-HP is unique in that it is its own insurer and all claims are handled and defended by a single legal department called the DAJ (Département des Affaires Juridiques). The DAJ protects and defends all AP-HP employees without the need to take out additional insurance. The procedure is as follows: in cases where patients or their relatives contest hospital care after a setback, local mediation is set up. When local mediation is successful, it never leads to a settlement. If local mediation fails or if financial compensation is sought, patients or their relatives may initiate legal proceedings to obtain medical expertise. Complaints seeking compensation are judged either by a specific independent body, the CCI, the Conciliation and Compensation Chamber. This commission, chaired by a magistrate and made up of members of civil society, analyses compensation claims free of charge when the potential damage exceeds a certain severity threshold. Analysis and advice were provided by forensic experts appointed by these courts and after confrontation between the two parties: plaintiffs (patients and/or relatives) accompanied by their lawyers and defendant including hospital concerned medical doctor and their own lawyer. The verdict must determine whether the institution is guilty of misconduct or breach of duty. In most cases, verdict follows advice of forensic experts appointed by these courts. If the damage assessments exceed the severity threshold defined by law, financial compensation is payable by the hospital in the event of fault or negligence, or by the State and the National Solidarity Fund for Medical Accidents (ONIAM) in the event of therapeutic risk. In complex situations involving negligence and therapeutic risks, responsibility is shared between ONIAM and the hospital.

An average of 600 cases are recorded by DAJ every year (ranging from 503 to 702 per year over the last 10 years). As experienced in many countries, these judicial proceedings mainly involve orthopedic surgery, primary care, obstetrics -gynecology, general surgery and neurosurgery [5, 6]. APHP collects information from 29 OT centres caring out around 1,500 OT per year, including seven kidney transplant (KT) units (810 KT/year, 54%), five liver transplant units (LT) (480 LT/year, 32%), six cardiac transplant units (CT) (170 CT/year, 11%) and four pulmonary transplant units (PT) (70 PT/year, 5%). The introduction of claims management software since 2015 has enabled the authors to examine proceedings whose verdict has been recorded from 2015 to 2022.

As far as organ transplantation from living donors is concerned, the short- and long-term risks of all procedures are first explained by the medical providers and nurse coordinators.

TABLE 1 | Total number of SOT proceedings registered and judged among all cases and SOT recorded in APHP from 2015 to 2022.

	2015	2016	2017	2018	2019	2020	2021	2022
Number of proceedings (n = 4,858)	562	676	702	675	660	503	548	532
Number of SOT (n = 11,324)	1,562	1,552	1,643	1,444	1,486	1,141	1,193	1,303
Number of proceedings in SOT (n = 52)	4	5	7	6	7	7	8	8
Proceedings in SOT %	0.71	0.73	0.99	0.88	1.06	1.39	1.45	1.50

TABLE 2 | Main alleged bases for proceedings after SOT (In some cases several complains are alleged).

Organ			Early post-operative complications < 90 days			Late complications > 90 days	Death (covid)
	Iatrogenic complication leading to SOT	Failure to refer in time	Errors in the choice of the graft or in the operative procedure	Alleged failure to diagnose or to treat critical licomplications	Acute neuropathy	Alleged failure to inform and to treat complications	
Heart (n = 5)	1	0	1	3	0	1	3
Lung (n = 3)	0	1	1	2	0		3 (1)
Liver *(n = 19)	3	3	4	10	1	2	13
Kidney **(n = 25)							
Recipients (n = 19)							
Cadaveric (n = 14)	0	0	3	5	7	8	6 (1)
Living (n = 5)	1	—	0	2	0	3	3 (2)
Donors: (n = 6)	0	—	—	4	4	2	0

**A patient underwent combined liver and kidney transplantation and alleged cruralgia. **One patient underwent a combined pancreas and kidney transplant and died due to a post-operative complication.*

A psychological assessment is systematically carried out for all living donors. An independent committee then checks that recipients and living donors have understood the risks and are psychologically fit to harvest organs. All SOT data is closely monitored by an independent body, the Agence de la biomédecine (ABM), which provides annual reports (activity, results) on transplant activity in France and in each transplant centre.[1]

Claims Files

All proceedings records with analysis and advice by forensic experts were reviewed and analysed by the first author, who has extensive experience in SOT (JB). Data recorded included patient age, gender, date of SOT, date of the event giving rise to complaint, mortality, incidence of other clinical events or conditions considered relevant to the litigation and court verdict. The main grounds for the plaintiffs' complaint were categorised as follows 1) iatrogenic complication leading to SOT; 2) failure to provide timely referral; 3) graft/recipient mismatch or technical failure during the operation; 4) failure to diagnose and treat life-threatening post-operative complications in the intensive care unit (ICU); 5) acute neuropathy attributed to nerve damage during the operation; 6) lack of information about the long-term risks of the operation, including the development of malignancy. Our study meets the criteria of reference methodology MR-004, which governs the processing of personal data for the purposes of study, evaluation or research not involving the human person, as defined by the CNIL (Commission nationale de l'informatique et des libertés), which governs personal data in France. More specifically, these are studies that do not meet the definition of research involving the human person, in particular studies relating to the re-use of data. The research must be in the public interest, which is the case for our study. Our declaration number is 2232922. Our research was conducted in accordance with the Helsinki and Istanbul declarations.

Statistical Analysis

Continuous variables are presented as medians (min-max) and were analysed using the Kruskal-Wallis or Mann-Whitney U test, as appropriate. Categorical variables were presented as numbers and percentages and were compared using the χ^2 test or Fisher's exact test. All statistical tests were two-tailed and a p-value < 0.05 was considered statistically significant in all analyses. Statistical analyses were performed using SPSS® version 24.0 software (SPSS Inc., an IBM Company, Chicago, Il, United States).

RESULTS

Characteristics of Plaintiffs

Of the 4,858 procedures recorded and adjudicated from January 2015 to December 2022 at the AP-HP, 52 (1.07%) concerned

[1]www.agence-biomedecine.fr

TABLE 3 | Proceedings regarding living kidney donors.

	Sex/age	Date of donation/Procedure	Operative procedure	Proceeding	Recipient/Outcome	Settlement
1	m/64	2008/2021	Laparoscopic	Chronic testicular pain	Spouse/Alive	No
2	f/52	2012/2021	Open	Chronic lower back pain	Child/Dead 2018	No
3	m/52	2015/2016	Laparoscopic	non-medical expanses	Brother/Alive	Yes
4	f/66	2015/2016	Open	Wound dehiscence/incision hernia/non-medical expanses	Son/Alive	Yes
5	f/61	2017/2018	Laparoscopic	Phrenic Para	Sister/Alive	Yes
6	m/54	2019/2022	Laparoscopic	Incisional hernia/chronic testicular pain	Brother/Alive	Yes

TABLE 4 | Main alleged bases for proceeding by verdict type in SOT.

