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DSA and liver transplant: the canary in the coalmine?

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TRANSPLANT TRIAL WATCH
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Transplant Trial Watch

Simon R. Knight[1,2]*, *John Fallon*[1]* and *Reshma Rana Magar*[1]

[1]*Centre for Evidence in Transplantation, Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom,*
[2]*Oxford Transplant Centre, Churchill Hospital, Oxford, United Kingdom*

Keywords: systematic review/meta-analysis, kidney transplantation (KT), delayed graft function, randomised controlled trial, antibody mediated rejection (ABMR)

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

Balanced Crystalloids Versus Normal Saline in Kidney Transplant Patients: An Updated Systematic Review, Meta-Analysis, and Trial Sequential Analysis.

by Carvalho Pereira, L., et al. Anesthesia & Analgesia 2024 [record in progress].

Aims

This study aimed to evaluate whether low-chloride solutions would reduce the incidence of delayed graft function and improve acid-base and electrolyte balance in kidney transplant recipients.

Interventions

Three electronic databases, including MEDLINE, EMBASE, and Cochrane, were searched for relevant literature. Studies were screened and data were extracted by two independent reviewers. The Cochrane Risk of Bias Tool for Randomized Trials 2 (RoB2) was used to assess the quality of the included randomised controlled trials.

Participants

12 studies were included in the review.

Outcomes

The primary outcome was the incidence of delayed graft function. The secondary outcomes included end of surgery chloride, bicarbonate, pH, base excess (BE) and potassium, and post-operative creatinine and urine output.

Follow-Up

N/A.

CET Conclusions

by Reshma Rana Magar

This systematic review aimed to examine whether using balanced crystalloid solutions would result in better clinical outcomes in kidney transplant recipients, compared to normal saline. Twelve studies

Transplant Trial Watch

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Correspondence
Simon R. Knight,
simon.knight@nds.ox.ac.uk
John Fallon,
john.fallon@nds.ox.ac.uk

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were included, all of which were randomised controlled studies. Study selection, data extraction and quality assessment were performed in duplicate. The meta-analyses revealed that the use of balanced low-chloride solutions resulted in a significant reduction in the incidence of delayed graft function (DGF), and improved acid-base and electrolyte control in kidney transplant patients, leading the authors to conclude that balanced lower-chloride solutions can be used as a safe alternative to normal saline and may even lead to better post-transplant outcomes. It is important to note that while the difference in the occurrence of delayed graft function was significant in the overall analysis that included both living and deceased donors, the subgroup analysis showed that this difference was only significant for deceased donor transplant recipients and not for living donor transplant recipients. A potential reason for this could be that only a few studies (three studies) reported DGF outcomes for living-donor transplant recipients, out of which one study had zero events for both arms. Heterogeneity was negligible for most of the primary outcomes. However, the influence of potential confounders were not accounted for in the analyses.

Trial Registration
PROSPERO - CRD42023447301.

Funding Source
No funding received.

RANDOMISED CONTROLLED TRIAL 2

A Randomized Phase 2 Trial of Felzartamab in Antibody-Mediated Rejection.

by Mayer, K. A., et al. New England Journal of Medicine 2024 [record in progress].

Aims
They aim to assess the safety of CD38 monoclonal antibody therapy, felzartamab in the treatment of AMBR in kidney transplantation.

Interventions
Participants received either felzartamab (9 IV doses of 16 mg over 20 weeks) or placebo.

Participants
22 adult kidney recipients with AMBR at least 180 days after transplantation and a eGFR >20 mL/min/1.73 m^2.

Outcomes
Primary outcome was ther safety and side effect profiles of felzartamab. Secondary outcomes included: resolution of ABMR, level of microvascular inflammation, classifier score of ABMR, DSA assessment, NK-cell count, donor cfDNA & eGFR slope.

Follow-Up
52 Weeks.

CET Conclusions
by John Fallon

The investigators present a blinded, placebo-controlled RCT for the safety of potentially exciting therapy for ABMR, felzartamab. They find an effective early response during the treatment window of the first 24 weeks, with resolution to chronic (inactive) rejection or no rejection in 9 of the 11 (82%) who received the anti-CD38, with only 2 of 10 (20%) having resolution in the placebo group. This was accompanied by reduction in the microvascular inflammation scores for those who received felzartamab compared to placebo. In the 6-month observation period following treatment the differences between the groups begins to wane, with 3 of those who had inactivity on biopsy at 6 months having activity at 12 months. Within the placebo group there is still only 2 of 10 with no activity on biopsy at 12 months, but these are 2 different participants from those at 6 months, who have become active. Along with this, the differences in microvascular injury score and probability score for AMBR have become narrower. The relevant clinical manifestation of this was the 1-year eGFR slope was shallower with felzartamab at −0.39 mL/min/1.73 m^2, compared with −4.53 mL/min/1.73 m^2 in placebo. It appears likely that during the treatment period there is an effect of the anti-CD38 on activity, but that without regular dosing, or additional treatments titrated to biopsy results this effect diminishes over time. With NK-cell depletion, the key safety considerations is infections, which were unsurprisingly numerically higher, but not significant in the felzartamab group, 91% compared with 64% in the control. The inherent limitation of small sample size within this safety RCT means commenting on efficacy or the risk benefit with adverse infection is not possible, but they have performed a robustly designed study demonstrating safety of felzartamab with convincing preliminary evidence for a larger multi-centre/multi-national efficacy study for the treatment for a condition which to date has no approved therapies.

Jadad Score
5.

Data Analysis
Strict intention-to-treat analysis.

Allocation Concealment
Yes.

Trial Registration
ClinicalTrials.gov - NCT05021484; EudraCT-2021-000545-40.

Funding Source
Industry funded.

CLINICAL IMPACT SUMMARY

by Simon Knight

Management of antibody mediated rejection (ABMR) in renal transplant recipients remains a significant challenge. Antibody

removal with a combination of plasma exchange, steroid and intravenous immunoglobulin remains standard of care, with no other therapies recommended in consensus guidelines [1]. Randomised trials of agents targeting plasma cells such as rituximab and bortezomib have failed to show convincing clinical benefit [2, 3]. The anti-IL6 antibody Clazakizumab showed promising results in phase 2 studies, although a recent phase 3 study was terminated early due to lack of efficacy [4, 5]. Clinical studies in this area are challenging due to difficulties in identifying patients and relatively slow recruitment rates.

In a recent issue of the New England Journal of Medicine, Mayer and colleagues report the results of a phase 2 trial of the CD38 monoclonal antibody felzartamab in renal transplant recipients with late antibody mediated rejection [6]. This small safety study is well designed, with block randomisation and placebo control to ensure blinding and allocation concealment. The investigators randomised 22 patients with late ABMR to 9 infusions of felzartamab over 20 weeks, or placebo infusions. Patients were then followed for a further 6 months following completion of treatment.

The primary focus of the study was safety. Eight patients had mild to moderate infusion reactions with felzartamab, but there were very few serious adverse events and these did not differ significantly between groups. Infections were numerically but not significantly higher in the treatment arm.

Interesting efficacy signals were also seen. At the end of treatment, there was resolution of ABMR in 82% of treated patients compared to 20% of controls. Microvascular inflammation, molecular risk of rejection score and cell-free DNA were all lower in the treatment arm. However, in the 6 months following cessation of treatment, 3 of 9 responding patients showed recurrence with increase in molecular and biomarker activity.

These results are very promising for treatment of a challenging condition. Strong conclusions are limited by sample size and a very narrow patient population, but they do suggest that felzartamab may have a role to play in the management of ABMR. The recurrences seen after the end of treatment suggest that careful monitoring and further dosing may be required for some patients.

Clinical Impact

4/5.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has 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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Edited by Reshma Rana Magar.

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ORIGINAL RESEARCH
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Antibody-Mediated Rejection in Liver Transplantation: Immuno-Pathological Characteristics and Long-Term Follow-Up

Luca Cicalese[1†], Zachary C. Walton[2†], Xiaotang Du[3†], Rupak Kulkarni[1†], Suimin Qiu[3], Mohamed El Hag[4†] and Heather L. Stevenson[3†]*

[1]Division of Transplant Surgery, Department of Surgery, University of Texas Medical Branch, UTMB, Galveston, TX, United States, [2]John Sealy School of Medicine, University of Texas Medical Branch, UTMB, Galveston, TX, United States, [3]Department of Pathology, University of Texas Medical Branch, UTMB, Galveston, TX, United States, [4]Department of Pathology, Cleveland Clinic, Cleveland, OH, United States

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***Correspondence**
Luca Cicalese,
lucicale@utmb.edu

†ORCID:
Luca Cicalese
orcid.org/0000-0002-9921-3078
Zachary C. Walton
orcid.org/0009-0002-0749-1079
Xiaotang Du
orcid.org/0000-0001-7444-6601
Rupak Kulkarni
orcid.org/0009-0009-5942-520X
Mohamed El Hag
orcid.org/0000-0002-0177-9074
Heather L. Stevenson
orcid.org/0000-0002-0645-7621

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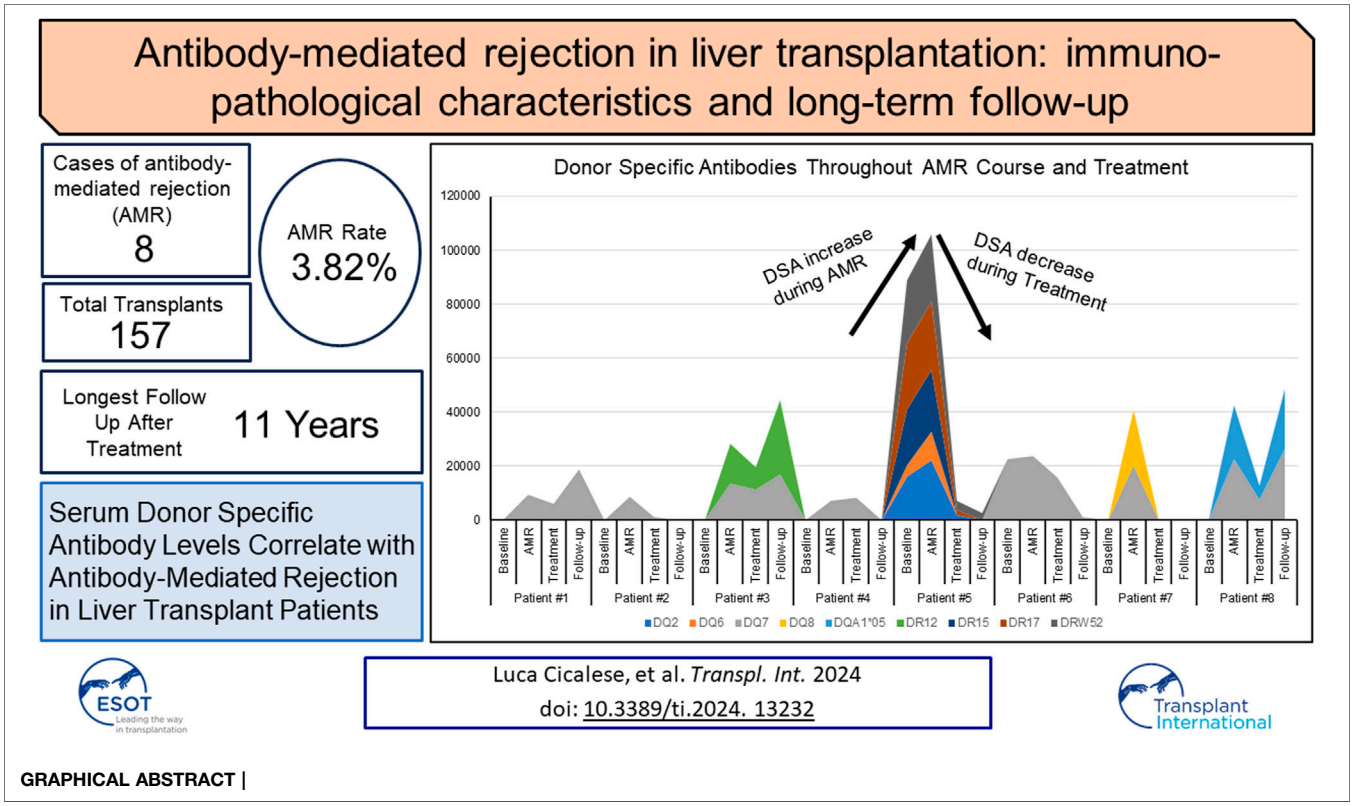
The diagnosis of liver antibody-mediated rejection (AMR) is challenging and likely under-recognized. The association of AMR with donor-specific antibodies (DSA), and its clinical course in relation to pathologic findings and treatment are ill defined. We identified cases of liver AMR by following the criteria outlined by the 2016 Banff Working Group. Patient demographics, native liver disease, histopathologic findings, treatment type, clinical outcome, and transaminase levels during AMR diagnosis, treatment, and resolution were determined. Patients (n = 8) with AMR average age was 55.2 years (range: 19–68). Seven of eight cases met the Banff criteria for AMR. Personalized treatment regimens consisted of optimization of immunosuppression, intravenous pulse steroids, plasmapheresis, IVIG, rituximab, and bortezomib. Five patients experienced complete resolution of AMR, return of transaminases to baseline, and decreased DSA at long-term follow-up. One patient developed chronic AMR and two patients required re-transplantation. Follow-up after AMR diagnosis ranged from one to 11 years. Because AMR can present at any time, crossmatch, early biopsy, and routine monitoring of DSA levels should be implemented following transaminase elevation to recognize AMR. Furthermore, treatment should be immediately implemented to reverse AMR and prevent graft failure, chronic damage, re-transplantation, and possibly mortality.

Keywords: solid organ transplant, allograft, rejection, DSA, AMR, C4d

Abbreviations: ALP, Alkaline Phosphatase; ALT, Alanine Transaminase; AMR, Antibody-Mediated Rejection; AST, Aspartate Transaminase; CM, Crossmatch; DSA, Donor Specific Antibody; FFPE, Formalin-Fixed and Paraffin-Embedded; H&E, Hematoxylin & Eosin; HCV, Hepatitis C Virus; HLA, Human Leukocyte Antigen; IRB, Institutional Review Board; LFT, Liver Function Test; LTX, Liver Transplantation; MCS, Mean Channel Shift; MFI, Mean Fluorescence Intensity; PLT, Platelet; T. Bili, Total Bilirubin; TAC, Tacrolimus; TCMR, T Cell-Mediated Rejection.



GRAPHICAL ABSTRACT |

INTRODUCTION

Antibody-mediated rejection (AMR) in liver transplantation (LTX) was first observed in ABO-incompatible recipients caused by preformed or *de novo* donor-specific antibodies (DSA) [1–3]. Over the years, evidence of AMR in ABO-compatible transplants has increased and has sparked increased interest in understanding the pathologic mechanisms and their effect on patient outcomes [4, 5]. Acute AMR occurrence in ABO compatible liver allografts is rare (less than 5%) and is slightly higher in kidney allografts (between 5–10%). Chronic AMR in the liver is less well defined than in kidney allografts, where it is a more common cause of long-term graft loss in approximately 10–20% of transplant recipients [6–9]. The liver is believed to be an "immune-privileged" organ resistant to DSA-mediated injury due to its vast vascular (sinusoidal) endothelial surface, secretion of soluble human leukocyte antigen (HLA) that can bind to and opsonize harmful antibodies and immune complexes, the facilitation of phagocytosis by Kupffer cells, and the presence of a powerful regenerative capacity [10].

The exact incidence of AMR in the liver allograft is likely underestimated. Though increasing evidence and clinical data show that AMR can cause allograft injury and allograft loss, most transplant centers do not monitor DSA prior to LTX and during post-transplant follow-up. Routine HLA testing of donors and recipients as well as lymphocyte crossmatch (CM) is not the standard practice in LTX due to the belief that this organ can absorb and neutralize antibodies with little or no consequence. In recent years, the role of lymphocyte CM, DSA, and complement reactivity, such as C4d, deposition have begun to be recognized as vital markers of graft success or risk of rejection [3, 11–17]. Histopathologic features of AMR in liver allografts, such as portal eosinophilia, portal vein endothelial cell hypertrophy, cholestasis, and microvascular and portal lymphocytic inflammation, while relatively nonspecific in isolation, can be used to recognize acute AMR independent of serology or C4d staining [18]. Additionally, these same histopathological features of AMR are now more recognized when associated with elevated DSA [18, 19].

To establish the Banff schema for histopathological grading of liver allograft rejection, an international consensus group met in 1995 [20], and after several additional meetings, published a comprehensive update and introduced the concept of AMR in 2016 [21]. These guidelines were developed following the presentation and discussion of cases throughout the world at previous Banff meetings over a period of 21 years. These criteria include the presence of serum DSA (>5,000 mean fluorescence intensity), microvascular C4d deposition, compatible histopathologic features (e.g., capillaritis and endothelial cell hypertrophy), and exclusion of other causes that may have similar features [21].

Treatment of AMR in LTX, due to the lack of randomized controlled clinical trials, is mostly adopted from the experience of AMR in kidney transplantation and varies widely among

transplant centers [11]. Despite studies recently describing various treatments and outcomes, no gold standard has been established [9, 22]. The mainstay of the management strategies is focused on optimizing immunosuppressors, plasma exchange, IVIG, anti-CD20, and proteasome inhibitors. The current preferred strategy to treat AMR is a personalized (more or less aggressive) approach based on its severity, liver function impairment, DSA levels, and apparent tissue injury on biopsy or the presence of additional risk factors (i.e., infections). Different drugs can be added if the liver disease progresses or if no improvement is seen, or they can be initiated together if the severity of AMR suggests the need to do so. If AMR continues to be present after all medical interventions are exhausted and is associated with worsening liver function and tissue injury, then re-transplantation needs to be considered [23].

In this study cohort, we evaluated CM, DSA levels, applied the 2016 Banff Criteria for the evaluation of liver AMR, and compared the treatment regimens, correlating these findings with long-term clinical outcomes.