Alleged proceeding	Defendant	Plaintiff	Settlements
Iatrogenic (*n* = 5)	1	4	5
No referral in time (*n* = 4)	2	2	3
Graft choice and technical operative failure (*n* = 9)	6	3	3
ICU management (*n* = 22)	20	2	2
Non-fatal early complication (*n* = 10)	10	0	4
Late complications			
Recurrence (amylose):1	1	0	0
CMV infection *n* = 1	1	0	0
Lymphoma/melanoma *n*= 3	3	0	0
Kaposi (*n* = 1)	1	0	0
Covid (*n* = 4)	4	0	0
Donors (*n* = 6)	6	0	4

SOT. While the overall number of complaints remained stable, the rate of complaints regarding SOT almost doubled over the study period, from 0.71% to 1.50% (**Table 1**). All adult centres performing SOT within the APHP were involved. The patients were female in 22 (42%) cases and the median age was 51 (19–74) years. No paediatric case was recorded. The surgeries were performed from 2006 to 2022 and 10 (21%) more than 5 years before the procedure. The main causes of these late complaints were *de novo* malignancies (*N* = 4) and death induced by COVID-19 (*N* = 3). Among the 46 SOT candidates or recipients, death was the reason for complaint in 28 (60%) cases. KT including one combined pancreas-KT was the main SOT involved with 25 (48%) cases. Of these, 11 (44%) concerned living donor procedures, with 6 donors procedures. Other SOT complaints were as follows 19 (37.0%) for LT including one liver-kidney transplantation; five (9%) for CT and three (6%) for PT.

Claims Analysis

Main alleged bases for proceeding after SOT are provided in **Table 2**.

Iatrogenic complications leading to SOT were the cause of litigation in five (10.6%) cases including three LT, one CT and one KT. With regard to LT, two cases were the consequence of fulminant hepatitis requiring LT due to the daily postoperative administration of 4 g of paracetamol to malnourished patients. One had good outcome after transplantation, and the other died rapidly of multivisceral failure before being put on the waiting list. The third LT patient had a good outcome after multiple liver abscesses and a biliary fistula due to arterial injury during biliary surgery. Regarding the single iatrogenic complication complaint after CT, a 47-year-old man, developed refractory biventricular dysfunction secondary to aortic aneurysm replacement, underwent emergency transplantation and had a favorable outcome. In the case of KT from a living donor, the recipient, a 35-year-old woman, developed thrombotic end-stage renal failure due to tranexamic acid administration during hemorrhage and a known prothrombic abnormality.

Four SOT candidates died before being put on the waiting list and their family complained of a lost opportunity. The three patients waiting for a liver transplant were a 63-year-old man with sickle cell disease who developed progressive liver and kidney failure leading to death; a 68-year-old man with fulminant hepatitis who died rapidly from multi-organ failure and a 48-year-old man who died of acute hepatitis B infection following a prescription omission. The fourth patient was a 50-year-old woman with pulmonary fibrosis, for whom a transplant was being considered, but who was not listed due to repeated severe episodes of pulmonary sepsis.

Early post-operative complications after SOT were the main causes of litigation. Among the 41 recipients, severe bleeding and septic complications with multi-organ failure were observed in 22 (54%) recipients and led to postoperative death (<90 days) in 12. From the complainant's perspective, these serious complications were directly attributed to transplant surgery, with a lack of information regarding the use of solid marginal organs in five cases and a technical error during the transplant procedure in four cases. Neuropathy attributed to the surgical procedure was

alleged in 12 cases, including plexus nerve in two, one after LT, the other after laparoscopic donor kidney harvesting. Among the 25 patients in the KT group, acute neuropathy with incision pain and femoral sensory and/or motor impairment was alleged in 10 (40%) cases.

Litigation concerning late complications after SOT included: 1) neoplasia with two lymphomas occurring respectively 9 years after LT and 6 years after KT, a Kaposi's sarcoma 1 year after KT and a fatal fulminant squamous cell carcinoma 2 years after CT; 2) infections with a CMV infection resulting in death recipient 1 year after LT, four deaths attributable to COVID-19, three after KT and one after PT; 3) *de novo* amyloid neuropathy 6 years after LT with domino amyloidosis graft.

The proceedings of the six living kidney donors are presented in **Table 3**. The sex ratio was 1, the age ranged from 52 to 66 and the donation was made to first-degree relatives in all cases. With the exception of the donor who suffered a brachial plexus stretch during surgery, all complaints were related to the abdominal wall incision, included incisional hernia in two cases and chronic testicular pain in two men. Donors suffering from persistent chronic pain for several years expressed their complaints after the death of the recipient in one case and after financial difficulties in two cases.

Of the 52 cases, 41 (79%) were resolved by verdicts in favour of the defendant without medical malpractice and 11 (21%) in favour of the plaintiff (**Table 4**).

Verdicts in favour of the defendant were obtained in 100% of late complications, including COVID-19 deaths, early non-fatal complications and living kidney donors' procedures. Verdicts were overwhelmingly in favour of the defendant in post-operative management of recipients (90% ($N = 20$) except for two including a suicide of a KT recipient attributed to lack of guardianship and a death by pulmonary embolism attributed to inadequate anticoagulant treatment and in graft selection and operative technical failure [66% ($N = 6$)]. Settlements were awarded for recognised therapeutic risk without medical fault in four donors for non-medical expenses, in four non-fatal early complications, in one iatrogenic transplant that underwent LT due to arterial injury that was considered a surgical therapeutic risk and in one case where the patient was not referred in time. The defendant's verdicts were associated with settlements paid by ONIAM ranging from 40,000 to 90,000 € for patients who developed non-fatal complications considered to be a therapeutic risk.

Verdicts in favour of the plaintiff were obtained in 11 cases. The categories were as follows all cases of iatrogenic SOT due to medical malpractice with the exception of one case described below, two cases of lack of timely referral due to insufficient information of the patient and his relatives in the case of the sickle cell disease patient who was waiting for a LT and the pulmonary fibrosis patient who was waiting for a PT, three cases blamed the selection of graft or a technical failure, two of which were due to disorganisation of the department, leading to primary non-function attributed to excessive cold ischemia time in one case of KT and to a pulmonary complication attributed to premature discharge; the final case involved a LT performed with a steatosis allograft. All plaintiffs' verdicts resulted in financial compensation ranging from €110,000 to €1,200,000. The highest amount corresponded to a lifetime pension for a young patient who had undergone LT.

Verdicts were not influenced by the patient's death: 21/41 (51%) in favour of the defendants compared with 7/11 (63%) in favour of the plaintiffs ($p = 0.831$).

DISCUSSION

All legal proceedings related to healthcare provided at the AP-HP are grouped together and handled by a specific unit, which has made it possible to collect all proceedings related to SOT. This has made it possible to draw up the first assessment of the nature and development of litigation related to SOT in one of Europe's largest university hospital centres. This series of 52 cases collected over the last few years showed that transplantation in France is also affected by an increase in litigation, in line with trends observed in the rest of medical society [7–9]. The small number of series published seems somewhat surprising. This is because organ transplantation is a complex operation, involving multiple technical procedures and several medical teams, and is carried out under time-sensitive conditions, which increases the risk of medical malpractice. The increase in the number of SOT-related complaints observed over the study period was not associated with an overall increase in the total number of procedures or an increase in the number of SOTs. Several factors may explain this result.

Firstly, the pandemic of COVID-19 and its high lethality in transplant patients, as shown by our 25% of causes of complaint in the event of death [10]. Intra-hospital contamination was blamed in all cases by the family, but the impossibility of establishing with certainty the contagion and the lack of knowledge about preventive measures resulted in verdicts with no responsibility for the establishment. The second factor is the existence in France of a law offering the possibility of compensation for all victims of a serious medical accident involving a therapeutic hazard [11]. During discussions before the court, we noted that this highly complex activity was not fully understood by families and lawyers. The high expectations of some families to obtain substantial financial compensation led some plaintiffs to question the surgical technique, the medical expertise and the occurrence of well-known long-term complications such as lymphoma [12]. The verdict rate in favour of the plaintiffs was low, around 20%, and logically concerned patients who had undergone SOT after a failure or a deviation from recommended practices and patients for whom a lack of information had been proven. In fact, the occurrence of fulminant hepatitis after intra-hospital administration of paracetamol warned against standardised prescribing in low-weight patients who had been fasting for a long time [13]. In the case of kidney transplantation, the time elapsed between registration on the waiting list and transplantation can be long, more than 5 years, and physicians should re-inform periodically potential kidney recipients about the complications of transplantation and repeat over and over again that transplantation does not mean a cure for the disease, but only a change in the disease.