PATIENTS AND METHODS

Study Population

The cases were identified and reviewed by interrogating the electronic medical record system (EPIC) and pathology database of 157 patients with LTX performed or followed at the University of Texas Medical Branch (UTMB) from 2009 to 2022. Patients with incompatible ABO donors were not considered as it is well known that ABO incompatibility can significantly increase DSA production and AMR rates [24, 25]. Patients with elevated liver function tests (LFTs), elevated DSA, and biopsy proven AMR according to 2016 Banff Criteria [21] were selected. Histology of AMR cases with elevated DSA were compared to liver biopsies from patients matched by age, sex, same native liver disease, and who did not have elevated DSA. Histology slides were independently reviewed by two transplant pathologists who were blinded to the diagnosis.

Patient demographics, native liver disease, LFTs (prior to the diagnosis, at the time of diagnosis, during treatment, and at most recent follow-up post-AMR episode), and histopathologic findings were noted. The type and duration of treatment and clinical outcome parameters were also analyzed.

Clinical and laboratory data were collected from EPIC according to the Institutional Review Board (IRB) rules and regulations and previous approval of a research protocol (#12-260).

All recipient sera were tested for anti-HLA antibodies using a multiplexed solid-phase-based microbeads array (Single Antigen Class I and II Kits, OneLambda, CA, United States). A pre-transplant serum was considered positive when the mean fluorescence intensity (MFI) was higher than 1,000 (MFI ≥1,000). Additionally, a flow crossmatch (Flow-XM) was conducted using the patient's serum incubating with donor lymphocytes. The B and T cell flow-XM positivity was defined with a mean channel shift (MCS) >/ = 20 for T cell and >/ = 30 for B cell using a 256-channel resolution on the recipient serum obtained at the time of transplantation.

Pathology Evaluation

Biopsy sections with hematoxylin and eosin (H&E), special stains including Masson's trichrome, PAS, PAS-D, iron stain and immunostaining for C4d were re-evaluated for morphologic and immunophenotypic features of acute and chronic AMR according to the 2016 Banff Criteria for allografts (**Table 1**) [21].

Two transplant pathologists (H.S.L and S.Q) scored the histology characteristics and C4d staining. The control and study cases were randomly mixed and evaluated by the pathologists who were unaware of the diagnosis. The two pathologists, unaware of other data, assessed biopsies for features including portal microvascular endothelial cell hypertrophy, portal capillary dilatation, dilated or tortuous portal inlet venules, presence of microvasculitis, edema, periportal hepatocyte necrosis and/or lymphocytic arteritis. C4d scores from 0 to 3 were used as recommended in the 2016 Banff criteria. A semi-quantitative grading system was used to demonstrate the histopathological features (**Table 1**). Final scores were obtained by calculating the average of the scores measured independently by the two pathologists. Graphs were created using Sigma Plot software (SPSS, Chicago, IL) and Excel (Microsoft).

RESULTS

Patient Demographics

Patient demographics and native liver diseases including cirrhosis from chronic hepatitis C (HCV), alcohol (ETOH) abuse, alcoholic fatty liver disease, alpha-1 antitrypsin deficiency, and hepatocellular carcinoma (HCC) are summarized in **Table 2**. Patient race was classified as reported by each patient and listed in EPIC. Among patients receiving a LTX from an identical ABO donor, eight patients were diagnosed with AMR at our institution during the study period. The AMR diagnosis in these patients was established at different intervals from transplantation for each patient. This interval ranged from 12 days to 16 years after transplantation. Two patients had AMR diagnosed within 1 month of transplant, and the others had AMR diagnosed 1, 2, 3, 4, 8, and 16 years after transplant. Two of these patients were followed at our center but received a transplant in another center or state. The rate of AMR observed in the patient population receiving a LTX in our institution was 3.82%. All patients transplanted at our institution received induction with IV basiliximab or methylprednisolone at the time of transplantation and maintenance immunosuppression with tacrolimus and mycophenolic acid and rapid taper to steroid free. The average age of the eight AMR patients was 55.2 years (range: 19–68): four were male and four were female.

TABLE 1 | Semi-quantitative histology scores of acute and chronic AMR, adopted from 2016 Banff criteria.

Semi-quantitative histology scores of acute AMR
h-scores (0–3) (0-none, 1-mild, 2-moderate, 3-severe)
Portal microvascular endothelial cell hypertrophy
Portal capillary and inlet venule dilation
Portal microvasculitis
Portal edema
Ductular retention
Cholestasis
Edema and periportal hepatocyte necrosis
Lymphocytic and/or necrotizing arteritis
Moderate portal/periportal, sinusoidal and/or perivenular fibrosis
C4d score (0–3) (0-none, 1-minimal, 2-focal, 3-diffuse)
Mononuclear infiltrates: portal/perivenular/interface (0–3) (0-none, 1-mild, 2-moderate, 3-severe)
Fibrosis: at least moderate portal/periportal, sinusoidal and/or perivenular (0–3) (0-none, 1-mild, 2-moderate, 3-severe)
Ductopenia (0–1) (0-none, 1-present)

TABLE 2 | Patient demographics.

Patient	Age range	Sex	Race	Cause of native liver disease
#1	61–70	M	White	HCV, ETOH
#2	61–70	F	Black	HCV
#3	21–30	F	White	Alpha-1 Antitrypsin Deficiency
#4	51–60	M	White	HCV
#5	51–60	F	White	HCV, HCC, ETOH
#6	61–70	F	White	HCV, HCC
#7	61–70	M	White	HCV
#8	61–70	M	White	HCV

Correlation of Lymphocyte Cross Match With Antibody-Mediated Rejection

All patients transplanted at our institution received a CM at the time of LTX. In total, eight positive CM were recorded. However, only two patients with AMR (Patients #5 and #6) had positive CM tests at the time of LTX, and the others were T and B cell negative. Data on the correlation of CM and AMR for individual patients is summarized in **Table 3**. In patient #5, both B and T cell positivity were detected with a mean channel shift (MCS) >/ = 20 for T cell and >/ = 30 for B cell using a 256-channel resolution on the recipient serum obtained at the time of transplant. DSA alleles A1, A24, B7, B8, DR15, DR17, DR52, DQ2, and DQ6 had mean fluorescence intensity (MFI) values ranging from 2,159–24,404. In patient #6, only B cell positivity was detected on flow cytometry with alleles A1, A24, and DQ7 detected with MFI values of 5,144; 7,586; and 15806, respectively. Patients #5 and #6 with positive CM experienced AMR early during the first-year post LTX. Patients with negative CM experienced AMR several years after transplant (2–4 years after LTX). CM information for patients #3 and #7 were unavailable due to being transplanted elsewhere, and experienced AMR 22 years after receiving a pediatric LTX and 10 years after adult LTX, respectively.

DSA Correlation With AMR

The presence of preformed or *de novo* HLA DSA has been previously associated with rejection, inflammation, fibrosis, and allograft loss in liver transplants [13, 26, 27]. DSA are one of the four criteria to diagnose AMR. In patients with a negative CM experiencing AMR, class I DSA were detected in only one patient while all had high levels of one or more class II DSA. In this patient, class I DSA allele CW4 had MFI of 1,234 several days after diagnosis of AMR, but shortly returned to zero and was not recorded again. HLA class II DSAs with MFI >5,000 at the time of AMR diagnosis alongside the values at baseline, after AMR treatment, and at the most recent follow-up are listed in **Table 3**. Two out of eight patients had baseline Class II DSA level positivity and B cell positive CM as described above. DSA baseline levels were unavailable in the two patients transplanted elsewhere. Class II DSA, most commonly against the DQ and DR loci, were elevated to MFI >25,000 at the time of diagnosis and decreased after treatment in all cases for which data was available (**Figure 1A**). Among the DSA elevated at diagnosis (**Figure 1A**), DSA against DQ7 was present in 5 out of 8 patients. The single patient without DQ7 antibodies showed multiple Class II DSAs against other loci with high MFI levels.

Histological Correlation With AMR

Two transplant pathologists reviewed the randomized liver biopsies without knowledge of any clinical or serological data from patients who experienced liver allograft AMR and control patients. Histopathologic features were graded with an h-score according to the 2016 Banff Criteria (**Figure 1B**). Seven out of eight patients received an h-score greater than 1, while all eight control patients received an h-score no more than 1. Patient #2 showed minimal pathologic changes in liver biopsy and received an h-score of zero. All biopsies from matched control patients showed minimal histopathologic changes except control patient #5 which showed relatively active and similar pathologic changes with AMR patients. A semi-grading system as a supplemental tool to h-score system adopted from 2016 Banff Criteria was utilized to demonstrate the break-down of histopathologic features of acute and chronic AMR (**Figures 1C, D**). Portal microvascular endothelial cell hypertrophy, portal capillary and inlet venule dilation, microvasculitis, portal edema, ductular reaction, cholestasis, periportal hepatocyte necrosis, lymphocytic and/or necrotizing arteritis, portal/periportal, sinusoidal and/or perivenular fibrosis have been carefully evaluated on each biopsy. Ductopenia, fibrosis, and portal and perivenular mononuclear infiltrates were evaluated for active chronic AMR. **Figure 1C** summarizes the classic histopathologic features observed in the eight AMR patients compared with the mild and unspecific histopathologic changes seen in the control patients. **Figure 1D** shows the histopathologic features evaluated for chronic AMR. Though the h-scores of the AMR patient group were higher than the control group, the difference between the two group was minimal. The biopsy of patient #2 shows minimal histologic changes compared to the matched control patient.

Figure 2 shows the representative liver biopsy histology of patient #3 at the time of diagnosis and 6-month follow up. Endothelial cell hypertrophy, capillary and inlet venule dilatation, mixed portal inflammation, portal edema and

TABLE 3 | Tacrolimus (TAC) levels with liver injury test profile and serum DSA MFI levels in eight patients who experienced AMR. Values recorded at baseline (post-transplant, but before AMR, or at earliest lab values on file if transplant was not performed at our institution), at the time of AMR diagnosis, during treatment, and at long-term follow up extracted from the most recent lab values on file. Liver injury test profile of patients included monitoring of platelet (PLT) count, total bilirubin (T. Bili), and concentration of the enzymes alanine transaminase (ALT) and aspartate transaminase (AST).

Patient	Time points	Liver injury profile					DSA								
	Follow-up	TAC	PLT	T. Bili	ALT	AST	DQ2	DQ6	DQ7	DQ8	DQA1[a]05	DR12	DR15	DR17	DRW52
	(Years from LTX - years from AMR)	ng/mL	X103/μL	mg/dL	U/L	U/L	(SI)	(SI)	(SI)	(SI)	(SI)	(SI)	(SI)	(SI)	(SI)
#1	Baseline	8	233	0.9	30	19			0						
	At AMR Diagnosis	<3	180	11.6	138	63			9,209						
	Treatment	6	164	0.9	76	47			5,980						
	Follow-Up (13-9)[c]	3	239	0.5	25	29			18,807						
#2	Baseline	<3	193	1	29	26			0						
	At AMR Diagnosis	13	150	5.3	101	163			8,665						
	Treatment	9	102	4.4	50	96			863						
	Follow-Up (13-11)	na	144	0.5	13	25			0						
#3	Baseline	4	185	0.8	56	48			NA			NA			
	At AMR Diagnosis	7	101	1.4	87	119			13,291			14,873			
	Treatment	8	110	1	54	69			11,308			8,200			
	Follow-Up (17-1)[b]	8	90	0.6	49	57			16,820			27,512			
#4	Baseline	8	211	0.8	40	36			0						
	At AMR Diagnosis	11	184	1.2	59	52			7,074						
	Treatment[d]	11	300	0.4	28	33			8,333						
	Follow-Up (8-5)	<3	286	0.6	23	31			NA						
#5	Baseline[a]	12	108	5.1	74	26	16,092	4,114					20,884	24,404	23,464
	At AMR Diagnosis	7	175	6.6	56	23	22,197	10,408					23,066	25,182	24,941
	Treatment	7	120	0.9	33	32	1,619	0					0	1901	3,476
	Follow-Up (6-6)	3	105	0.8	25	37	0	0					0	0	2,592
#6	Baseline[a]	6	292	0.7	88	36			22,348						
	At AMR Diagnosis	5	188	1	325	162			23,469						
	Treatment	6	84	1.9	38	29			1,221						
	Follow-Up (4-4)	8	175	0.6	11	21			1,088						
#7	Baseline	7	208	1.1	119	62			NA	NA					
	At AMR Diagnosis	7	172	4.9	434	203			20,172	20,495					
	Treatment	7	242	1.1	211	91			NA	NA					
	Follow-Up (11-3)[b]	6	295	2.1	83	51			NA	NA					
#8	Baseline	10	876	0.5	42	47			0		0				
	At AMR Diagnosis	7	643	12	921	622			22,514		20,089				
	Treatment	8	551	8.6	170	132			7,575		5,119				
	Follow-Up (3-2)	6	598	0.5	23	24			26,110		22,373				

[a]*Represents a positive crossmatch at time of transplant.*
[b]*Represents patients requiring re-transplantation.*
[c]*Represents patients experiencing chronic AMR.*
[d]*Represents patients with history of noncompliance with immunosuppressive medications.*
NA represents lab values that were unavailable.

ductular reaction were observed. Though serum DSA was persistent in patient #3, the histopathology of the liver biopsy at 6-month follow-up improved substantially.

Representative histology in biopsies of AMR patients at the time of diagnosis and 6–12 months follow up are summarized in **Figure 3**. Masson's trichrome stains of the biopsies at the time of diagnosis and follow up are also included in **Figure 3** to compare the amount of fibrosis. Follow-up liver biopsies of AMR patients showed improvement and returned to baseline after treatments in 6–12 months.

C4d Scores Correlated With AMR

Positive microvascular endothelial cell C4d staining is one of the key diagnostic criteria for AMR in the liver allograft. C4d deposition in the liver biopsy of the AMR patients was scored using the Banff Criteria. C4d staining in portal veins, portal capillaries, portal stroma, sinusoidal and central vein endothelium was graded as negative (score 0), minimal (<10%, score 1), focal (10%–50%, score 2) and diffuse (>50%, score 3). Seven out of eight AMR patients had a C4d score greater than one. Patient #2 with minimal histologic changes had negative C4d staining.

Bilirubin and Transaminase Levels and Correlation With AMR

Laboratory tests including total bilirubin (T. Bili), alanine transaminase (ALT), aspartate transaminase (AST), and platelets (PLT) have been summarized at baseline 1-2 months

after LTX, when AMR was diagnosed, and at last available follow-up. The number of years from transplant and from the AMR episode are also summarized in **Table 3**. Patient's liver function returned to baseline after treatments. **Figure 4** shows the representative trending of liver function of patient #3.

Treatment Regimens for AMR in Liver Transplant Recipients

The treatment regimens used in these eight liver transplant recipients with AMR are listed in **Table 4**. According to our experience, an individualized combination of the treatments was implemented. Treatment regimens varied from using only IV steroid with simultaneous increase of tacrolimus and mycophenolic acid dose to a more aggressive combination of steroids, IVIG, plasma exchange, bortezomib and rituximab.

Outcomes and Long-Term Follow-Up

Five patients with liver AMR had complete resolution, return of transaminases to baseline and decreasing DSA levels at follow-up. One patient (Patient #1) developed chronic AMR and two patients (Patients #3 and #7) required re-transplantation. Of the patients requiring re-transplantation, one did not have concomitant T cell-mediated rejection (TCMR), and the other only had a mild TCMR component that was not responsible for the graft loss. Re-transplantation was indicated due to AMR. After the AMR episode and treatment, these patients were followed long-term with periodic DSA monitoring. Up to the latest follow-up of this study in April 2022 (range of follow-up from LTX 4–23 years and from AMR episode 1–9 years), no additional acute AMR episodes were recorded and all patients' liver laboratory tests continued to remain within normal range and stable. DSA levels remained stable after normalization except for one case (patient #1) who had elevated DQ7 9 years after the initial episode of AMR (PI = 18,807) but with no evidence of AMR and with normal liver function. Of these patients, only one patient (Patient #4) is now deceased.

DISCUSSION

Analysis of LTX patients at our institution revealed that 3.82% of LTX patients experienced AMR, which is on the higher end of the expected 2%–5% range [9]. It is possible that this higher rate of AMR observed could be secondary to more aggressive monitoring instituted in our program. In fact, in addition to the CM we also frequently measure DSA levels when there is an increase of LFTs, or suspected rejection, either TCMR or AMR. In numerous occasions, TCMR (mild or moderate) was diagnosed without DSA variation and no histological evidence of AMR. However, patients with elevated DSA had AMR as histologically confirmed using the Banff Criteria as previously described. In one patient, AMR occurred 6 months after a successfully treated episode of TCMR and another patient had concomitant histological findings of TCMR and AMR.