Throughout the world, organ transplantation remains limited by the insufficient availability of grafts, which makes

access to transplantation difficult, and we can expect an increase in complaints about organ allocation [14]. In France, around 5,000 deaths of patients on the waiting list were reported during the period covered by this study. The surprising absence of litigation concerning this category of patients can be seen as an adherence to the rules laid down in our country by the ABM. These rules, drawn up by our state agency, are established and regularly revised in collaboration with the transplant community, and explained to future recipients and their relatives by the medical team and the coordinating nurses [15]. During the legal debates in this series, the quality of the information provided by this group of advanced practice nurses was never called into question. On the other hand, the inadequate quality of the information provided by the medical team to the patient and his relatives has often been criticised and judicially sanctioned, as illustrated by the plaintiff's verdict in the case of a medical contraindication to inclusion on the waiting list, which had not been sufficiently communicated to the family. However, no conclusions could be drawn, as patients and their families may have different expectations of the medical team and the coordinating nurses.

Indeed, the inadequacy of information shared and recorded in the presence of the patient and their relatives throughout the organ transplantation process is a key factor in the analysis of this series [16]. The high rate and fatal risk of post-transplant complications highlights the need to share information and knowledge at a time when recipients are becoming older and have more co-morbidities, increasing the possibility of receiving high-risk organs [17]. In this context, the large number of people with different levels of expertise involved can make it difficult to understand patient care and the risks involved. Our results suggest that patients and their families should be given more information at all stages of SOT, and that this information and major decisions should be traceable throughout the transplantation process in the transplant units.

One of the main causes of serious post-transplant complications is organ failure immediately after transplantation, associated with the use of so-called extended criteria grafts. This study revealed that none of the patients or their families were aware of the risk associated with these transplants. This lack of information may be justified from a legal and ethical point of view [18]. In fact, it has been shown that most patients undergoing long-term transplantation wanted to be informed and involved in the decision at the time of organ proposal regarding the risks associated with the donor [19]. A marginal transplant is always accepted by clinicians with a reasonable degree of safety, but it may be judicially deemed to be defective, i.e., it does not offer the safety that a person is entitled to expect [20]. Although only two verdicts in this series have called into question the information relating to the transplant, it is probably reasonable to introduce specific consent in France concerning the risks associated with the donor, along the lines of what is practised in the United Kingdom [16].

The majority of cases in this series illustrate the high level of KT activity in France, with around 3,500 cases per year. While living donor KT (LDCT) accounts for 15% of KT in France, more than 40% of the KT cases included in this series involved a procedure involving a living donor. Although LDKT is associated with better outcomes for the recipient than deceased organ donation, the high rate of legal disputes reported here illustrates a singular aspect of living organ donation [21]. Indeed, the complications and failure of living organ donation are often associated with the donor's guilt over the failure of this gift. Even in the event of a favourable outcome for the recipient, disputes with donors could reflect the profound and complex impact of organ donation by living people [22]. Having been a saviour, they have to get used to their vulnerability due to the absence of the donated organ [23]. The relationship with the beneficiary, their social environment and the medical system is strongly affected by frequent and constant disappointment in relation to what they expected from their donation. It would be worth highlighting the need for better attention and follow-up for donors, many of whom feel neglected too quickly. One of the original features of this study is that it brought together the legal proceedings brought by six donors against the institution. In both the laparoscopic and open approaches, the alleged complications were attributed to abdominal wall complications, including chronic testicular pain, which is often overlooked in men [24, 25]. In this series, complications related to donations are often associated with non-medical expenses, which explains why some settlements have been awarded despite the absence of fault or negligence. The principle of financial neutrality applies to donations, which means that they are free of charge. The results of this series confirm that these complications and their potential impact are not detailed and that a standardised informed consent form specific to nephrectomy from a living donor is strongly recommended [16]. We could also suggest improving the psychological assessment of the living donor before and after the operation in order to limit donor disappointment after the transplant and the feeling of being abandoned.

The main limitation of this study is the exclusive selection of proceedings aimed at obtaining financial compensation. Several claims that were resolved by local mediation without settlement were not included. Although the number of cases presented is significant, it cannot be ruled out that some proceedings are resolved quickly and confidentially, perhaps to minimise media coverage in order to protect the public image of occupational therapy and/or the reputation of the hospital/staff involved.

CONCLUSION

This study has shown that transplantation activity in France is also affected by the trend towards increased litigation against the medical community. Although no liability was found against the institution in almost 80% of the verdicts, certain major trends should be taken into account in order to maintain this activity and slow down or reduce the rate of litigation. One of the main recommendations is to improve the quality of information provided to patients and their relatives about the risks of emergency surgery, and the development and treatment of complications. The second is to provide, where

appropriate, information on the specific risk to the donor, which should be in line with what is done in many other countries. Improving the information and psychological assessment of living donors is essential if the technique of transplantation is to be sustainable, given its excellent overall results.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The requirement for ethical approval was waived by IRB CER APHP.Centre (#00011928), as the study doesn't involve the human person as defined by the French law n°2012-300. The requirement for written informed consent was also waived.

AUTHOR CONTRIBUTIONS

JB, FC, GC, and MM designed the study, collected patient data, interpreted the data, made critical revisions to the intellectual content, drafted the manuscript and gave final approval of the version to be published. CA collected the patient data and interpreted the data. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

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ORIGINAL RESEARCH
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Meeting the Shortage of Human Cells and Tissues: The Andalusian Quality Assurance Programme for Tissue Donation

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Background: A quality assurance programme for the tissue donation process was launched in Andalusia in 2020 to facilitate the integration of tissue donation into end-of-life care, and to respond to the growing need for human tissue for therapeutic purposes. The results of this programme are presented here.

Methods: After identifying the hospital departments in which to intensify the detection of tissue donors, expanding training activities and designing a specific data collection system for possible tissue donors who do not donate their tissues, the results of the donation activity were quantified and the causes of non-donation were analysed by applying the critical pathway for deceased tissue donation methodology.

Results: After an initial drop in activity, which coincided with the coronavirus pandemic, the number of tissue donors increased by 48.4% in 2022 compared to 2019. From the eligible donors, 83% were actual tissue donors and 71% were utilised donors. The modifiable causes of tissue donation loss, in order of frequency, were family refusal, followed by organisational or logistical issues, failure to notify or failure to identify possible donors, and failure to complete donor evaluation.

Conclusion: As a result of the collaboration of the various professionals involved in the programme, tissue donation activity has increased remarkably, the potential and effectiveness of the donation process have been evaluated, and areas for improvement have been identified, which we hope will lead to continuous improvement of the process.