In our center, the induction immunosuppressive treatment has been performed with basiliximab, 40 mg at time of transplant and a second dose of 20 mg on post-operative day (POD) 4 and/or methylprednisolone 500 mg at the time of transplant followed by a taper to steroid free in the following week. Thymoglobulin or alentuzumab induction were not used in our program. Maintenance immunosuppressive therapy was performed with

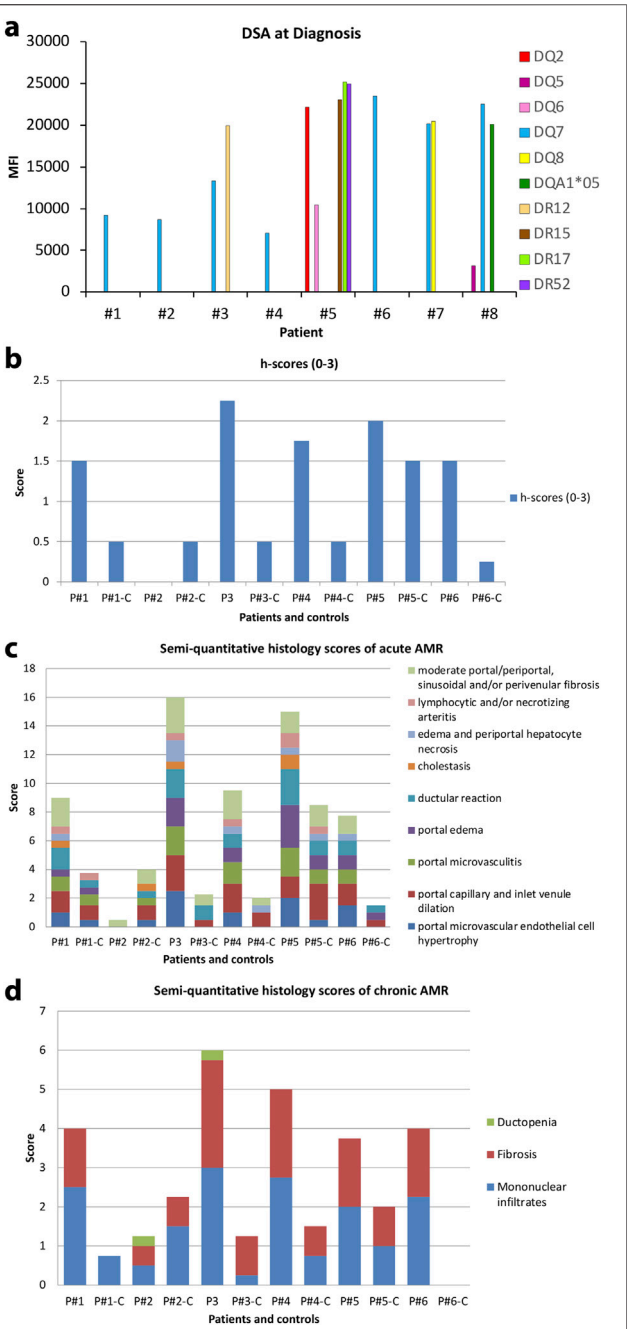


FIGURE 1 | (A) Serum DSA levels at the time of diagnosis of AMR in the eight patients. **(B)** h-score of eight AMR patients according to 2016 Banff Criteria for liver allografts. Of these, seven out of eight patients are greater than one. Patient #2 showed minimal pathologic changes in liver biopsy and h-score is zero. **(C)** Semi-quantitative histology scores of acute AMR in patients where "C" denotes matched control patients. **(D)** Semi-quantitative histology scores of chronic AMR in patients "C" denotes matched control patients.

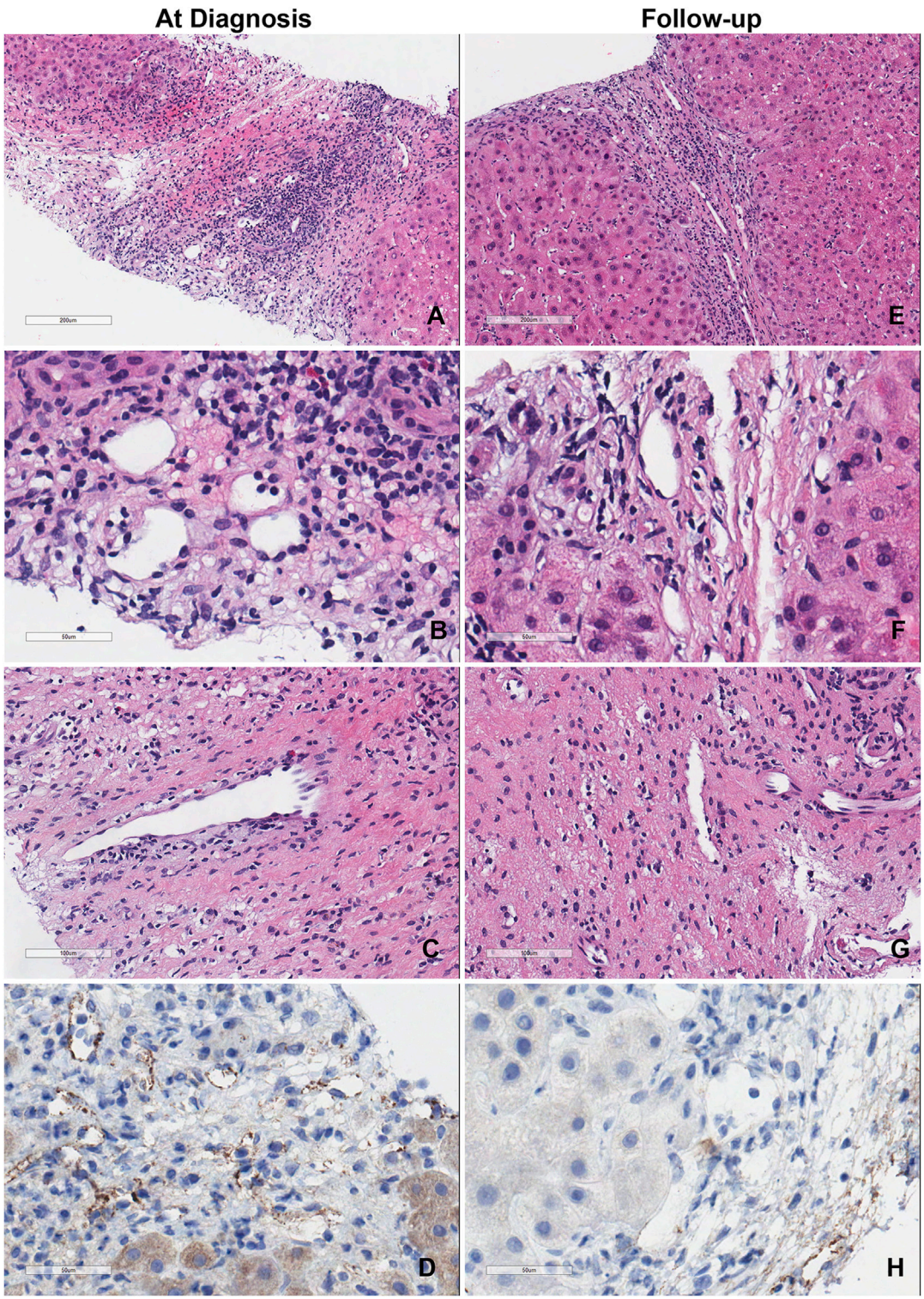


FIGURE 2 | Representative liver biopsy histology of patient #3 at diagnosis and 6-month follow-up. **(A–D)** Liver biopsy of the patient at the time of diagnosis showed the classic acute AMR microvascular pathology lesions. **(E–H)** Liver biopsy of the same patient at time of 6-month follow-up.

dual therapy of oral tacrolimus and mycophenolic acid. This possibly less aggressive induction therapy was utilized to limit post-operative infectious complications and better control hepatitis C virus (HCV) infection prior to the availability of the new and more effective antiviral treatments and reduce the risk associated with COVID-19 in recent years.

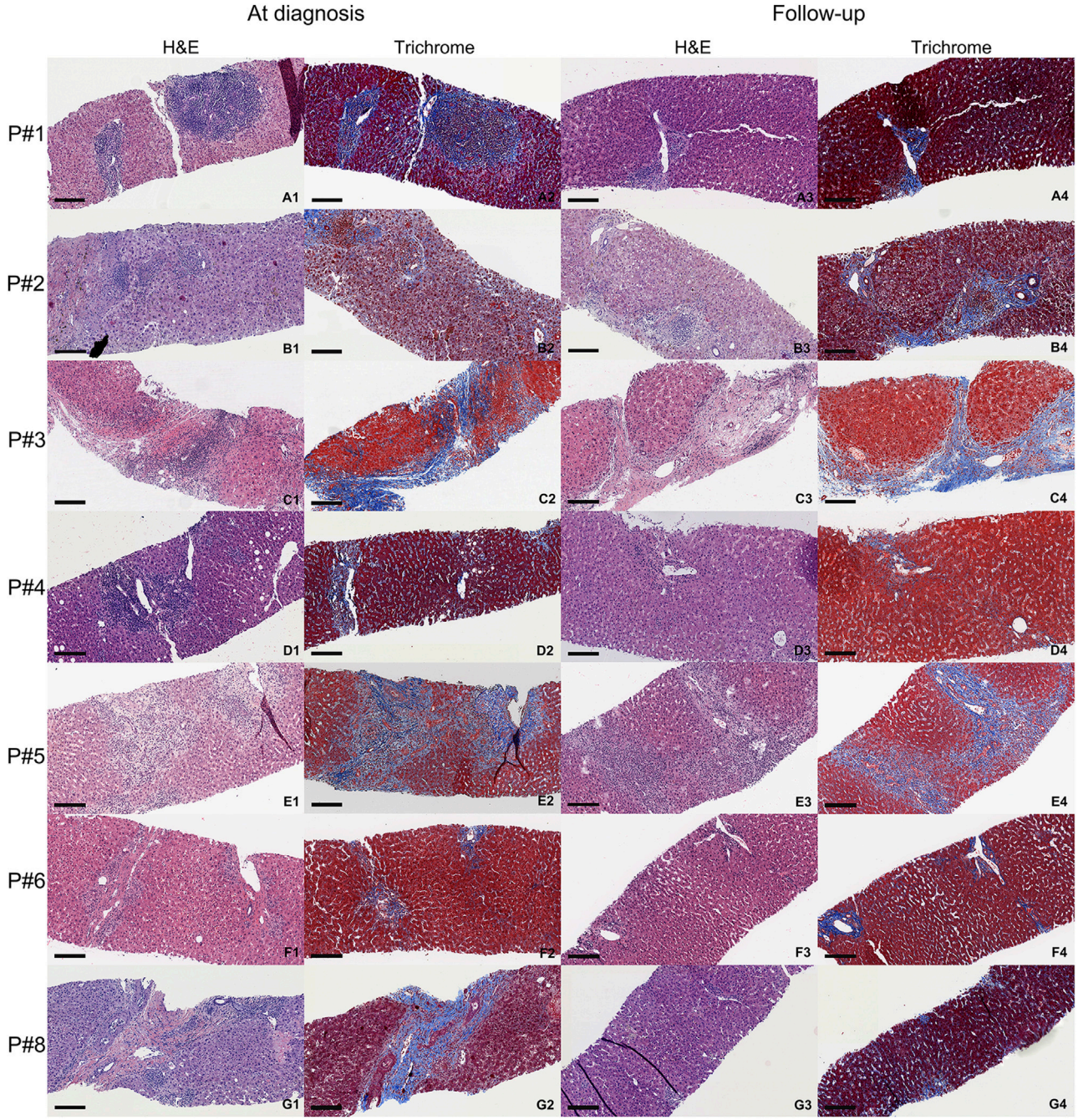


FIGURE 3 | Representative histology of AMR patients at the time of diagnosis (first two columns) and 6–12 months follow-up (last two columns). Each biopsy shows H&E and Masson's trichrome stain (fibrotic areas are blue). Black scale is 200 μm. **(A1–A4)** are the biopsies from AMR patient #1. **(B1–B4)** are the biopsies from AMR patient #2. **(C1–C4)** are the biopsies from AMR patient #3. **(D1–D4)** are the biopsies from AMR patient #4. **(E1–E4)** are the biopsies from AMR patient #5. **(F1–F4)** are the biopsies from AMR patient #6. **(G1–G4)** are the biopsies from AMR patient #8. Patient #7 did not have a follow up biopsy after diagnosis.

The higher rate of AMR observed could be also secondary to this immunosuppressive approach. However, we have no direct evidence of this since most patients experienced AMR several years after transplant and, therefore, when the effects from stronger induction would have faded away [29–31]. Two of the patients who had AMR in the first-year post-transplant also had a positive CM as previously described. Therefore, this observation should trigger the selection of a different induction or maintenance therapy with a higher drug dose/level or steroids to possibly mitigate such risk. The CM results and induction therapy used were unknown for the two patients originally transplanted elsewhere; however, they were maintained on similar

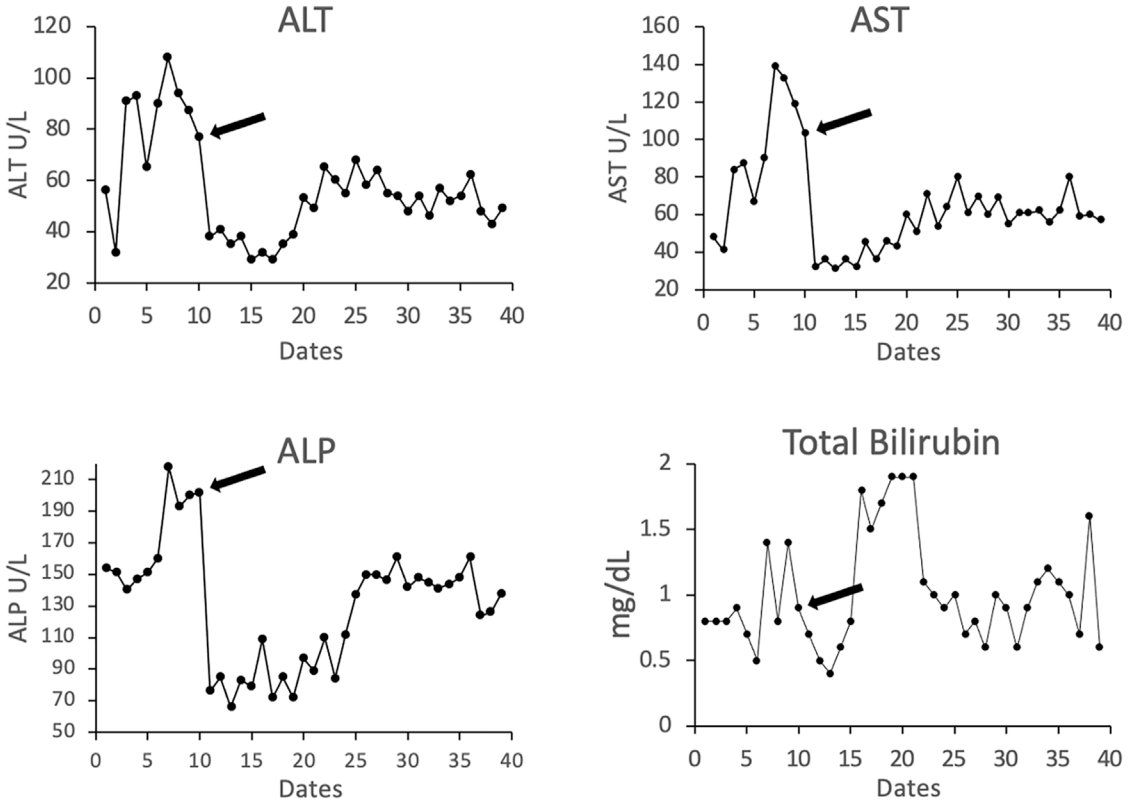


FIGURE 4 | Representative liver-related laboratory testing of total bilirubin and the enzymes alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) in patient #3. Arrow indicates the time point at the start of treatment.

TABLE 4 | Immunosuppression treatments utilized for antibody-mediated rejection (AMR).

Patient	IVIG	TPE	Steroids	Bortezomib	Rituximab
1	Yes	Yes	No	Yes	No
2	No	Yes	No	Yes	Yes
3	Yes	Yes	Yes	Yes	Yes
4	Yes	No	No	No	No
5	Yes	Yes	No	Yes	Yes
6	No	No	Yes	No	No
7	No	No	Yes	No	No
8	Yes	Yes	Yes	No	No

maintenance therapy as the other patients in this study. Because of this, it is difficult to draw conclusions, and a clinical trial with a larger number of patients is warranted to establish strong therapeutic indications. However, the correlation of early AMR and positive CM indicates these patients should receive more aggressive graft monitoring with DSA measurements and early biopsy including C4d staining when LFTs rise. Additionally, six out of eight patients with positive CM did not develop AMR during the post operative follow up.

In this study, and similarly to what is observed in kidney allografts, a negative CM at the time of transplant does not appear to exclude the possibility to develop AMR later as we observed in several patients and as was previously described [32]. Therefore, from our limited observations, we conclude that positive CM is not predictive of AMR, but when AMR develops in patients with positive CM it appeared earlier and was more severe.

As stated above, TCMR was associated with, or temporarily preceded, AMR. This can be explained with a secondary stimulation of plasma cells and antibody production from an initial T cell response. Such clinical observations in LTX patients indicates regular monitoring of DSA and C4d measurements similar to what is performed in kidney transplants to rule out AMR in liver allografts [11].

Treatment of AMR varied in our experience. It was individualized based on the severity of the clinical findings ranging from IV steroids to an aggressive combination of plasmapheresis, and Rituximab. The two patients requiring re-transplantation were treated, one with IV methylprednisolone and the other with a combination of IV steroids, TPE, IVIG, bortezomib, and rituximab. The one patient who developed chronic AMR received IV methylprednisolone, IVIG, TPE, and Bortezomib. These results indicate that despite complete resolution of AMR and DSA in five out of eight patients (62.5%) the remaining were probably either undertreated, suggesting that a more aggressive therapeutic approach should be implemented early upon diagnosis of AMR, or resistant to treatment. For patients #3 and #7 it is difficult to evaluate since both received LTX and received immunosuppressive management outside our facility prior to

AMR diagnosis. Having received their LTX outside of our facility, it is unknown how long they were experiencing AMR before they presented to us, which supports the idea that more aggressive immunosuppressive treatment should be implemented early in the diagnosis of AMR, and further suggests that LTX patients should be regularly evaluated and tested for DSA and evaluated for liver biopsy evidence of AMR if LFTs rise. Importantly, we observed that earlier intervention with increased immunosuppression following AMR diagnosis resulted in quicker resolution of AMR episodes. Thus, the exact immunosuppressive regimen does not appear to be as important for AMR resolution as the timing of the intervention. The importance of early diagnosis and treatment implementation is supported by other authors [23, 33].

We observed that mainly HLA Class II DSA were identified in these patients. Of the HLA Class II DSA, DQ (especially allele DQ7) antibodies were more clinically relevant to diagnose AMR. No Class I DSA were detected in any of these patients during these rejection episodes. In at least 2 patients, there were *de novo* antibodies, and in four patients there were preformed antibodies. In two patients (Patients #3 and #7), the lack of baseline data does not allow us to determine *de novo* or preformed DSA levels prior to AMR diagnosis at our institution. The two patients with positive CM had preformed DSAs: high levels of DQ7 with positive B cell CM in one case and several DRs but no DQ resulting in T and B cell positivity in the other case. However, our findings are in line with other studies indicating that Class II DSAs play a role in determining graft survival and AMR [34–37].

In long-term follow-up, most patients responded to treatment with complete resolution of AMR as evidenced by the return of LFTs to baseline and lack of histological evidence of AMR. However, in some cases the DQ family of class II DSA remained persistently elevated similar to other studies [33, 38]. The significance of this finding could be explained by a possible neutralization of the present DSA by the "primed and regenerating" liver parenchyma after AMR without consequent evident clinical injury, basically a form of chronic subclinical AMR, but this remains largely unexplained [39–41].

Limitations of this study include small sample size from a single center and non-standardized treatment regimens. Further studies involving a larger number of patients from multiple centers are needed to corroborate our findings. Additionally, whether or not certain immunosuppressive medications may be more adept for treatment of AMR episodes is currently unknown. As mentioned previously, it appears that swift implementation of immunosuppression following AMR diagnosis is sufficient regardless of treatment regimen. However, additional studies involving different treatment regimens for AMR are indicated to determine optimal medications and treatment time, length, and intensity for AMR resolution and overall graft survival.

From the observations made in our series of patients, we can conclude with confidence that AMR is a clinically underestimated and underdiagnosed entity in LTX recipients. The current Banff Criteria, albeit conservative, is well accepted and is an important diagnostic tool in the identification of AMR in LTX patients. AMR can present at any time, including many years after transplant or possibly earlier if a positive CM was detected at the time of transplant, or if the patient is non-compliant with taking immunosuppressive medications. More aggressive monitoring with DSA measurement, especially DQ and DR, as well as early biopsy and C4d staining should be routinely implemented when LFT elevation is observed and when TCMR is suspected/identified to recognize AMR [19]. Consequently, treatment should be immediately implemented to completely reverse AMR and to prevent graft failure, chronic damage, re-transplantation, and possibly mortality in this patient population.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by the Institutional Review Board University of Texas Medical Branch at Galveston 3.634 Rebecca Sealy 301 University Blvd Galveston, TX 77555. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

AUTHOR CONTRIBUTIONS

Conceptualization: LC; pathologic analysis: HS, SQ, ME, and XD; patient management and chart review: LC, RK, ZW, and XD; supervision: LC and HS; manuscript writing and editing: LC and ZW. 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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SYSTEMATIC REVIEW AND META-ANALYSIS
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Normothermic Regional Perfusion in Controlled Donation After Circulatory Death Liver Transplantation: A Systematic Review and Meta-Analysis

Carly Mastrovangelis[1*†], *Charles Frost*[1†], *Amy Hort*[1,2], *Jerome Laurence*[1,2,3], *Tony Pang*[1,2,4] *and Henry Pleass*[1,2,3]

[1]*Westmead Clinical School, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia,* [2]*Department of Surgery, Westmead Hospital, Westmead, NSW, Australia,* [3]*Department of Surgery, Royal Prince Alfred Hospital, Sydney, NSW, Australia,* [4]*Surgical Innovations Unit, Westmead Hospital, Westmead, NSW, Australia*

Liver grafts from controlled donation after circulatory death (cDCD) donors have lower utilization rates due to inferior graft and patient survival rates, largely attributable to the increased incidence of ischemic cholangiopathy, when compared with grafts from brain dead donors (DBD). Normothermic regional perfusion (NRP) may improve the quality of cDCD livers to allow for expansion of the donor pool, helping to alleviate the shortage of transplantable grafts. A systematic review and metanalysis was conducted comparing NRP cDCD livers with both non-NRP cDCD livers and DBD livers. In comparison to non-NRP cDCD outcomes, NRP cDCD grafts had lower rates of ischemic cholangiopathy [RR = 0.23, 95% CI (0.11, 0.49), p = 0.0002], primary non-function [RR = 0.51, 95% CI (0.27, 0.97), p = 0.04], and recipient death [HR = 0.5, 95% CI (0.36, 0.69), p < 0.0001]. There was no difference in outcomes between NRP cDCD donation compared to DBD liver donation. In conclusion, NRP improved the quality of cDCD livers compared to their non-NRP counterparts. NRP cDCD livers had similar outcomes to DBD grafts. This provides further evidence supporting the continued use of NRP in cDCD liver transplantation and offers weight to proposals for its more widespread adoption.

Keywords: liver transplantation, donation after circulatory death, normothermic regional perfusion, cDCD, NRP

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***Correspondence**
Carly Mastrovangelis,
c.mastrovangelis@outlook.com

[†]*These authors share first authorship*

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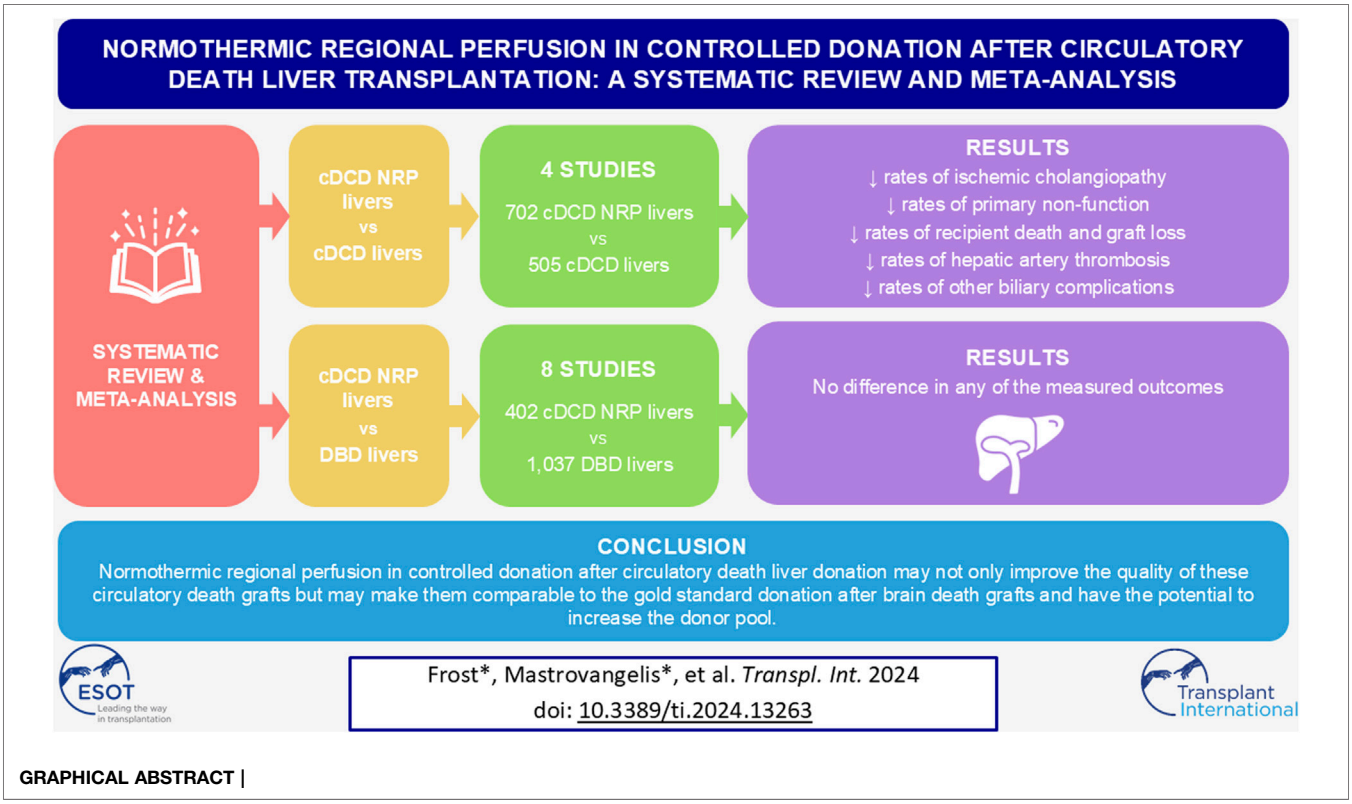
Abbreviations: cDCD, controlled donation after circulatory death; D-HOPE, dual hypothermic oxygenated machine perfusion; DBD, donation after brain death; DCD, donation after circulatory death; EAD, early allograft dysfunction; HAT, hepatic artery thrombosis; IC, ischemic cholangiopathy; ICU, intensive care unit; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; PNF, primary non-function; SCS, static cold storage; SRR, super rapid recovery; uDCD, uncontrolled donation after circulatory death; WLST, withdrawal of life sustaining treatment.



GRAPHICAL ABSTRACT |

INTRODUCTION

Due to a shortage of suitable donor livers, there is a need for expansion of the liver donor pool [1]. One proposed method of addressing this shortage has been to utilize livers from donation after circulatory death (DCD) donors. In these donors, declaration of death is made following cessation of circulation as determined by heartbeat, blood pressure, and/or electrocardiography [2]. This is followed by a super-rapid recovery procurement technique, during which the blood is flushed and the organ is cooled *in situ* prior to placement on ice. This is contrasted with donation after brain death (DBD) donors where, although the donor's heart is still beating, brain death has been declared based on neurological criteria. DCD donors are commonly further classified as controlled (cDCD) or uncontrolled (uDCD) [3]. cDCD livers are generally considered less desirable than those recovered from DBD donors, as they are associated with higher rates of graft loss, ischemic cholangiopathy (IC), and inferior recipient survival [4, 5]. Therefore, there is significant interest in the development of novel organ procurement and preservation techniques to help improve outcomes associated with cDCD liver transplantation.

The current mainstay of organ preservation in liver transplantation is static cold storage (SCS) [6]. SCS in carefully selected DBD liver grafts have relatively low rates of known transplant complications such as early allograft dysfunction (EAD), primary non-function (PNF), and IC [6–9]. However, SCS alone in the cDCD context is associated with a higher incidence of graft complications and poorer recipient outcomes when compared with SCS in DBD livers [6]. IC is of particular concern with DCD livers (incidence of approximately 16% DCD vs. 3% DBD) [4, 10]. It has been postulated that warm ischemia (around the time of procurement) and vascular congestion contributes to microthrombus formation and subsequent biliary ischemia, leading to IC [5, 11, 12]. Compared with DBD livers, the PNF rate is greater in DCD livers (odds ratio of 3.6), as is the rate of total biliary complications (26% DCD vs. 16% DBD), and graft failure (odds ratio of 1.9) [4, 10]. These poorer outcomes contribute to higher rates of non-utilization of cDCD grafts for liver transplantation [13].

In normothermic regional perfusion (NRP) protocols, warm oxygenated perfusion with blood is restored *in situ* after declaration of circulatory death using an extracorporeal membrane oxygenation circuit. Although many technical variants exist, the circuit can be used to perfuse abdominal-only or all abdominal and thoracic organs simultaneously [13, 14]. Although the cellular mechanisms by which NRP works are not yet clear, it certainly allows for *in situ* assessment of organ function via macroscopic inspection, biopsy, and biochemical evaluation [13–16]. However, NRP does utilize more resources than super rapid recovery (SRR); including increased operating theatre time, disposables, and specifically trained perfusion staff [14].

The adoption of NRP varies significantly worldwide. It is policy to routinely use NRP in cDCD liver transplantation in

TABLE 1 | Newcastle Ottawa Scale bias appraisal.

Study	Selection				Comparability		Outcome			Quality
	1	2	3	4	1	Median follow up	1	2	3	
DeGoeij et al. [20]	★	★	★	★	-	23 months	★	★	-	Poor
Gaurav et al. [8]	★	★	★	★	-	38 months	★	★	-	Poor
Hessheimer et al. [21]	★	★	★	★	-	31 months	★	★	-	Poor
Mohkam et al., [22],	★	-	★	★	★	22 months	★	★	-	Good
Fernandez-delaVarga et al. [23]	★	★	★	★	★	23.1 months	★	★	-	Good
Minambres et al. [24]	★	★	★	★	-	6 months	★	-	-	Poor
Rodriguez et al. [25]	★	★	★	★	-	22.7 months	★	★	-	Poor
Rodriguez-Sanjuan et al. [26]	★	★	★	★	-	18 months	★	-	-	Poor
Ruiz et al. [27]	★	★	★	★	★	36 months	★	★	-	Good
Savier et al. [28]	★	★	★	★	★	34.8 months	★	★	-	Good
Viguera et al. [29]	★	★	★	★	-	>12 months	★	★	-	Poor

Bold values refer to scoring categories for Selection, Comparability, and Outcome domains.

Italy, France, and Norway, while also permitted for use in various other jurisdictions [13, 14, 17]. Some international centres combine NRP with additional ex-vivo machine perfusion technologies. The goal of NRP utilization is primarily to increase utilization of deceased donor organs and reduce mortality on the liver transplant waiting list. This systematic review and meta-analysis aims to compare outcomes from transplanted livers using NRP cDCD donors with non-NRP cDCD donors, as well comparing cDCD NRP outcomes with outcomes from DBD donation. We hypothesise that NRP improves the outcomes of cDCD livers and yields outcomes comparable to DBD livers.

MATERIALS AND METHODS

Search Methods and Criteria

A literature search was conducted following the PRISMA 2020 Guidelines and was registered with PROSPERO (CRD42023432345) [18]. The databases searched included Medline, Embase and Scopus. The final search was conducted on 9th June 2023. Article screening, full text review, data extraction, and bias appraisal was conducted independently by Author 1 and Author 2. A third reviewer was used to resolve any conflicts. Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) was used for title and abstract screening as well as full text review.

The search was restricted to human studies in the English language published after 1st January 2000. The search terms focused on capturing liver transplantation and NRP. Search terms defining the comparator groups were deliberately not included to prevent over-filtering otherwise eligible studies.

Studies eligible for inclusion were randomised controlled trials and cohort studies of adult recipients of cDCD livers that had undergone NRP. Comparator groups of cDCD livers with SRR ± non-NRP machine perfusion, or DBD livers with SCS ± non-NRP machine perfusion were eligible. All indications for transplant and all MELD scores were included.

Abstracts, case reports, and systematic reviews were excluded. Studies with <5 NRP livers transplanted, NRP livers from uncontrolled donation after circulatory death (uDCD) donors, and paediatric recipients (<18 years) were excluded. Studies specifying a no-touch-time ≥5 min or containing data from jurisdictions with mandatory no-touch-times ≥5 min were also excluded [19]. The studies included in the data extraction were assessed using the Newcastle-Ottawa Scale Risk of Bias for Cohort Studies tool. Full inclusion/exclusion criteria are available in the **Supplementary Material**, and appraisal results are available **Table 1**.

Figure 1 is a PRISMA flow chart outlining the screening process undertaken in this review. Twelve studies were excluded from analysis due to containing duplicate data with other included studies. Preference for inclusion in these cases was given to studies published more recently and studies with higher participant numbers. Eleven studies were included in the final analysis.

Data Extraction

Data was independently extracted by Author 1 and Author 2 into a preformed template and cross-checked. Disparities were settled with discussion and repeated review. The data extracted included number of livers transplanted, recipient death, graft loss, ischemic cholangiopathy (IC), primary non-function (PNF), hepatic artery thrombosis (HAT), early allograft dysfunction (EAD), other biliary complications, intensive care unit (ICU) length of stay, and hospital length of stay.

The following outcomes were defined for the purpose of our analysis:

- IC: non-anastomotic strictures identified through appropriate imaging with a patent hepatic artery
- PNF: graft failure leading to urgent re-transplantation or death within 1-week post-surgery
- EAD: as per Olthoff criteria [30].
- HAT: thrombosis in the hepatic artery identified through relevant imaging
- Other biliary complications: defined as anastomotic strictures and leaks, and other biliary complications identified by the study excluding IC and HAT.
- The discard rate was defined as the rate of liver grafts which were not utilized post-procurement or NRP initialisation.