Keywords: critical pathway, tissue donation, tissue establishments, tissue procurement, quality assurance programme

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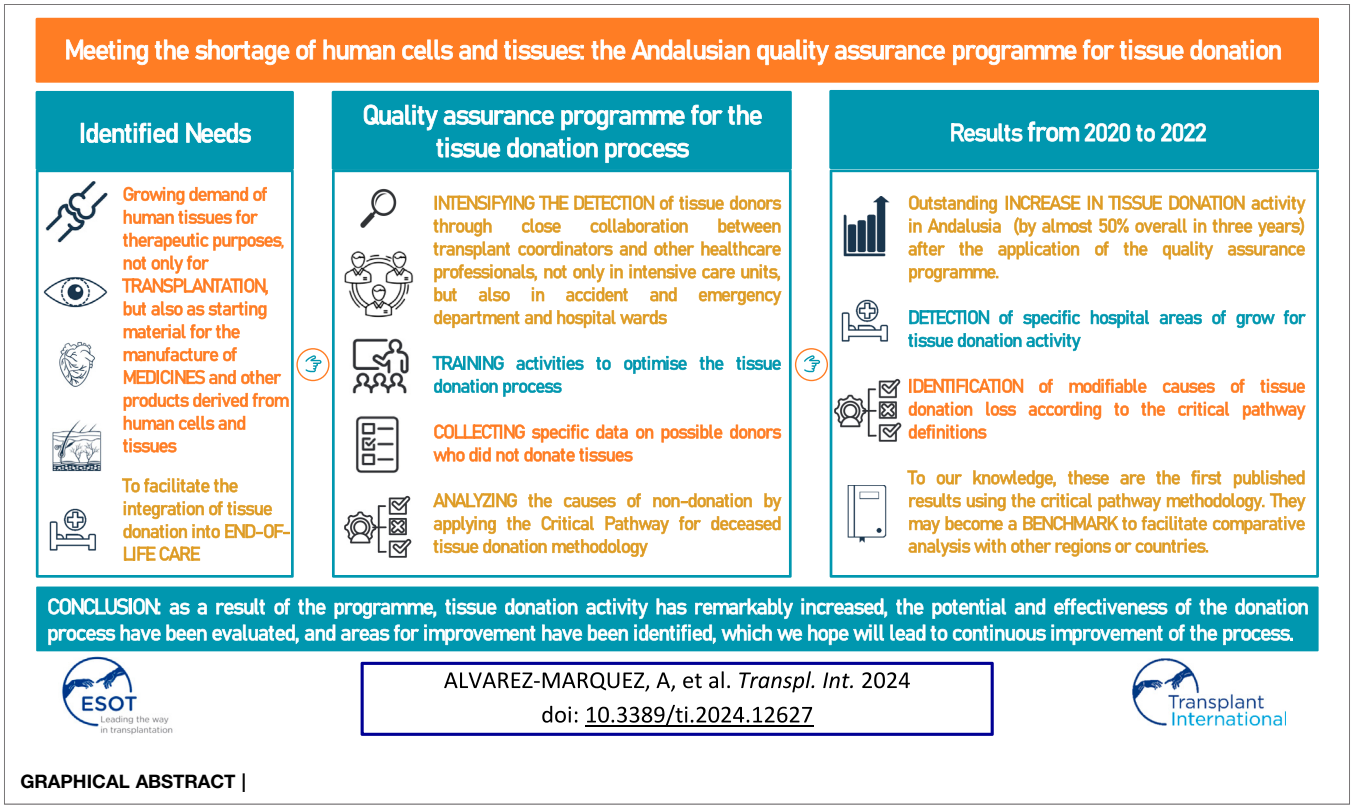
Abbreviations: CATA, Coordinación Autonómica de Trasplantes de Andalucia; TC, Transplant Coordinator; CD-P-TO, European Committee on Organ Transplantation of the Council of Europe; eProgesa, Information management system of the Andalusian Tissue Banks; SICATA, Sistema de Información de la Coordinación Autonómica de Trasplantes de Andalucía.



GRAPHICAL ABSTRACT |

INTRODUCTION

Spain has been the world leader in organ donation for transplantation for the last three decades [1] and Andalusia, Spain's largest region with a population of almost 8.5 million inhabitants, achieves donation rates that are usually above the Spanish average [2]. The Spanish and Andalusian success derives from a specific organizational approach, the so-called Spanish model [3].

The key element of the Spanish model is the figure of the transplant coordinator (TC) appointed at each procurement hospital. The TCs, responsible for developing a proactive donor detection programme and effectively converting potential into actual donors, are in-house professionals and members of staff of the procurement hospital concerned. They are nominated by and report to the medical direction of the hospital, and therefore do not report to the transplantation team. Most of the TCs are involved in donation activities on a part-time basis, which enables them to be appointed even at hospitals with low deceased donor potential. Notably, a majority of TCs are critical care physicians so their daily work is carried out precisely in those units where more potential donors are detected [3].

The Spanish quality assurance programme for the organ donation process, launched in 1999 after a pilot programme in Andalusia and several other Spanish regions in 1998, has been another key factor in helping Spain maintain this position. This programme allows potential areas for improvement to be identified, with the aim of implementing measures to increase donation rates according to each hospital's potential and characteristics [4, 5].

With respect to human tissue donation, in the last two decades Andalusia has progressively increased the donation rates, reaching the highest donation activity in 2019, although insufficient to meet the demand for human tissues. For that reason, the Regional Transplant Coordination of Andalusia designed and promoted a quality assurance programme for the tissue donation process by adapting the methodology of the quality assurance programme for organ donation. The reason for this was to achieve self-sufficiency [6, 7] in the face of the growing need for human tissue donation, not only for transplantation, but also as starting material for the manufacture of medicines and other products derived from human cells and tissues.

Facilitating tissue donation for every patient who dies in hospital, and thus truly integrating donation at the end-of-life into hospital care, is another equally important aim of this quality assurance programme for the tissue donation process [8, 9]. In order to achieve this goal, it is essential to raise awareness of this issue among healthcare professionals [10].

The programme was launched in January 2020 and is based on three principles: i) intensifying the detection activities for possible tissue donors in certain hospital departments, with a special focus on cornea donation, ii) training to optimise the tissue donation process and cornea procurement, and iii) a

system, which is progressively being implemented in hospitals in Andalusia, for collecting specific data on possible donors who do not donate their tissues to identify modifiable causes of donation loss.

This manuscript illustrates how the results obtained in Andalusia regarding tissue donation have evolved from 2019, the year before the programme was implemented, to 2022. Additionally, the reasons for non-donation of tissues in the last year have been analysed using the definitions in the critical pathway for deceased tissue donation, developed by the European Committee on Organ Transplantation of the Council of Europe (CD-P-TO) published in 2021 [11], in order to obtain information that is comparable with other regions or countries that have implemented the critical pathway for deceased tissue donation methodology.

MATERIALS AND METHODS

Intensification of the Detection Activities

In 2019, as part of the regular six-monthly meetings held by the entire Andalusian transplant coordination network, transplant coordinators from the main hospitals in Andalusia were asked to draw up a plan to increase tissue donation activity, and identify the hospital departments or units where tissue donor screening activities should be intensified, particularly regarding cornea donation, in accordance with the characteristics of each hospital and the staff who could collaborate in these activities.

Data Collection and Analysis

For the purpose of this study we have included those deceased donors of somatic tissues except haematopoietic tissue, including donors of ocular tissues, skin, cardiovascular tissue and musculoskeletal tissue.