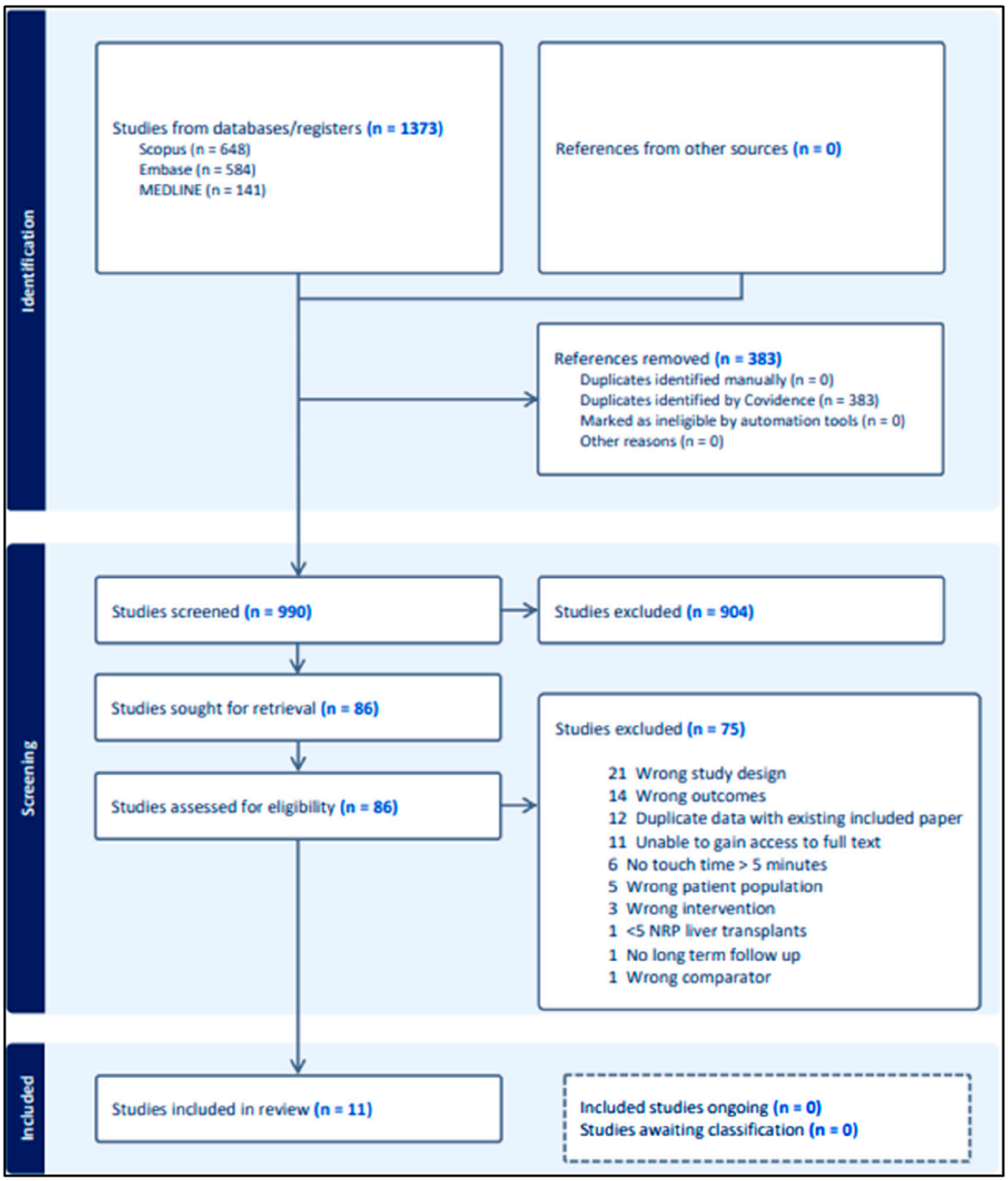


FIGURE 1 | PRISMA chart.

Statistical Analysis

Analysis was divided to make two separate comparisons: NRP vs. non-NRP for cDCD donation, and cDCD NRP vs. DBD donation. Further sub-group analysis was not possible due to study numbers.

Length of stay data underwent logarithmic transformation and subsequent conversion from median and interquartile range into mean and standard deviation as per Wan et al. [31] Patient death and graft loss data were analyzed by pooling hazard ratios (HR). If not reported, Kaplan-Meier plots were measured to estimate patient level survival data, which was then used to estimate hazard ratios by Cox regression. SPSS version 28.0.0.0 (IBM, United States) was used for this calculation.

Meta-analysis was performed using inverse variance random effects models. Risk ratios were calculated for dichotomous variables, mean difference was calculated for length of stay data, and hazard ratios calculated for survival data. For dichotomous variables, any study where zero events occurred in both arms was excluded. However, to ensure robustness of pooled effect, sensitivity analysis was performed by also

TABLE 2 | NRP vs. non-NRP for cDCD study characteristics.

Author	Year	Location	Type	Comparison	NRP livers	Non-NRP livers
Hessheimer et al. [21]	2022	Spain	Multicentre	NRP vs. SCS	545	258
Mohkam et al. [22]	2022	France/Switzerland	Multicentre	NRP vs. NMP	68	34
Gaurav et al. [8]	2022	UK	Single centre	NRP vs. SCS/NMP	69	164
De Goeij et al. [20][a]	2022	Netherlands	Multicentre	NRP ± DHOPE vs. SCS ± DHOPE	20	49
Total					702	505

[a]*Includes 2 uDCD donations.*

TABLE 3 | cDCD with NRP vs. DBD study characteristics.

Author	Year	Location	Type	Comparison	cDCD livers with NRP	DBD livers
Rodriguez et al. [25]	2020	Spain	Single centre	NRP vs. DBD	39	78
Rodríguez-Sanjuán et al. [26]	2019	Spain	Single centre	NRP vs. DBD	11	51
Ruiz et al. [27]	2021	Spain	Single centre	NRP + DHOPE vs. DBD	100	200
Savier et al. [28]	2020	France	Multicentre	NRP vs. DBD	50	100
Viguera et al. [29]	2021	Spain	Multicentre	NRP vs. DBD	144	447
De Goeij et al. [20][a]	2022	Netherlands	Multicentre	NRP ± DHOPE vs. DBD ± DHOPE	20	81
Fernandez-de la Varga et al. [23]	2022	Spain	Single centre	NRP vs. DBD	22	51
Minambres et al. [24]	2019	Spain	Multicentre	NRP Vs. DBD	16	29
Total					402	1,037

[a]*Includes 2 uDCD donations.*

estimating pooled effect size after continuity correction (factor of 0.5) for such studies [32]. The cut-off for statistically significant results and confidence intervals (CI) were defined as $p < 0.05$ and 95% respectively.

Pooled incidence of IC and PNF were estimated using the *metaprop* in Stata version 15.1 for Windows (StataCorp LLC, TX, United States) [33]. A random-effects model was used. As the incidence rates are at or close to zero for many studies, we enabled Freeman-Tukey double arsine transformation and used score confidence intervals for the individual studies. Heterogeneity was assessed using I^2 values.

RESULTS

Table 1 summarises the bias appraisal of each study as per the Newcastle Ottawa Scale. Four of the studies received an overall appraisal of "good," and seven studies received an overall appraisal of "poor." Of these seven studies, five studies received "poor" appraisal because they did not control for confounders between the two groups and hence failed to score points in the comparability domain. Two of the included studies received a "poor" appraisal in any of the other scoring domains.

Table 2 summarises the characteristics of each study included in the NRP vs. non-NRP for cDCD donation analysis. Three of the studies utilized NRP alone, and one study utilized NRP in combination with dual hypothermic oxygenated machine perfusion (D-HOPE) for some of the transplanted livers. The comparator groups are a mix of SCS alone and in combination with machine perfusion. The number of livers transplanted in the NRP and non-NRP groups totalled 702 and 505 respectively.

Table 3 summarises the characteristics of studies included in the comparison of cDCD with NRP vs. DBD donation. Two studies utilized NRP in combination with ex-vivo machine perfusion, whilst six studies utilize NRP alone. The comparator groups all utilized standard DBD techniques, except for one which utilized D-HOPE for some DBD transplants. The number of transplants in the cDCD with NRP and DBD groups totalled 402 and 1,037 respectively.

cDCD NRP vs. Non-NRP

Figure 2 summarises the analysis of IC, PNF, and recipient death for the NRP vs. non-NRP comparison. These demonstrated statistically significant results favouring the NRP group [IC: RR = 0.23, 95% CI (0.11, 0.49), p = 0.0002, PNF: RR = 0.51, 95% CI (0.27, 0.97), p = 0.04, recipient death: HR = 0.5, 95% CI (0.36, 0.69), p < 0.0001]. Overall incidence of IC in the NRP group was 2.6% [95% CI (0.13%–6.9%)], and 13.2% [95% CI (7.3%–21%)] in the non-NRP group. The incidence of PNF was 1.4% [95% CI (0.28%–3.0%)] in the NRP group and 3.5% [95% CI (1.7%–6.0%)] in the non-NRP group. NRP was associated with lower rates of graft loss, HAT, and other biliary complications [Graft loss: HR = 0.44, 95% CI (0.33, 0.58), p < 0.00001, HAT: RR = 0.53, 95% CI (0.31, 0.92), p = 0.02, other biliary complications: RR = 0.61, 95% CI (0.44, 0.84), p = 0.003]. There was no difference in the rate of EAD [RR = 0.78, 95% CI (0.51, 1.21), p = 0.27]. The discard rate for the NRP and non-NRP groups was 30% and 31% respectively.

cDCD With NRP vs. DBD

Figure 3 Summarises the analysis of IC, PNF and recipient death for the NRP vs. DBD comparison. These demonstrated no difference between the groups [IC: RR = 1.73, 95% CI (0.48,

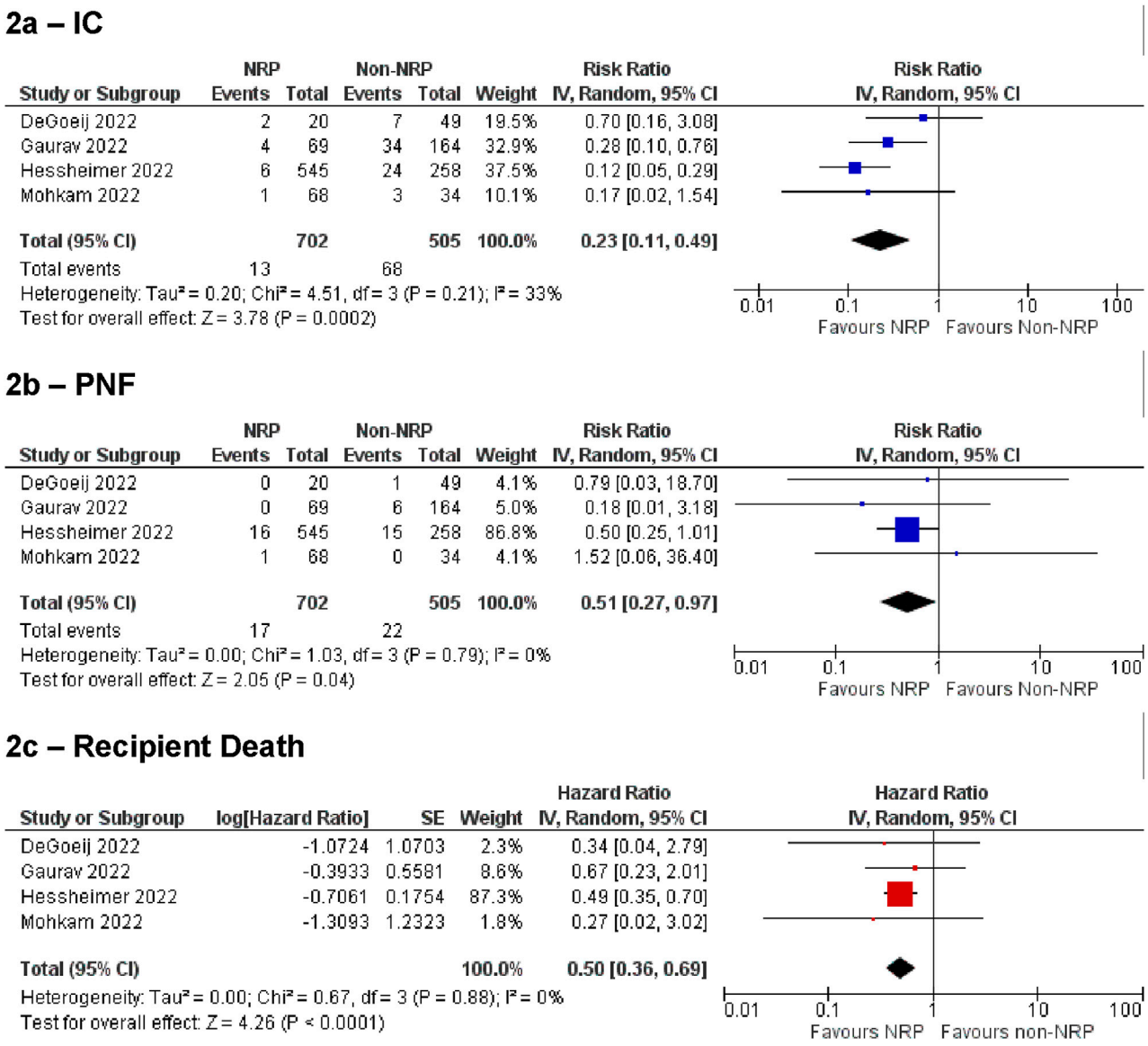


FIGURE 2 | Summary of primary outcomes for NRP vs. non-NRP for cDCD. **(A)** ischemic cholangiopathy, **(B)** primary non-function, **(C)** recipient death.

6.24), p = 0.4, PNF: RR = 2.0, 95% CI (0.48, 8.37), p = 0.34, recipient death: HR = 0.74, 95% CI (0.39, 1.41), p = 0.36]. Sensitivity analysis by including studies with zero events on both arms (by continuity correction) confirmed these findings to be robust [IC: 1.93, 95% CI (0.66 to 5.65), p = 0.23; PNF: 2.16, 95% CI (0.62–7.52)]. The estimated overall incidence of IC was 0.13% [95% CI (0.0%–1.9%)] in the cDCD with NRP group, and 0.37% [95% CI (0.0%–2.0%)] in the DBD group. The incidence of PNF was 1.1% [95% CI (0.0%–6.2%)] in the cDCD with NRP group, and 0.69% [95% CI (0.02%–1.9%)] in the DBD group.

Statistical analysis of secondary outcomes demonstrated no difference between the two groups for any outcome [graft loss: HR = 0.75, 95% CI (0.47, 1.20), p = 0.23, HAT: RR = 0.64, 95% CI (0.24, 1.73), p = 0.38, EAD: RR = 0.94, 95% CI (0.64, 1.39), p = 0.77, other biliary complications: RR = 0.99, 95% CI (0.64, 1.53), p = 0.96, ICU stay length: MD = −0.03, 95% CI (−0.08, 0.03), p = 0.34, hospital stay length: MD = −0.07, 95% CI (−0.15, 0.02), p = 0.12].

DISCUSSION

The outcomes examined in this systematic review were chosen because of their clinical importance and their past association of these outcomes with DCD liver transplantation. In the comparison of the NRP and non-NRP groups for cDCD livers, NRP is unanimously associated with lower rates of IC, PNF, HAT, and other biliary complications in conjunction with

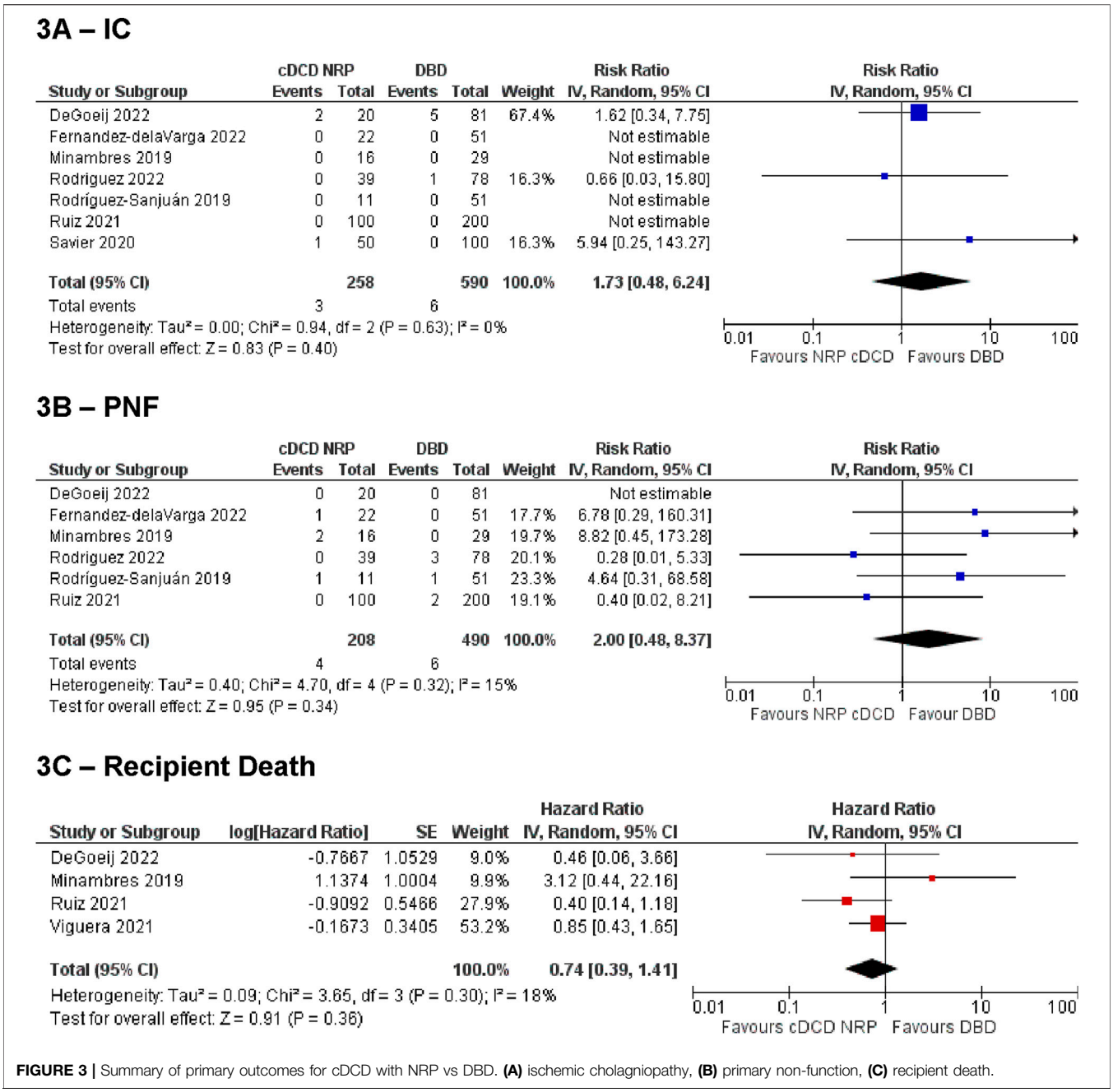


FIGURE 3 | Summary of primary outcomes for cDCD with NRP vs DBD. **(A)** ischemic cholangiopathy, **(B)** primary non-function, **(C)** recipient death.

lower rates of recipient death and graft loss. The discard rate in each group was comparable, suggesting that the improved outcomes seen with NRP were not due to selection bias in the discard of organs in the NRP group. The analysis of utilization is potentially confounded by the fact that the comparison is performed after a decision to proceed to donation is already made. NRP utilization is often associated with more liberal organ acceptance criteria in terms of donor age, agonal time, and graft steatosis. Grafts of poorer quality that would not commonly be utilized as part of the non-NRP denominator are compared with some livers that were considered appropriate for procurement only because NRP was available. Hence, NRP is associated with a greater overall utilization, but a similar non-utilization rate from the point of intended recovery. This parameter is not captured in the reported data, but the advantage may be inferred. Ideally, further meta-analysis on donor and recipient factors such as degree of steatosis, MELD scores, BMI, and specific NRP protocols would have been included; however, the included articles did not consistently provide this data, and the articles that did were notably heterogenous with varied graft management options in addition to NRP.

Although the heterogeneity of interventions of the included studies is recognized, we considered that this was outweighed by the benefit of such analysis in a practical sense; cDCD NRP vs. non-NRP liver transplantation studies with strictly no additional perfusion technologies are limited and are unlikely to become available in the future as it would be unethical to withhold treatment from these organs when global standards permit their use and the emerging evidence supports their effectiveness. In the clinical setting, it is also more practical to compare cDCD NRP vs. non-NRP livers that may have been treated with other perfusion technologies as this is more reflective of current practice.

In the comparison of NRP cDCD vs. DBD, NRP cDCD livers perform equally well as DBD livers, exhibiting comparable complication and survival rates. A previous systematic review by De Beule *et al.* reported an overview of NRP for liver and kidney transplantation, including cDCD transplantation [34]. That review compared outcomes of NRP against SCS for cDCD livers. Although the authors reported lower rates of IC, EAD, biliary strictures (of any type), and anastomotic biliary strictures, there was no difference in PNF, 1 year patient survival or HAT. Additionally, no comparison could be made for cDCD NRP vs. DBD livers at that time. The conclusion made by the authors was that NRP could possibly provide benefits for reducing biliary complications for cDCD donation. In our review, the rate of discard with NRP DCD was comparable to DCD liver programs around the world. Haque *et al.* describes a 30% discard rate for all DCD liver donation within the US, and Oniscu *et al.* describes a 29.6% discard rate for non-NRP DCD donation in the UK. [17, 35]. Oniscu *et al.* did however describe a lower discard rate of 18.3% for NRP DCD donation in the UK. The same study also reported a higher overall utilization rate when using NRP for liver grafts. This was attributed to two main factors; the ability for functional evaluation of organs *in situ*, and a higher acceptance rate of the initial graft offer when NRP is known to be utilized. This review has focussed on liver transplantation, however, previous analyses have shown improved post-transplant outcomes and organ utilization for other abdominal organs, such as the kidneys, when employing NRP compared to standard DCD techniques [36, 37]. All studies included in our cDCD NRP vs. non-NRP analysis reported liver transplant outcomes only, and no studies were found meeting the inclusion criteria which reported multiple organ donation outcomes. NRP circuits may be configured in a manner that allows simultaneous perfusion to multiple other abdominal and thoracic organs, allowing the potential benefits of NRP to be extended to other transplanted grafts. Further studies looking at the outcomes of multiple grafts from the same NRP donor may be beneficial.

A notable limitation of our study is that all included studies were observational, as no randomised controlled trials satisfied the inclusion criteria. The need for randomised trials to provide high quality evidence of the benefit of NRP has been previously outlined, although conducting such studies is now arguably unethical in the context of the results demonstrated above [38]. Additionally, more than half of the included studies are classified as "poor" according to the Newcastle Ottawa Scale due to the nature of the scoring system of the scale. Any paper that does not score in the comparability domain receives an automatic "poor" designation, although they may score well in all other respects. Importantly, the majority did specify that there was no statistically significant difference between the donor and recipient groups in a variety of metrics, however this demonstration is not considered sufficient to score points for comparability on the Newcastle Ottawa Scale. Another limitation is that although this review examines the use of NRP compared to non-NRP, we were unable to make any direct comparison of NRP vs. SCS, HOPE, or NMP. Hence, the outcome may be slightly confounded by livers receiving a combination of NRP, HOPE, and NMP in addition to NRP. The number of studies currently published is insufficient to facilitate direct comparisons between each technology combination. Ideally, the effect of NRP on recipient outcomes would be isolated from the effects of other ex-vivo perfusion technologies, however this is not currently possible with the available data. The control groups in each comparison (non-NRP cDCD and DBD groups) also contain liver grafts treated with HOPE or NMP in addition to standard SCS. The inclusion of these technologies in the control groups may lead to an underestimate of NRP effect. One included study contained 2 uDCD livers which could not be separated from our cDCD with NRP vs. DBD analysis. The decision was made to include this study even with the increased risk of bias, as the effect of only 2 livers in the sample size was highly unlikely to alter the results in any meaningful way and their inclusion allowed for the inclusion of 49 additional cDCD livers to increase the power of our analysis. As uDCD livers are of poorer quality, the inclusion of these livers would more likely disadvantage the NRP analysis than advantage it, making the positive effect of NRP results even more persuasive.

The most important future analysis should focus on the effect of NRP to increase utilization from the point of organ offer due to the more liberal acceptance criteria (principally on account of acceptance of more advanced donor age, longer agonal times, and higher rates of steatosis). Direct comparisons of NRP with ex-vivo machine perfusion may also be useful. It is certainly possible that some combination of NRP, HOPE, and NMP will provide the optimal combination of maximal utilization and acceptable recipient outcomes, but this will be challenging to investigate robustly on account of the possible number of combinations [13]. It should be noted that a randomised controlled trial examining NMP vs. SCS for liver transplantation demonstrated no change in biliary complication rate, graft survival, or patient survival rates whilst increasing the number of transplantable grafts by 20% [39].

In summary, this review demonstrates that the use of NRP in cDCD liver transplantation is associated with lower rates of many significant post operative complications as well as improved graft and patient survival. NRP cDCD outcomes were comparable to DBD outcomes. The use of NRP appears to also increase the utilization of cDCD livers for transplantation, although non-utilization rates of recovered DCD livers are similar between NRP and standard techniques following donation. NRP has the potential to allow for the expansion of the donor pool and improvement of outcomes so reducing the mortality for those patients needing liver transplantation.

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

All authors participated in the review of the manuscript. CM and CF conducted the review, participated in the statistical analysis and wrote the manuscript. AH and HP supervised the project and edited the manuscript. TP conducted the statistical analysis, and JL edited 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.2024.13263/full#supplementary-material

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SYSTEMATIC REVIEW AND META-ANALYSIS
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Prophylactic Peri-Nephric Drain Placement in Renal Transplant Surgery: A Systematic Review and Meta-Analysis

Adil S. Lakha[1,2*†‡], *Shahzaib Ahmed*[3], *James Hunter*[2,4] *and John O'Callaghan*[4,5]

[1]Oxford University Hospitals National Health Service (NHS) Foundation Trust, Oxford, United Kingdom, [2]Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom, [3]Bristol Royal Infirmary, Bristol, United Kingdom, [4]University Hospitals Coventry and Warwickshire, Coventry, United Kingdom, [5]Centre for Evidence in Transplantation, University of Oxford, Oxford, United Kingdom

Renal transplantation is common worldwide, with >25,000 procedures performed in 2022. Usage of prophylactic perinephric drains is variable in renal transplantation; drains are associated with risks, and there is a lack of consensus regarding benefit of routine drain placement in these patients. This meta-analysis assessed whether prophylactic drainage reduced need for reintervention postoperatively. This systematic review and meta-analysis was carried out using the Preferred Reporting Items in Systematic Reviews and Meta-Analysis, and prospectively registered on PROSPERO. Summary statistics for outcomes of interest underwent meta-analyses to a confidence interval (CI) of 95% and are presented as Forest Plots for Odds Ratio (OR). A systematic literature search in June 2023 revealed 1,540 unique articles across four databases. Of these, four retrospective cohort studies were selected. Meta-analysis of three studies showed no significant reduction in reintervention rate with pre-emptive drain placement, OR = 0.59 (95% CI: 0.16–2.23), $p = 0.44$. Meta-analysis did not show a significant reduction in perinephric collections with prophylactic drain insertion OR = 0.55 (95% CI: 0.13–2.37), $p = 0.42$. Finally, there is not good evidence that drain placement reduces superficial wound complications or improves 12-month graft survival. Further work is needed, including well-designed, prospective studies to assess the risks and benefits of drain placement in these patients.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023422685, Identifier PROSPERO CRD42021255795.

Keywords: drain, renal transplant, prophylactic drainage, collection, perinephric drain

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***Correspondence**
Adil S. Lakha,
asl48@cantab.ac.uk

†ORCID:
Adil S. Lakha
orcid.org/0000-0002-9525-127X

‡Present address:
Adil S. Lakha,
Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom

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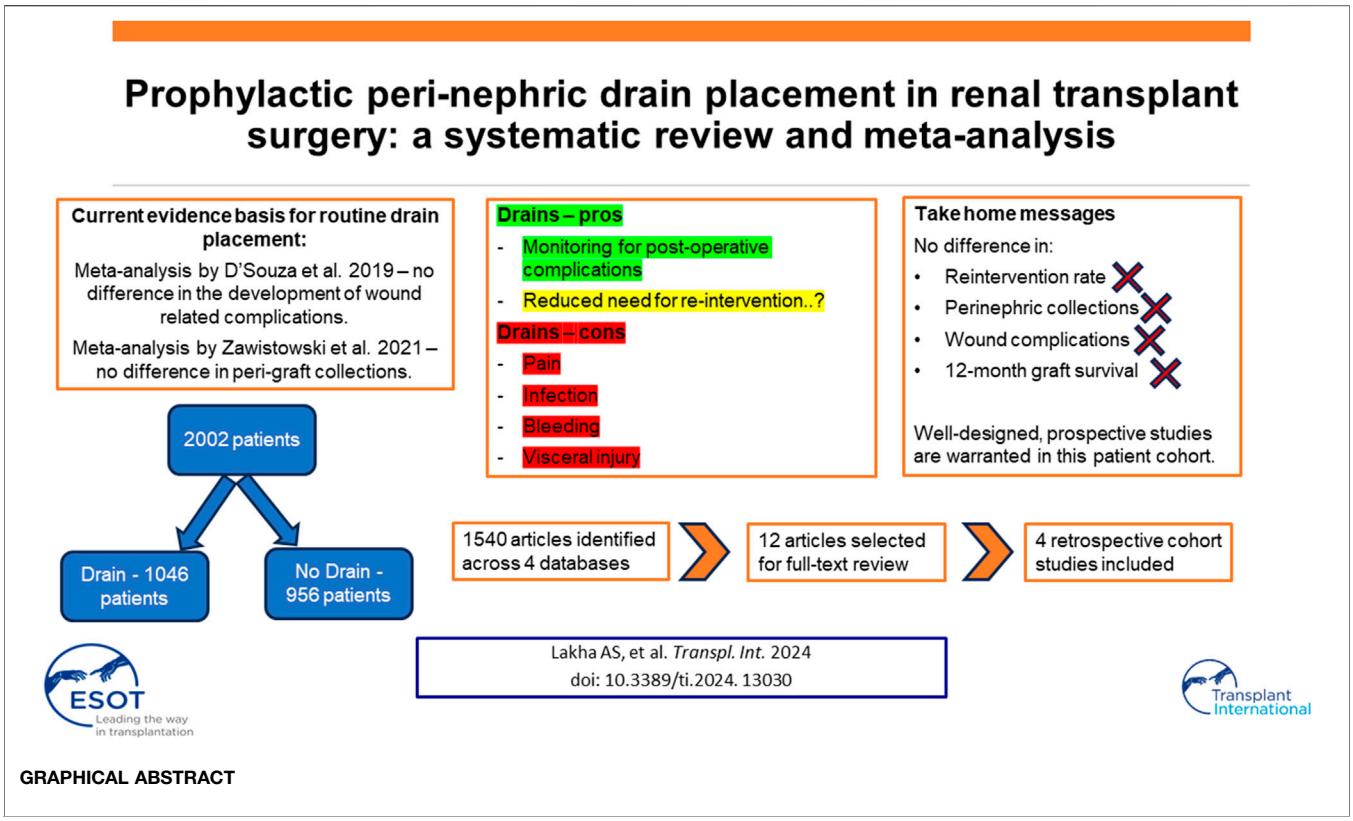
INTRODUCTION

Usage of prophylactic perinephric drains is variable in renal transplantation, and there is a lack of consensus as to the relative benefit of placing an abdominal drain intraoperatively in this patient cohort [1]. Drainage of post-operative fluid collections and prevention of the development of perinephric collections are the main indications for placing such drains in this cohort of immunosuppressed surgical patients [2]. However, there is debate over the necessity of these drains, and whether they may introduce



GRAPHICAL ABSTRACT

more risks. For example, placement of a drain can result in several complications, including but not limited to post-operative pain, visceral injury, surgical site infection, bleeding or malposition [3, 4]. Prospective studies in general and colorectal surgery have shown a higher surgical site infection risk when drains are inserted intraoperatively [4]. Furthermore, meta-analysis of randomised trials as well as prospective interventional studies suggest drain insertion results in more pain for patients who received intraoperative drain placement [5, 6].

The pathological basis for the development of collections is multifactorial, however immunosuppression, increasing age, obesity, smoking, difficulty of the operation such as bleeding or damage to surrounding structures such as lymphatic tissue in the recipient's iliac lymph trunk are all thought to contribute to fluid collections post-operatively [7, 8]. Placing a drain during the index transplantation operation therefore is thought to serve as prophylaxis against these relatively common surgical complications. However, these complications are often sub-clinical, may occur after a surgical drain is removed, and not all post-operative collections require drainage. In addition, intraoperative haemostatic techniques may also be utilised to minimise fluid effusion post renal transplantation [9].

This systematic review aims to investigate the impact of prophylactic perinephric drains placed during renal transplantation surgery on immediate and short-term post-operative surgical complication rates. In addition, the broader impact on graft function will be assessed, as well as relevant important outcomes such as deep wound complications, and surgical site infection.

METHODS

This study was carried out following the Preferred Reporting Items in Systematic Reviews and Meta-Analysis (PRISMA) [10]. The protocol was prospectively registered on the PROSPERO system from the University of York (CRD42021255795) on 10th May 2023 [11].

Literature Search

A literature search was carried out on 1st June 2023, using a combination of Medical Subject Heading (MeSH) terms, free text and keywords to limit the search to renal transplantation operations and drain placement. Complete search strategy is available in **Appendix 1**. Cochrane protocols, trials and reviews, Transplant Library, Embase, and Medline were all searched on the same date. Each article was assessed using the inclusion criteria outlined below, and any disagreement regarding the eligibility of an article was discussed. Agreement was reached by consensus with a third, and independent, reviewer.

Inclusion and Exclusion Criteria

There were no language or time-period restrictions. Abstract-only and conference presentation publications were excluded, as were studies assessing paediatric populations and combined transplantation procedures such as simultaneous pancreas-kidney. We included papers which compared outcomes of patients who had a perinephric drain placed intraoperatively during renal transplantation. Patients with drains placed

superficial to the musculofascial layer (superficial drain), or patients with drains inserted percutaneously, were excluded.

Quality Assessment

Methodological quality of included studies was assessed using the Newcastle-Ottawa Score (NOS) tool, a validated scale for assessing the quality of cohort studies [12]. Two independent reviewers performed quality assessment with discrepancies discussed.

Data Extraction

Data were extracted using a standardised and predesigned data collection form. Data were extracted, where available, on study design characteristics (type of study design, follow-up length), donor kidney type (live or deceased), and outcomes of interest. Post-operative reintervention rate of any kind (either percutaneous image guided drainage, or return to theatre) was the primary outcome for comparison between drain and drain-free patient groups. Additional outcomes such as superficial and deep wound complications, graft survival at 12 months (where available) and delayed graft function were also collected.

Data Synthesis

Data analyses were performed and figures were extracted from Microsoft Excel and the statistical package RevMan Version 5.8.0, The Cochrane Collaboration, 2020. Heterogeneity was calculated for the meta-analyses using the I^2 statistic, with the Mantel-Haenszel method and random-effects model utilised due to heterogeneity between the studies.

Summary statistics for outcomes of interest underwent meta-analyses to a confidence interval (CI) of 95% and are presented as Forest Plots for Odds Ratio (OR).

RESULTS

Across all four databases, 1,627 papers were identified, of which 87 were identified as duplicates and discarded. Our search therefore revealed 1,540 unique titles and abstracts across all four databases. Of these, four retrospective cohort studies were selected according to the methodology outlined above, and these are presented in **Table 1**. **Figure 1** outlines a PRISMA flow diagram in selecting articles for inclusion. Across the four studies selected, a total of 2,002 patients' outcomes data were extracted for analysis. 1,046 had an intraoperative drain placed, 956 did not. Drains were removed when the output recorded less than <50 mL/24 h consistently across three of the studies, and was not reported in the remaining study. Only Farag et al. reported the type of drain used (a Jackson-Pratt suction drain). Furthermore, three out of the four studies reported complete data on type of donor (live vs. deceased), **Table 1**.

Quality Assessment

Methodological quality of included studies was assessed using the Newcastle-Ottawa Score (NOS), and **Table 2** shows all included studies and their respective quality assessments. All studies were rated as "good quality" when NOS scores were converted to Agency for Healthcare Research and Quality (AHRQ) descriptors according to the following threshold: three or four stars in the selection domain, and one or two stars in the comparability domain, and two or three stars in the outcome/exposure domain.