The tissue donation activity was analysed from 2019 to 2022. The information systems used included the Information System of the Regional Transplant Coordination of Andalusia (*Sistema de Información de la Coordinación Autonómica de Trasplantes de Andalucía, SICATA*), where all actual organ and/or tissue donors are registered, and the information management system of the Andalusian Tissue Banks (eProgesa) which registers data of utilised tissue donors and provides information on the effectiveness of the tissue donation process.

The evolution of tissue donation activity in general, and that of corneas in particular, was analysed by breaking down the type of donor, who may be a deceased organ donor who is brain dead or who died due to cardiocirculatory criteria who, in addition to organs, also donates tissues, or a donor exclusively of tissues.

In order to study the reasons for non-donation of tissue, the Regional Transplant Coordination (*Coordinación Autonómica de Trasplantes, CATA*) designed a form (**Figures 1**, **2**) to collect data on deceased patients in the selected units who were identified as possible tissue donors, who ultimately did not donate. The form has been adapted from the one designed for the quality assurance programme for the organ donation process which was implemented in Andalusia in 1998. It includes information related to the hospital departments and healthcare professionals who identify possible donors, the possible donor's characteristics, reasons for rejection, and information on family and legal interviews, if applicable. Data collection forms were always fulfilled by transplant coordinators reviewing medical charts and checking with the responsible doctor of the patient when necessary. An online form has also been developed to facilitate the collection and submission of data to the CATA.

Data collection on the reasons for non-donation of tissues started in 2020 and was analysed in 2022 using the critical pathway for deceased tissue donation methodology and the definitions listed in **Table 1**.

RESULTS

Since 2020, the implementation of local plans has been promoted and most hospitals have focused their detection activities on various intensive care units. In some hospitals, the accident and emergency department was involved, and in others, medical oncology wards were used to identify potential cornea donors. The units and departments were mainly selected based on whether the hospital ward supervisor nurse was able to collaborate.

The change in the number of actual tissue donors and cornea donors from 2019, the year before the quality programme was implemented, to 2022, is shown in **Figure 3**. It also shows the total number of donors, and the number of donors in each of the following three categories: deceased donors who only donated tissues; brain-dead organ donors who also donated tissues; organ donors who also donated tissues after circulatory death.

Tissue donation in general, and cornea donation in particular, showed an important decline in 2020, which coincided with the outbreak of the coronavirus pandemic. However, in 2021, the activity exceeded that of 2019, and in 2022, once the pandemic was over, there was an extraordinary increase in activity compared to 2019. Specifically, the number of tissue donors increased from 366 to 543, which corresponds to an increase of 48.4%, and the number of cornea donors increased by 54.6% from 346 to 535 donors.

With regards to the type of donor, the number of tissue donors from brain-dead organ donors increased by 1.7%, 12.1% from organ donors after circulatory death, and 174% from deceased tissue-only donors. The increases were 5.6%, 17.2%, and 180.2% for the number of cornea donors in the same groups, respectively.

Regarding the reasons for non-donation of tissues from possible donors identified in the selected units, although data collection started in 2020, uniform data collection did not begin until the end of the pandemic. **Figure 4** shows the results obtained in 2022 and the reasons for non-donation according to the critical pathway definitions. This information comes from the registry of 902 possible tissue donors who ultimately did not donate, along with information from SICATA on 396 actual tissue donors in hospitals that participated in the data collection, for a total of 1,298 possible tissue donors. This information was collected in 18 of the 30 (60%) public hospitals in Andalusia that are authorised for organ donation and where 73% of the actual

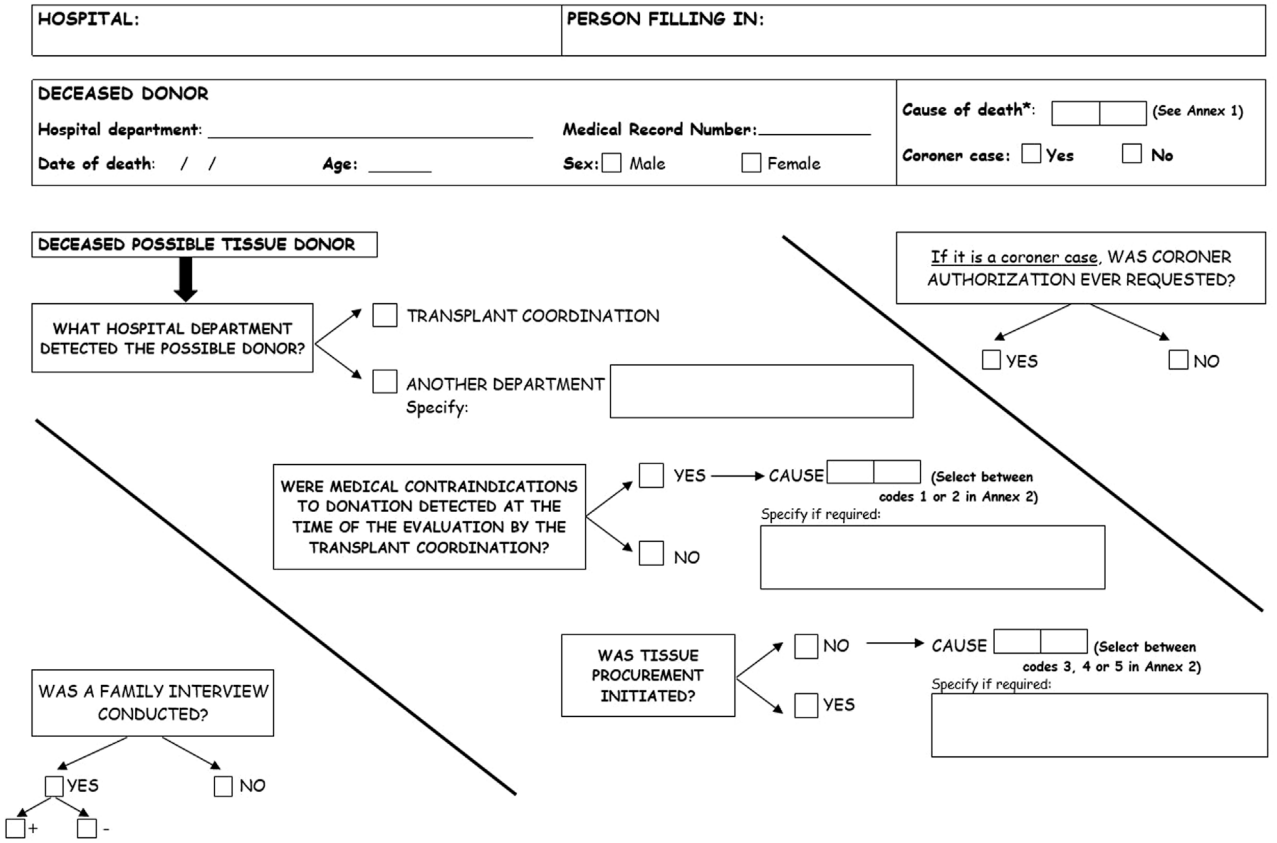


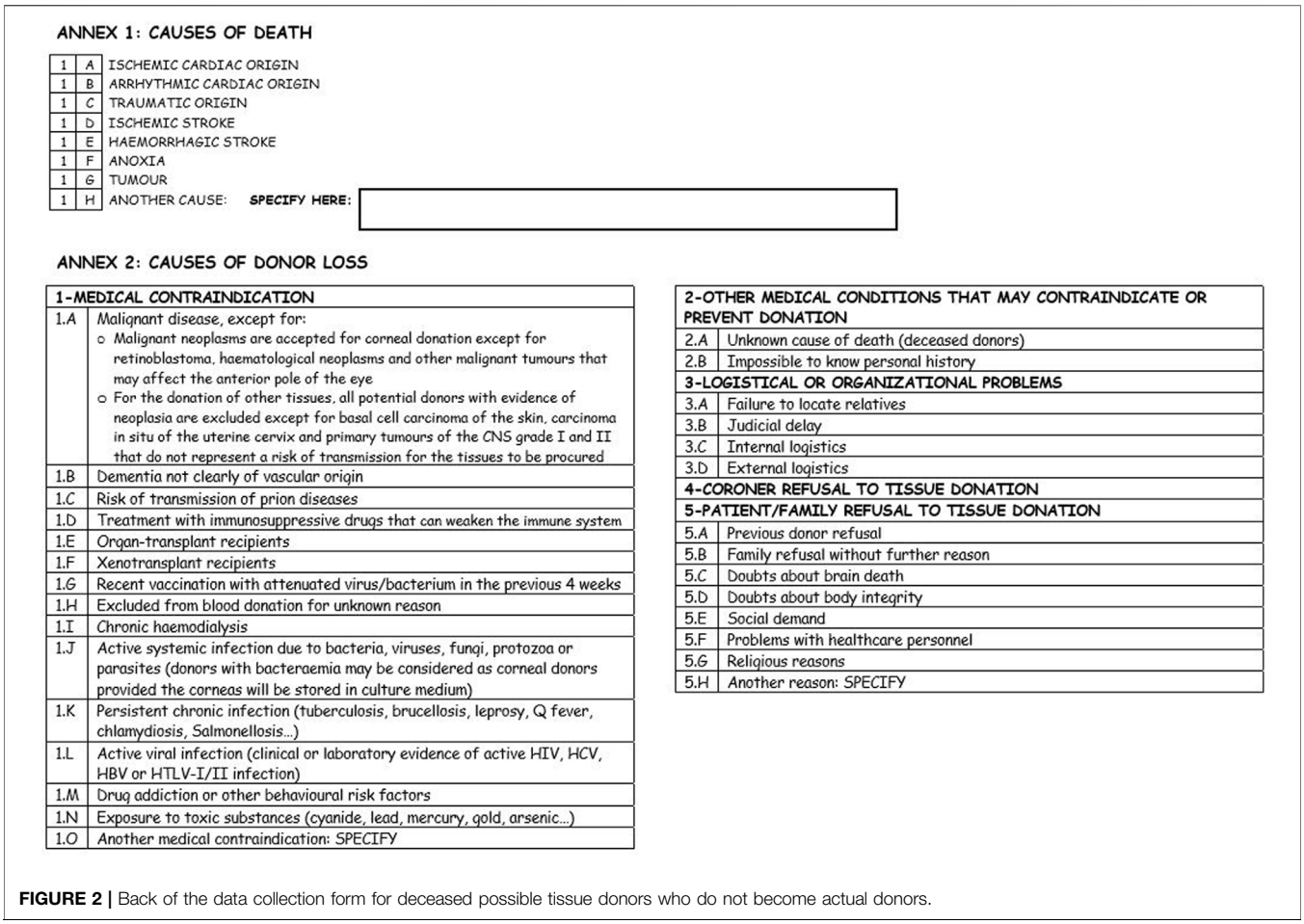
FIGURE 1 | Front of the data collection form for deceased possible tissue donors who do not become actual donors.

tissue donation activity occurs. The eProgesa data was then used to determine the number of utilized donors, 340.

Regarding the units and departments where 902 possible tissue donors were identified but ultimately did not donate, 71% were identified in different intensive care units, including coronary care and post-anaesthesia recovery units, 14% in the accident and emergency department, and 15% in hospital wards, not only in medical oncology but also in neurology, internal medicine, pneumology, haematology, neurosurgery, and orthopaedic surgery. The healthcare professionals who identified potential donors were transplant coordinators in 64% of cases, followed by intensive care doctors who were not part of the transplant coordination teams in 15% of cases, ward nurses in 6% of cases and the emergency department doctors in 4% of cases. The remaining 11% were identified by healthcare professionals from the aforementioned departments.

Of the 1,298 possible tissue donors (**Figure 4**), 527 had absolute contraindications to donation and 79 cases were not reported to the transplant coordinators of the hospital, bringing the number of potential tissue donors to 692. Of these, 477 were eligible donors because they were presumed medically suitable for the donation of at least one type of tissue, as well as having family consent for donation and, in judicial cases, also with judicial consent. The number of eligible donors who did not complete the donation process due to logistical or organisational issues was 81, bringing the number of actual donors, those from whom at least 1 tissue was procured, to 396, which corresponded to 83% of eligible donors. Finally, the number of utilised donors, those from whom at least part of a valid tissue was available to be released for clinical application, was 340, which corresponded to 85.9% of actual donors, and 71.3% of eligible donors.

Overall, around half of the possible donors (641, 49.4%) did not become utilised donors due to non-modifiable reasons. Of these, 527 were not donors because they had a previous absolute contraindication to tissue donation, to which 52 possible donors must be added, who were medically unsuitable, 6 who had some specific exclusion criterion for the tissue to be donated, and 56 who, after having some tissue recovered, were not viable for some of the reasons listed in **Figure 4**. Specifically, 26 were excluded due to known post-donation serological/microbiological status, 10 due to post-donation clinical information and 20 due to insufficient tissue quality.



ANNEX 1: CAUSES OF DEATH

1	A	ISCHEMIC CARDIAC ORIGIN
1	B	ARRHYTHMIC CARDIAC ORIGIN
1	C	TRAUMATIC ORIGIN
1	D	ISCHEMIC STROKE
1	E	HAEMORRHAGIC STROKE
1	F	ANOXIA
1	G	TUMOUR
1	H	ANOTHER CAUSE: SPECIFY HERE:

ANNEX 2: CAUSES OF DONOR LOSS

1-MEDICAL CONTRAINDICATION	
1.A	Malignant disease, except for: o Malignant neoplasms are accepted for corneal donation except for retinoblastoma, haematological neoplasms and other malignant tumours that may affect the anterior pole of the eye o For the donation of other tissues, all potential donors with evidence of neoplasia are excluded except for basal cell carcinoma of the skin, carcinoma in situ of the uterine cervix and primary tumours of the CNS grade I and II that do not represent a risk of transmission for the tissues to be procured
1.B	Dementia not clearly of vascular origin
1.C	Risk of transmission of prion diseases
1.D	Treatment with immunosuppressive drugs that can weaken the immune system
1.E	Organ-transplant recipients
1.F	Xenotransplant recipients
1.G	Recent vaccination with attenuated virus/bacterium in the previous 4 weeks
1.H	Excluded from blood donation for unknown reason
1.I	Chronic haemodialysis
1.J	Active systemic infection due to bacteria, viruses, fungi, protozoa or parasites (donors with bacteraemia may be considered as corneal donors provided the corneas will be stored in culture medium)
1.K	Persistent chronic infection (tuberculosis, brucellosis, leprosy, Q fever, chlamydiosis, Salmonellosis…)
1.L	Active viral infection (clinical or laboratory evidence of active HIV, HCV, HBV or HTLV-I/II infection)
1.M	Drug addiction or other behavioural risk factors
1.N	Exposure to toxic substances (cyanide, lead, mercury, gold, arsenic…)
1.O	Another medical contraindication: SPECIFY

2-OTHER MEDICAL CONDITIONS THAT MAY CONTRAINDICATE OR PREVENT DONATION	
2.A	Unknown cause of death (deceased donors)
2.B	Impossible to know personal history
3-LOGISTICAL OR ORGANIZATIONAL PROBLEMS	
3.A	Failure to locate relatives
3.B	Judicial delay
3.C	Internal logistics
3.D	External logistics
4-CORONER REFUSAL TO TISSUE DONATION	
5-PATIENT/FAMILY REFUSAL TO TISSUE DONATION	
5.A	Previous donor refusal
5.B	Family refusal without further reason
5.C	Doubts about brain death
5.D	Doubts about body integrity
5.E	Social demand
5.F	Problems with healthcare personnel
5.G	Religious reasons
5.H	Another reason: SPECIFY

FIGURE 2 | Back of the data collection form for deceased possible tissue donors who do not become actual donors.