Reintervention Rate

We performed a meta-analysis to ascertain whether intraoperative perinephric drain placement was associated with a reduced need for either image-guided percutaneous drainage or return to theatre post renal transplantation. Meta-analysis of three studies showed no evidence of a significant reduction in reintervention rate with drain placement, OR = 0.59 (95% CI: 0.16–2.23), $p = 0.44$, **Figure 2**. The study from Sidebottom et al. did not report reintervention rate post renal transplant, therefore was not included in the meta-analysis.

Deep Wound Complications

Three studies reported figures for deep wound complications and were therefore included for meta-analysis. Meta-analysis did not show a significant reduction in perinephric collections with prophylactic drain insertion OR = 0.55 (95% CI: 0.13–2.37) $p = 0.42$, **Figure 3**. One study could not be included in meta-analysis as they only reported an odds ratio (rather than raw patient-level data) for reduced risk, favouring drain insertion due to lower rates of peri-graft collections OR = 0.62 (95% CI: 0.43–0.88), $p = 0.01$.

Superficial Wound Complications

Only two studies reported the rates of superficial wound complications with a standardised definition, with superficial complications inclusive of wound evisceration, infection and dehiscence. Derweesh et al. reported no significant difference between the percentage of wound complications in the drain (13.6%) and no drain group (22.6%), $p = 0.13$. Farag et al. reported superficial wound complications (inclusive of subcutaneous seroma or wound dehiscence), with no statistically significant difference in the incidence of wound complications between the drain and drain-free groups ($p = 0.35$).

Graft Survival at 12 months

Finally, we intended to assess graft survival at 12 months and whether or not there was any difference between drain and drain-free cohorts. Sidebottom et al. reported a 30 days follow up, and Cimen et al. reported 1 month longest follow up data. Farag et al. reported 98.5% and 96.4% graft survival rates in drain-free and drainage groups, respectively ($p = 0.20$). Similarly, Derweesh et al. reported graft survival rates of 83% and 88% in drain-free and drainage groups, respectively ($p = 0.43$).

DISCUSSION

This review found no overall benefit when placing perinephric drains prophylactically during renal transplantation, including when assessing need for re-intervention post-operatively. Similarly, this review found no overall benefit of prophylactic drainage on reducing superficial or deep wound complications.

TABLE 1 | Summary of studies included, and overall recommendations regarding prophylactic drainage.

Study	Methodology	Drain insertion, n	No drain insertion, n	Drain insertion donor type		No drain insertion donor type		Overall recommendation
				Live donor (%)	Deceased donor (%)	Live donor (%)	Deceased donor (%)	
Derweesh et al.	Single centre, retrospective cohort study	81	84	56	44	64	36	Use drain in patients receiving sirolimus
Cimen et al.	Single centre, retrospective cohort study	374	283	38	62	39	61	No benefit with drain insertion
Farag et al.	Single centre, retrospective cohort study	112	388	13	87	42	58	No benefit with drain insertion
Sidebottom et al.	Single centre, retrospective cohort study	479	201	—	—	—	—	No benefit with drain insertion

Finally, there is not good evidence that perinephric drain placement is associated with improved graft survival outcomes at 12 months post renal transplantation.

Current literature demonstrates the range of complications associated with prophylactic drain insertion. One prospective study suggests that surgical site infection risk is increased when drains are inserted during general surgery procedures (OR 2.41, 95% CI 1.32–4.30, $p = 0.004$), however less of an effect is seen in vascular and orthopaedic surgery [4]. Furthermore, a systematic review and meta-analysis of twelve randomised controlled trials involving 1763 patients showed patients who underwent drainage had significantly higher pain scores as measured by the visual analogue scale (MD 10.08, 95% CI 5.24 to 14.92; $p < 0.00001$) [5]. There are limited studies reporting the incidence of bleeding and iatrogenic visceral injury secondary to perinephric drain placement. In one case series of deep pelvic collection drainage, a 2% haemorrhage rate was reported [16]. Fluid collections within the liver parenchyma may be amenable to percutaneous drainage, however this carries a reported 4% risk of major complications such as hepatocolic fistula creation, biliary peritonitis, and arterioportal fistula formation [17–19]. For retroperitoneal perinephric drains, a treatment failure rate exceeding 30% has been reported, often due to drain malposition [17].

Early post-operative collections such as seromas and haematomas occur post-transplant but the majority are discovered incidentally and are usually managed conservatively. The incidence of post operative surgical site haemorrhage detected by imaging and associated with a concurrent serum haemoglobin drop of more than 20 g/L over a 24 h period is relatively low (4.9%), with 90% of cases occurring within 1 day of implantation [20]. Collections more likely to require intervention such as urinomas, abscesses and lymphoceles, typically present later in the post-operative course, and the association with drain insertion is unclear. Lymphoceles in particular are common post renal transplant, with an incidence of 0.6%–51% reported in the literature, and 6.4% according to one recent retrospective study [21]. Urine leak has a reported incidence of 0.6%–6% and generally appears in the early post-transplant period [22, 23].

There have been two similar reviews in this area published previously. In 2019, D'Souza et al. showed that drain placement is associated with a higher incidence of peri-transplant fluid collections (RR 0.62; 95% confidence interval, 0.42–0.90), however no significant difference in the development of wound related complications [24]. A later review by Zawistowski et al. provided an update with the inclusion of a 2021 retrospective single-centre cohort study by Farag et al. The primary end-point in the Zawistowski meta-analysis was also perigraft collections [1]. No significant difference was seen between drain-free and drainage groups (pooled unadjusted OR = 0.77, 95% CI: 0.28–2.17). Similarly, there was no statistically significant difference in the secondary end points of surgical site infection, lymphocele, haematoma, and wound dehiscence between patients who did or did not receive prophylactic drainage. This review provides the most recent and extensive review of the current literature assessing the role of prophylactic perinephric drainage on short and long term clinically significant complications post kidney transplant. While previous reviews focused on the incidence of common post-operative complications, these are not necessarily clinically significant, as not all collections require drainage. By focusing our primary outcome on reintervention rate for post-operative collections, we aimed to better demonstrate the clinical significance of prophylactic drainage on renal transplant patients. More generally, the search criteria were robust and consistent across a range of generic and transplant-specific databases, with no language or time-period restrictions applied during article selection. All studies were rated as "good quality" when rated for quality via the Newcastle-Ottawa Score.

However, this review and analysis has several limitations. Given the retrospective nature of the studies identified in the literature, it is not possible to confidently demonstrate causality between our exposure (drain placement) and outcome

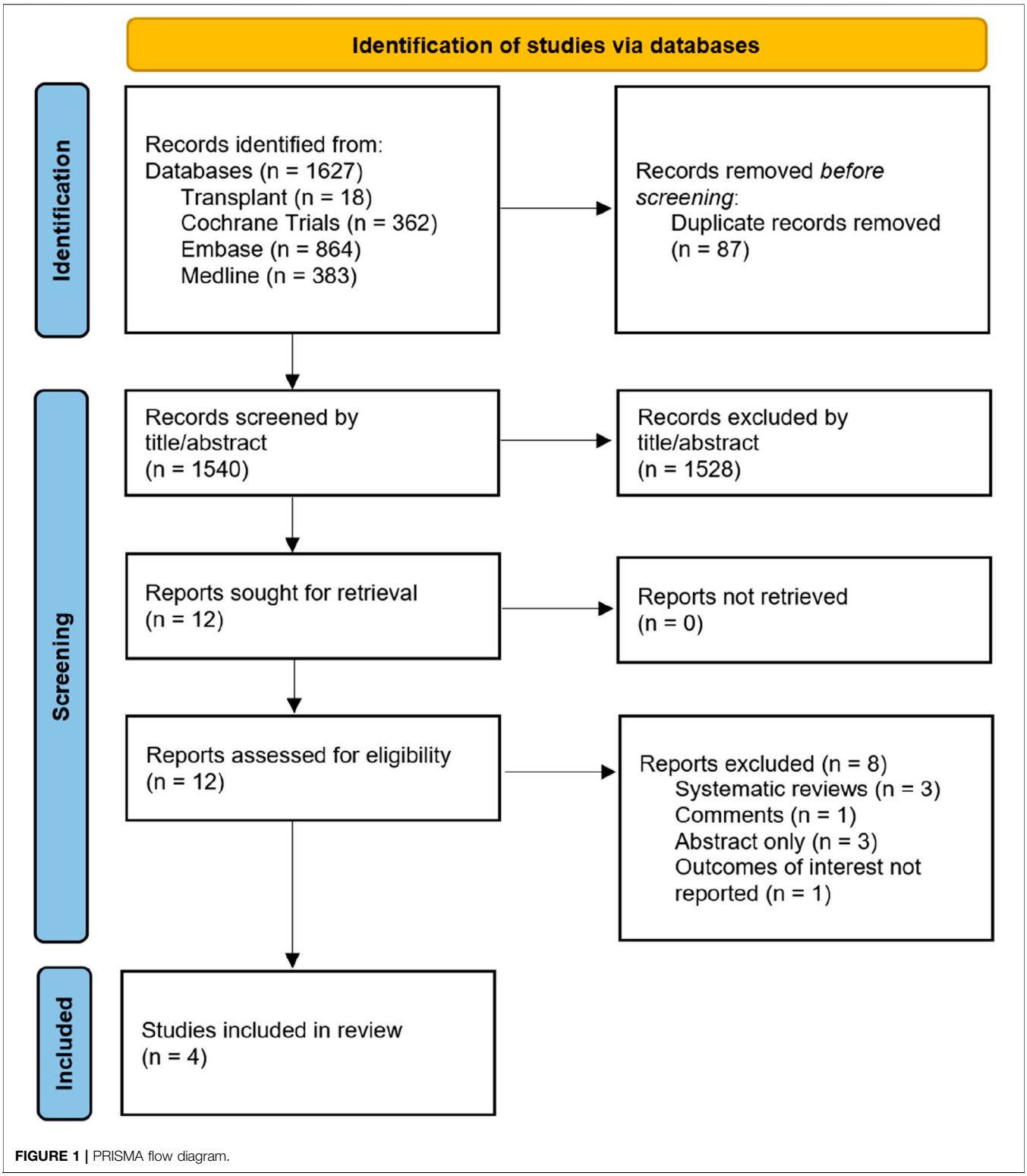


FIGURE 1 | PRISMA flow diagram.

(reintervention rate) of interest. The control groups included in the studies (no drain placement) would likely also be affected by selection bias. For instance, the Derweesh et al. study shows significant differences between the groups with respect to patient body mass index (BMI) and immunosuppression use (specifically sirolimus). These are both factors which are known to affect wound healing, surgical site infection, and wound complications specifically in renal transplantation, therefore the results cannot

TABLE 2 | Quality assessments using the NOS.

Study	Selcection of cohorts				Comparability	Outcome		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts
Derweesh et al. 2008 [2]	☆	☆	☆	☆	☆	☆	☆	☆
Sidebottom et al. 2014 [13]	☆	☆	☆	☆	☆	☆	—	☆
Cimen et al. 2016 [14]	☆	☆	☆	☆	☆☆	☆	—	☆
Farag et al. 2021 [15]	☆	—	☆	☆	☆	☆	☆	☆

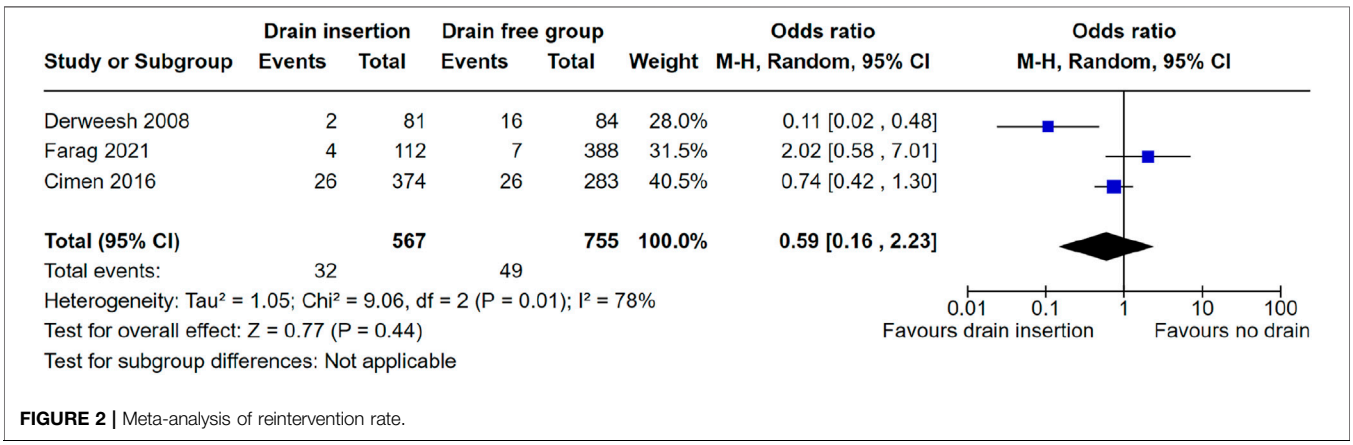


FIGURE 2 | Meta-analysis of reintervention rate.

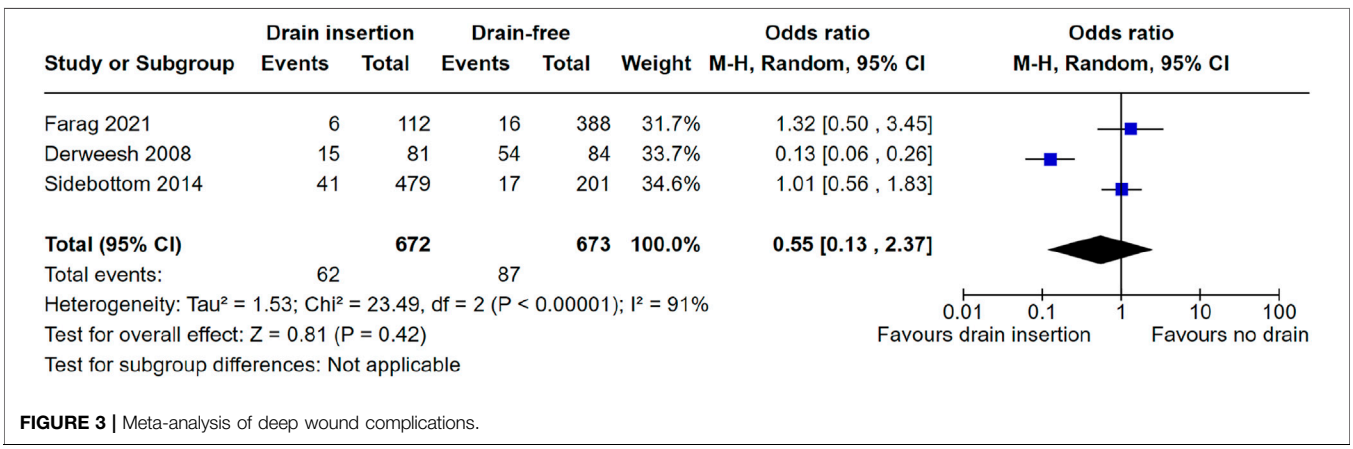


FIGURE 3 | Meta-analysis of deep wound complications.

reliably be interpreted due to the selection bias present in the cohorts [25, 26]. Owing to the small number of studies included in this analysis (less than 10), publication bias could not be accurately assessed using Egger's regression test for funnel plot asymmetry [27]. We found significant heterogeneity in the reporting of outcomes, and so meta-analyses were performed where specific outcomes were published. We also intended to record outcomes such as post-operative pain around the wound or drain site, opiate usage, length of hospital stay, and overall mortality, however these data were not available in the published literature in relation to drain use. Analysis of these outcomes would allow us to more effectively examine the complications associated with drain insertion, however due to the lack of availability we were not able to do so. Patient-reported outcomes and measures following drain insertion in particular would be an important aspect of drain insertion to assess and

report upon, and one which we advocate should be investigated in future prospective studies. Regarding **Figure 3**, we intended to include Cimen et al. results in our meta-analysis, however were unable to contact the authors to obtain raw data to include in the meta-analysis. This represents a drawback to our review because Cimen et al. found lower odds of peri-graft collection, thus favouring drain insertion (p = 0.01). Finally, there was heterogeneity in the definitions of parameters such as "wound complications," whereby authors divided into either clinically significant vs. not significant, or superficial vs. deep, or specifically looking at individual complications such as surgical site infection, wound dehiscence, or superficial wound collection. We therefore only included data from studies where we were confident that the data reflected the specific outcomes of interest described above.

One of the key rationales for intraoperative drain placement is pre-emptive control of post-operative collections such as lymphocele, seroma, haematoma, urinoma or infected tissue fluid. Ongoing monitoring for bleeding and infective collection around the graft site are the main indication for routine placement of a perinephric drain, however placement of the drain itself is associated with risks. In a meta-analysis of 28 randomised trials involving 3,659 patients, Gurusamy et al. showed that a drain-free approach to open cholecystectomy was associated with significantly lower wound infection rates, and no difference in the incidence of post-operative abdominal collection [28]. Partly as a result of this, drains are now no longer placed for uncomplicated open cholecystectomy operations. Furthermore, a single-centre experience of combined liver-kidney transplants showed no difference in the incidence of superficial/deep wound complications, collection size, intervention rate, graft failure, and overall patient survival between drainage and non-drain patient cohorts [29].

Better access to cross-sectional imaging provides a non-invasive tool for surgeons to utilise in the investigation for post-operative collections. Ultrasound provides accurate assessment of vascular flow to the graft, and can assess the presence of perinephric fluid collection and associated graft parenchymal compression [30]. Imaging is not always performed routinely, however in association with symptoms such as fever or pain, signs of graft failure such as high serum creatinine, ipsilateral leg swelling or hydronephrosis, drainage of these collections is indicated [31].