TABLE 1 | Types of tissue donors. Definitions from the critical pathway for deceased tissue donation.

Types of tissue donors
POSSIBLE TISSUE DONOR: a person who has died (with death determined by neurological or circulatory criteria) or who is in a situation of imminent death
POTENTIAL TISSUE DONOR: a possible deceased donor with no apparent absolute contraindication for tissue donation and whose body has been preserved according to requirements for tissue procurement
ELIGIBLE TISSUE DONOR: a potential consented tissue donor who is medically suitable and meets specific criteria for the donation of at least one type of tissue
ACTUAL TISSUE DONOR: an eligible tissue donor from whom at least one tissue was recovered with the primary intention of clinical application
UTILISED TISSUE DONOR: an actual tissue donor from whom at least one, or part of a tissue is ready to be released for its clinical application

The total number of possible donors who were not actual donors due to modifiable causes was 317, corresponding to about a quarter (24.4%). The modifiable causes, in order of frequency, were family refusal (132), followed by organisational or logistical issues (81), failure to notify or failure to identify possible donors (79) and failure to complete the donor evaluation (25).

DISCUSSION

The quality assurance programme for the tissue donation process was designed by the Regional Transplant Coordination of Andalusia and launched in 2020 thanks to the collaboration of the network of hospital transplant coordinators. This programme has been fundamental in increasing tissue donation activity in our region, so much so that 3 years after the start of its progressive implementation, activity has increased by almost 50% overall, and by more than 50% for cornea donation. This is despite the negative impact that the coronavirus pandemic had in 2020 and 2021 on donation and transplantation activity both in Spain and in most other countries [12, 13].

In fact, organ donation activity in Spain in 2020, 2021, and 2022, with 1,777, 1,905, and 2,196 organ donors respectively, represented 77.2%, 82.8%, and 95.4% of the activity recorded

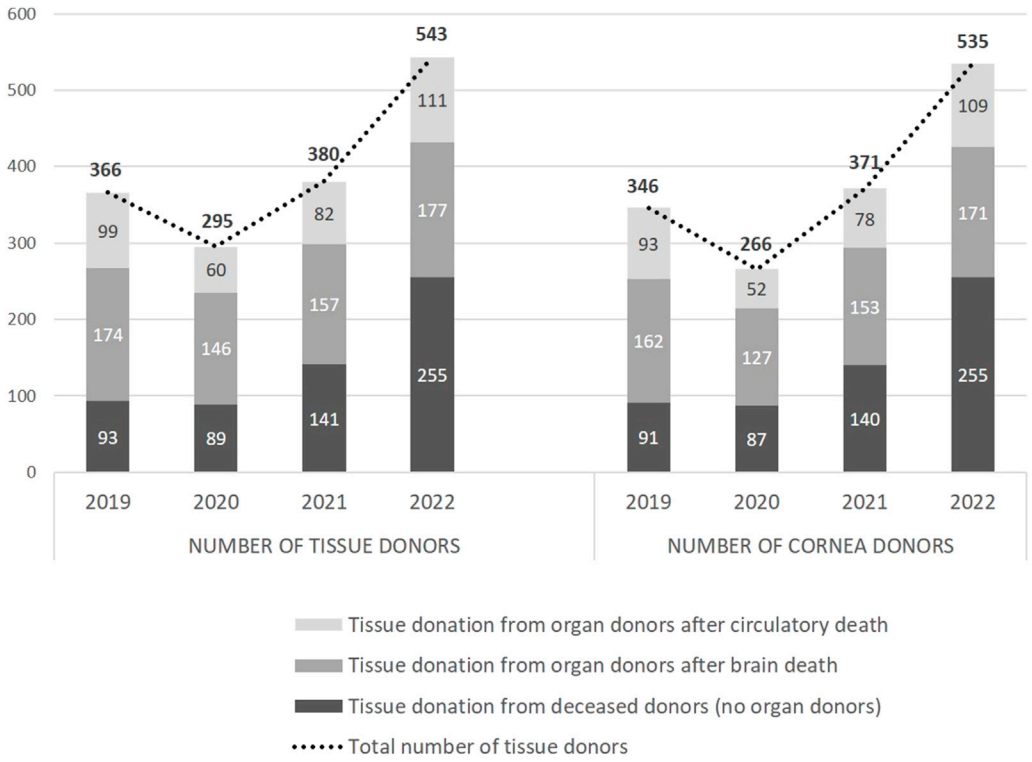


FIGURE 3 | Change in the number of tissue donors and corneal donors from 2019 to 2022 in Andalusia according to the type of donor.

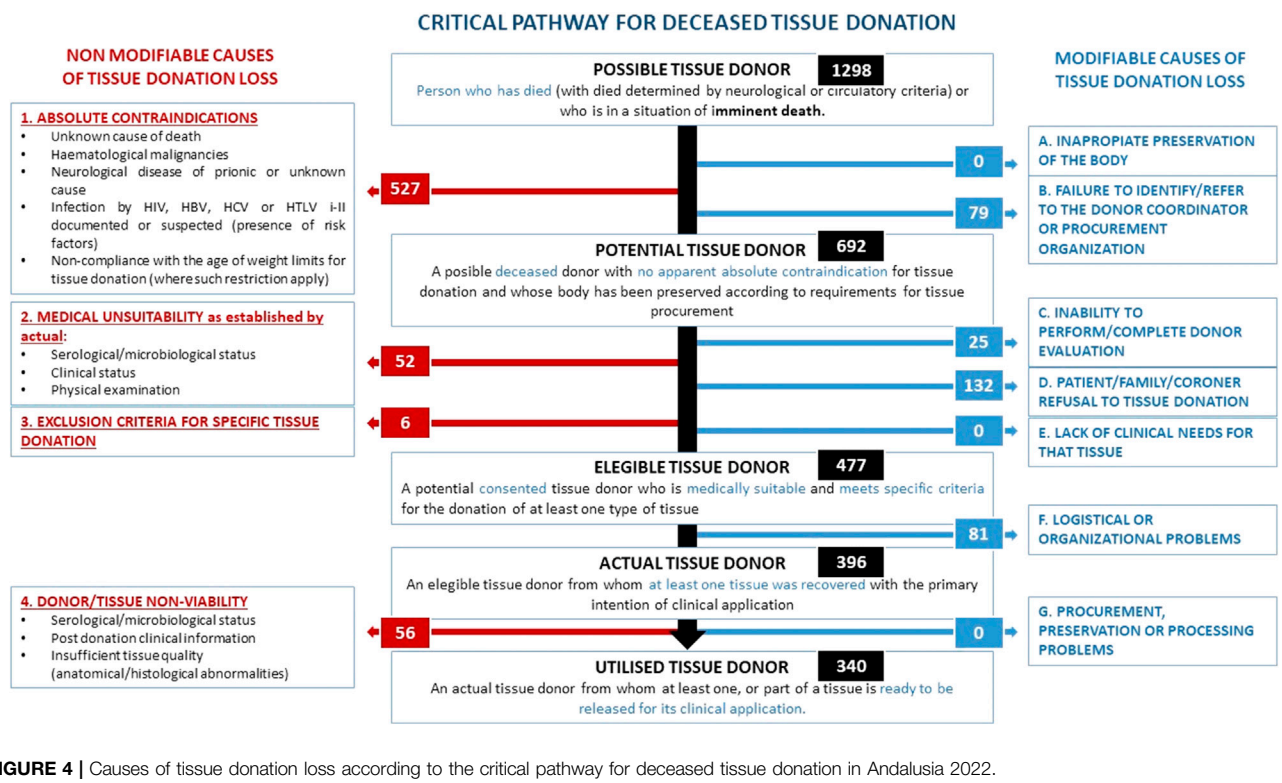


FIGURE 4 | Causes of tissue donation loss according to the critical pathway for deceased tissue donation in Andalusia 2022.

before the start of the pandemic in 2019 with 2,302 organ donors [2]. Similarly, in Andalusia, the number of organ donors changed from 430 in 2019 to 321, 335, and 415 donors in 2020, 2021, and 2022 respectively, representing 74.7%, 77.9%, and 96.7% of the activity in 2019.

The analysis of the change in tissue donation activity by type of donor shows that, in 2020 and 2021, there was a considerable decrease in the number of tissue donors who were also organ donors, with tissue-only donation maintaining similar figures in 2020 compared to 2019 and experiencing very substantial growth in 2021 that continued in 2022. It is possible that the initial recommendations of international [14] and national [15] organisations regarding the prioritisation of certain organ donation and transplantation programmes, and other substances of human origin, due to the risks of transmitting the infection, which were not well characterised in the early stages of the pandemic influenced the boost of tissue-only donation. The exhaustion of the health system and intensive care units during this initial period could be another factor.

The growth in tissue donation activity observed in 2022 cannot be attributed to the fact that the donation acceptance criteria were expanded between 2019 and 2022. Moreover, in 2022 the criteria were more restrictive than in 2019, given that COVID-positive tissue donors were still being rejected in that year. All other acceptance criteria remained unchanged. On the other hand, 2019 was the year that presented the best results in the history of Andalusia related to tissue donation, with an increase of 11% and 25% compared with the activity observed in 2018 and 2017 respectively, with no relevant growth in the population of Andalusia.

From the information collected through the specific form for potential tissue donors who ultimately did not donate, we have seen that identification is mainly performed in intensive care units by the transplant coordination teams, in many cases with the assistance of other intensive care specialists in these units. However, about 30% of potential unsuccessful donors were identified in the accident and emergency department and hospital wards as a result of the collaboration between several medical and nursing professionals. This data highlights the importance of training and close collaboration between transplant coordinators and other healthcare professionals, not only in intensive care units, but also in accident and emergency department and hospital wards, which is possibly the main specific area of growth for tissue donation activity.

The analysis of the results for the year 2022 according to the critical pathway for deceased tissue donation methodology developed by the CD-P-TO provides valuable information on the areas for improvement in tissue donation. Although the information comes from a sample of hospitals, where three-quarters of the donation activity took place, we believe that these preliminary data are noteworthy and, to our knowledge, are the first to be published internationally using this methodology. They may therefore become a benchmark to facilitate comparative analysis with other regions or countries as they implement the critical pathway for deceased tissue donation methodology.

We have found that tissue donation activity could be substantially increased if we could reverse the modifiable causes of donor loss, although reversing some of these causes is partly dependent on factors beyond the control of the transplant coordination network, or difficult to control such as family refusal, which is the main modifiable cause of loss of possible tissue donors. However, there are other modifiable causes that are easier to address. Losses due to organisational and logistical reasons, which in some cases are due to limitations in the availability of operating theatres or human resources, require more detailed analysis and support from hospital managers in order to be reversed, as in the case of failure to complete donor evaluation. Meanwhile, the lack of notification or failure to identify the possible donors could be more easily rectified by establishing a closer relationship with the units that could potentially provide tissue donors, improving the training of the professionals working in these units and implementing fast notification systems. In 2022, the Regional Transplant Coordination of Andalusia, which promotes and develops important training activity [16], launched a large-scale virtual training programme on general aspects of donation and transplantation, which in its first year was taken by more than 1,800 professionals from the Andalusian Health Service. This large-scale training programme has been added to the 19 training courses already in place on specific aspects of donation and transplantation, and we hope it will lead to an increase in the identification of possible donors.

Regarding the efficacy of the tissue donation process, 396 of the 1,298 possible donors were actual donors, which represents 30.5%. If we compare these results with the most recent results of the quality assurance programme for the organ donation process in Spain for 2021 [17], we see that this efficacy is much lower than that observed in organ donation, where 48.8% of possible donors become actual donors. However, it should be noted that the medical criteria for tissue donation are more stringent [18] than those for organ donation [19], and therefore part of this difference in efficacy is due to a higher percentage of rejected cases due to lack of medical suitability for donation. This resulted in 34.6% of possible organ donors being rejected due to lack of medical suitability in Spain in 2021, while the percentage of possible tissue donors rejected for medical reasons (527 possible donors with absolute contraindications, 52 medically unsuitable and 6 with exclusion criteria for some type of tissue) amounted to 45.1% in our sample. Related to the other causes of loss of possible donors, when comparing organ and tissue donation, we found that losses due to family or legal refusal were 10.2% for tissue donation compared to 10.6% for organs, losses due to logistical or organisational issues were 6.2% compared to 0.3%, and losses due to identification notification failures were 6.1% compared to 0.8%, respectively.

The analysis of effectiveness, i.e., the percentage of actual tissue donors who became utilised donors, amounted to 86% in 2022 in our analysed sample. This figure was slightly higher than the 85% effectiveness achieved in Andalusia in organ donation and was slightly lower than the 89% effectiveness achieved in Spain [2] in the same year.

A notable aspect is the optimisation of the resources involved in the implementation of the programme, as it has been carried out without increasing the number of staff. This has been made possible thanks to the efforts of the network of transplant coordinators and the collaboration of many healthcare professionals who are not involved in the donation and transplant programmes. In some cases, these collaborators performed their care activities in units other than those traditionally involved in organ procurement, such as medical oncology departments in the case of corneal donation.

Finally, it is important to emphasise that our tissue donation quality assurance programme, supported by the information systems in Andalusia, has allowed us not only to increase tissue donation activity, but also to evaluate the potential and effectiveness of the tissue donation process. It is also useful to establish benchmarks for comparison between donation centres as well as for identifying areas and measures for improvement, which we hope will lead to continuous improvement of the process.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethics approval or specific consent procedures were not required for this study.

AUTHOR CONTRIBUTIONS

Conception and design of the study: AA-M, JH, JP-V, and NC. Acquisition of data: AA-M, JH, PC, and NC. Analysis and interpretation of data: AA-M, JH, JP-V, DD-R, CD-A, PC, and NC. Drafting or revising the manuscript: AA-M, JH, JP-V, DD-R, CD-A, PC, and NC. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

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