Current practice also shows a variety approaches to prophylactic drainage. In 2020, a survey of 43 renal transplant surgeons across Australia and New Zealand revealed 61% of surgeons practising routine drain insertion, while 21% rarely inserted drains [32]. A more recent (2023) survey of UK-based transplant surgeon practices suggests over two-thirds of respondents routinely insert one drain, while 8.3% indicated insertion of two or more drains on a routine, prophylactic basis. Only one-fifth of surgeons insert drains selectively as reported in this study [33]. This suggests the need for a paradigm shift in how prophylactic drainage in renal transplantation is viewed, especially in the absence of overwhelming evidence supporting its impact on favourable post-operative outcomes.

Given the lack of clear benefit of placing perinephric drains intraoperatively during renal transplantation, negative impact on patient experience, and the potential risks, we advocate for a an approach whereby drains are only placed for specific indications on a case by case basis. Prospective data is needed to support this position, and trial-level evidence is warranted to support or discourage routine perinephric drainage.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

AL: first author, study design, data collection, data analysis, manuscript write up. SA: study design, data collection, data analysis, manuscript write up. JH: study design, data analysis, manuscript write up. JO'C: lead investigator, study design, data collections, data analysis, overall responsibility for the study. 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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APPENDIX 1

Transplant Library Search URL: https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=3TvHv11Dt4cw1NlxqWFB6MvMmZDjDjslUOaG2iETazua2DxHJlBL1wKyGfIVYFHQn.

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ORIGINAL RESEARCH
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The Impact of Early Brain-Dead Donor Detection in the Emergency Department on the Organ Donation Process in Iran

*Arman Hasanzade[1], Seyed Mohammad Reza Nejatollahi[2], Mojtaba Mokhber Dezfouli[1], Mahdieh Hazrati[3], Soheil Sheikholeslami[3], Masoud Imani[4], Bardia Mohseni[5] and Fariba Ghorbani[5]**

[1]Lung Transplantation Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [2]Hepato-Pancreato-Biliary and Transplant Surgery, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3]Organ Transplantation and Donation Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [4]Department of Biostatistics, School of Public Health, Iran University of Medical Sciences, Tehran, Iran, [5]Tracheal Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Alborz, Iran

We aimed to assess the impact of hospital characteristics on the outcomes of detected possible brain-dead donors, in our organ procurement network in Iran. Data was collected through twice-daily calls with 57 hospitals' intensive care units and emergency departments over 1 year. The donation team got involved when there was suspicion of brain death before the hospital officially declared it. The data was categorized by hospital size, presence of neurosurgery/trauma departments, ownership, and referral site. Out of 813 possible donors, 315 were declared brain dead, and 203 were eligible for donation. After conducting family interviews (consent rate: 62.2%), 102 eligible donors became actual donors (conversion rate: 50.2%). While hospital ownership and the presence of trauma/neurosurgery care did not affect donation, early referral from the emergency department had a positive effect. Therefore, we strongly recommend prioritizing possible donor identification in emergency rooms and involving the organ donation team as early as possible. The use of twice-daily calls for donor identification likely contributed to the consistency in donation rates across hospitals, as this approach involves the donation team earlier and mitigates the impact of hospital characteristics. Early detection of possible donors from the emergency department is crucial in improving donation rates.

Keywords: organ donation, emergency department, donation policy, donor identification, brain dead donor, donor detection, conversion rate, hospital characteristics

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***Correspondence**
Fariba Ghorbani,
dr.f.ghorbani@gmail.com

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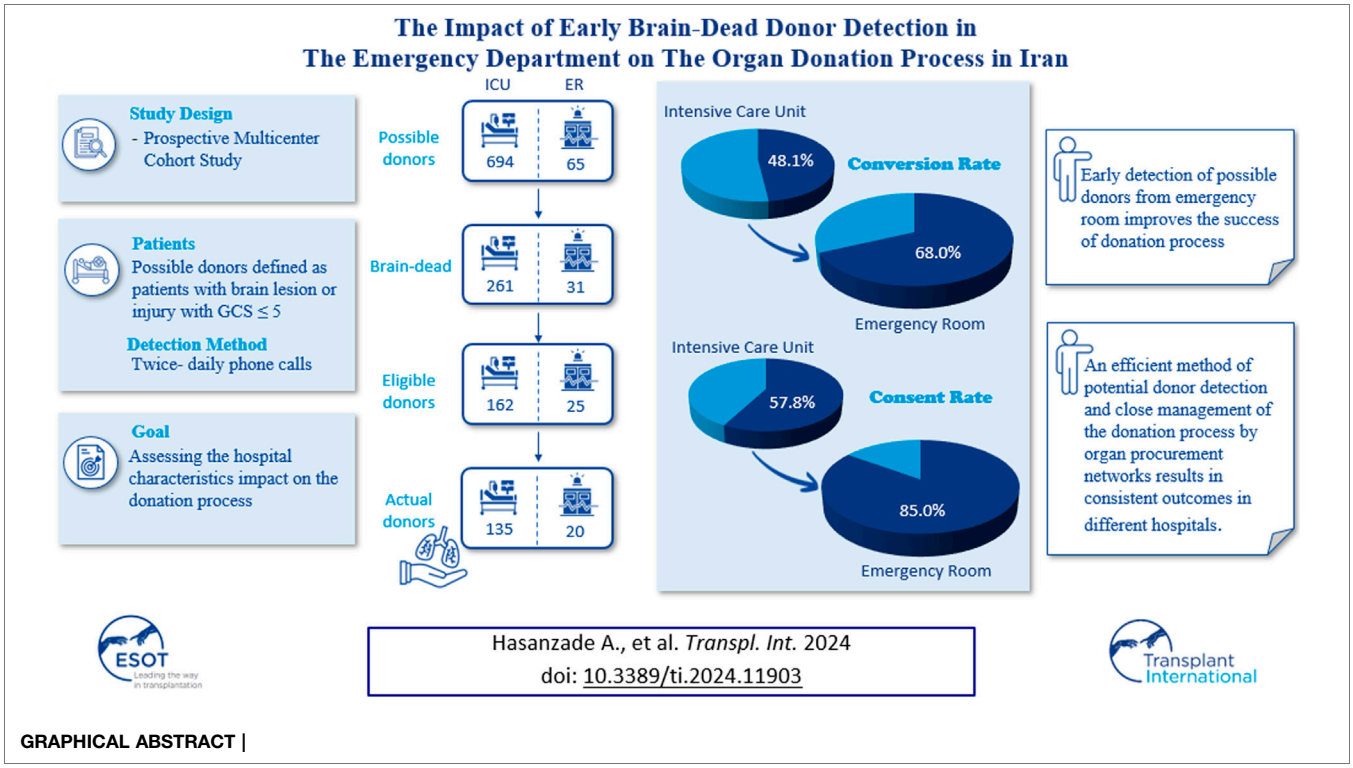
Abbreviations: OPN, Organ Procurement Network; ICU, Intensive Care Unit; ED, Emergency Department; GCS, Glasgow Score; LOC, Loss Of Consciousness; CVA, Cerebrovascular Accident; BDD, Brain Dead Donor; CR, Conversion Rate; EDR, Eligible Death Ratio; OLR, Organ Loss Ratio; CsR, Consent Rate; RR, Risk Ratio; OR, Odds Ratio; CI, Confidence Interval.



GRAPHICAL ABSTRACT |

INTRODUCTION

Organ transplantation is the most effective treatment in end-stage organ diseases [1]. Despite numerous efforts to increase the global donation rates, the gap between the demand and supply of organs is increasing due to the rising incidence of organ failure diseases [2]. The most significant limitation of donation is limited donor pool [3, 4]. While, organs can be recovered from living donors and from donors after circulatory death, still significant proportion of donation are dependent on brain dead donors (BDDs) [1, 2]. In the United States in 2021, there were 30,874 BDDs, which is much higher than the 6,539 living donors [5].

The process of donation from BDD is complex. The first step is identification of the possible donor [1]. A possible donor is a patient with brain lesion or injury, having a Glasgow Score (GCS) less than 5 or 8, according to the policy of jurisdiction [1, 6, 7].

The condition of possible donors may either improve or deteriorate. If in any possible donor, deep coma (GCS = 3) occurs, evaluation of brain death should be considered. A potential donor is a patient, whose condition is suspected to meet the criteria for brain death [7]. The evaluation of brain death involves serial examinations for coma and brainstem reflexes over at least 6 h, as well as ancillary tests [8, 9]. According to the American Academy of Neurology, brain death is an irreversible loss of brainstem and brain functions, confirmed by permanent coma, apnea, and brain stem reflexes absence [9].

However, not all brain-dead potential donors meet the criteria for eligible donor. An eligible donor is a legally declared brain-dead patient who is medically suitable for donation and has no contraindication of donation, with the criteria defined by the related jurisdiction [7]. For example, according to the Organ Procurement and Transplantation Network Policy, these criteria consist of age ≤ 75, weight > 5 kg, and a body mass index ≤ 50 kg/m^2, without any exclusion criteria such as demonstrating any neoplastic or infectious disease risk for the recipient [5]. An Actual donor is an eligible consented donor from whom at least one organ was recovered for donation, or at least a surgical incision was made with the purpose of organ recovery for transplantation [7, 10].

In addition, managing potential donors and family interview are other crucial steps in the organ donation process [8, 10]. Therefore, organ donation is a multi-step process, and loss of brain-dead donors and organs can occur at any stage. Failure to identify potential donors, donor circulatory death, ineffective management and family refusal are the main reasons of failure [3, 8, 10].

In Iran, we have 24 Organ Procurement Units and more than 60 BDD detection units. In 2022, the donation rate was 12.2 PMP and 2,234 organ transplantations were performed from deceased donors, mostly from donation after brain death rather than circulatory death. For instance, out of 1,016 actual deceased donors in 2022, only 3 were from circulatory death [11]. Hence, donation after brain death holds significant importance. Living donation is also common in Iran, and some of these living donations are in exchange for compensation. While this issue is not prohibited by law, deceased donation in exchange for money is illegal, with strict

surveillance. Over the past decade, efforts have been made to decrease living donation and promote donation after brain death. The number of living donors decreased from 1,540 in 2013 to 1,276 in 2022, while deceased donors increased from 670 to 1,016 [11, 12]. Therefore, it is important to investigate the process of donation after brain death and strive for improvement.

Hospitals policies and staff play an important role in this process, and donation rates vary among different hospitals. Some hospital characteristics are associated with higher donation rate such as larger size, being trauma center, having more intensive care unit (ICU) beds, having neurology and neurosurgery department, being an academic hospital, and being located in an urban area [10, 13–15]. Therefore, in this study, we aimed to evaluate our method of early identification of possible donors and the hospitals characteristics that may affect donation process in our Organ Procurement Network (OPN).

MATERIALS AND METHODS

Our OPN Protocol

In Iran, the majority of deceased donations come from brain-dead donors, and the process of donation from BDDs begins with the detection of possible donors. The identification of possible donors within this OPN involves five well-trained and experienced coordinators initiating telephone calls to the ICUs and Emergency Departments (EDs) of the 57 affiliated urban hospitals, conducted twice daily. During these calls, we inquire with the head nurse about any patients with a GCS≤ 5 in their ward. Their responses rely on examinations by the attending physicians, predominantly intensivists, neurologists, internists, or neurosurgeons. Notably, all ICU and ED nurses in these hospitals are trained in the field of brain death and organ donation, having successfully passed a training course examination. Also, their reports undergo random checks through unannounced visits by our supervisors.

Beyond the ED and ICU, hospitals are obligated to report if any possible donor is identified in other hospital wards. In such cases, that specific ward is included in our twice-daily calls to monitor the possible donor. Notably, promptly transferring possible donors to the ICU from various wards and the ED is mandatory to ensure supervision by both intensivists and attending physicians.

Patients reported with GCS ≤ 5 are enrolled in our database. Subsequent calls track these possible donors until one of three events: improvement in the patient's condition and consciousness, circulatory death, or a decrease in the consciousness.

For patients with GCS = 3, a coordination team is sent, as there are no donation professionals at hospitals. A comprehensive neurologic examination, including GCS, brain stem reflexes, and the apnea test, is conducted. These examinations are carried out separately by the neurologist or intensivist (attending physician) of the center and the coordinator. To ensure the irreversibility of the loss of brain stem reflexes, the assessment should be carried out for at least 6 h according to this jurisdiction's law. Brain death is declared only when both attending physician and donation team agree on the diagnosis. Following the brain death, potential brain-dead donors are assessed for donation eligibility criteria. For those eligible donors, the viability of organs, is examined for donation.

Physicians and coordinators jointly attend the family interview when delivering the bad news regarding brain death. However, neither discusses donation. Following this, a period is given to the family to grieve and believe the death. Throughout this time, coordinators engage with the family, fostering a supportive relationship. If the coordinator senses that the family has accepted the death, they cautiously mention the donation. It's notable that the family will approach only if at least one organ of the eligible donor is viable for donation. Throughout this process, donor management takes place in the ICU, supervised by both the hospital intensivist and this OPN.

Eligible donors, whose families have consented for donation, are transferred to the OPN. Following the jurisdiction's protocol outlined by the Ministry of Health, four physicians who are affiliated to Ministry of Health (an internist, a neurosurgeon, a neurologist, and an intensivist) are randomly assigned to the eligible donor to confirm brain death, once more. Additionally, ancillary tests such as two EEG by the interval of 6 h and according to the clinical features, transcranial doppler ultrasound, or four-vessel computed tomography angiography maybe performed. Organ allocation occurs after brain death is confirmed by these physicians, and the allocation process is overseen by the Ministry of Health.

Study Design and Setting

This prospective cohort study was conducted at Masih Daneshvari Organ Procurement Network based in Iran, aimed to evaluate hospital characteristics influencing the donation process. The study received approval from the ethics committee of the National Research Institute of Tuberculosis and Lung Diseases with reference number IR.SBMU.NRITLD.REC.1402.058. Data pertaining to all possible donors registered in the detection database were extracted from January to December 2022. These data encompass hospital and possible donor characteristics, along with the outcome of the donation process for each potential donor.

Independent variables:

1. Hospital characteristics:
   - 29 Private hospitals vs. 27 public hospitals.
   - The number of beds in ICU, neurosurgery and neurology ward, with the range of 14–200.
   - 20 hospitals providing both trauma and neurosurgery care are defined as type I, while 37 hospitals with no trauma and neurosurgery care are considered type II hospitals. It's notable that there is no hospital connected to our OPN that only has one of the mentioned departments.
   - The referral site including ICU or Emergency Department. While possible donors are detected in other hospital wards some instances, due to the variety of these wards and lower number of detected potential donors, we only compared the donation process between ICU and ED.

TABLE 1 | Baseline Characteristics and Outcomes of 813 Possible Donors.

		Mean ± SD
Age (years)		42.3 ± 18.8
Follow-Up Duration (days)		4.53 ± 8.6
		N (%)
Male (%)		539 (66.3)
Cause of LOC	Trauma	153 (18.8)
	Poisoning	134 (16.5)
	Cerebrovascular Accident	244 (30.0)
	Brain Tumor	71 (8.7)
	Hypoxemia	131 (16.1)
	Other	79 (9.7)
Hospital Characteristics	Type I	766 (94.6)
	Type II	44 (5.4)
	Public	714 (88.1)
	Private	96 (11.9)
Detection Site	ICU	694 (85.6)
	ED	65 (8.1)
	Other wards	51 (6.3)
Patient Outcome[b]	Improvement	243 (29.9)
	Circulatory Death	247 (30.4)
	Brain Death	315 (38.7)
Donation Details of Potential Brain-Dead Donors[a]	Eligible Donors	203 (64.4)[†]
	No Viable Organ	35 (11.1)[†]
	Consent to Donate	102 (32.4)[†]
	Actual Donors	102 (32.4)[†]

[a]: *The reported percentages pertain to the entire pool of potential brain-dead donors (315). The key studied ratios providing a better understanding of the donation process are as follows: Conversion Rate: 50.2%, Actual Donor/Brain Dead: 32.4%, Eligible Death Ratio: 36.1%, Organ Loss Ratio: 17.2%, Consent Rate: 62.2%.*

[b]: *Unfortunately, data on the follow-up of 8 possible donors were not recorded.*

2. Possible donor characteristics including age, gender, cause of loss of consciousness (LOC), final outcome and follow-up duration.

The follow-up duration is the time from the detection of possible donors to the occurrence of one of the three outcomes (improvement, circulatory death, or the first diagnosis of brain death). Therefore, the period of monitoring the irreversibility of brain death for 6 h and the donation process, from evaluating eligibility criteria to organ recovery, is not included in this term.

Outcomes:

- The conversion rate was calculated by dividing the number of actual donors by the number of eligible donors.
- The actual Donor to Brain Dead Ratio (AD/BD) is a measure that indicates the proportion of brain-dead potential donors from whom organ donation occurred.
- The Eligible Death Ratio (EDR) was defined as the ratio of the number of eligible donors to the total number of possible donors who have died, whether due to circulatory death or brain death.
- The Organ Loss Ratio (OLR) is a measure that reflects the proportion of eligible donors from whom no suitable organs could be donated.
- The Consent rate considered as the proportion of obtained consents from families interviewed.

Statical Analysis

The data collected in Google Sheets were exported to SPSS version 25 for this study. Descriptive evaluations were presented as mean ± standard deviation (SD) for quantitative variables and frequency (percentage) for categorical variables. The effects of hospital characteristics, including private vs. public and type I vs. type II hospitals, as well as referral of possible donors from ED vs. ICU, on the five mentioned outcomes were analyzed using Chi-square test and reported using Risk Ratio (RR), 95% Confidence Interval (CI), and P-value. To assess the impact of hospital size and follow-up duration on the binomial outcomes, Logistic Regression was employed, and the results were described by Odds Ratio (OR), CI, and P-value.

RESULTS

Study Population

Between January 1st, and December 31st, 2022, 813 possible donors were enrolled. The baseline characteristics of these possible donors, including age, gender, patient's outcome, follow-up duration, the detection site, hospital characteristics, and donation outcomes, are fully detailed in **Table 1**. Furthermore, the data related to the donation process, categorized by hospital characteristics, is mentioned in **Table 2**.

TABLE 2 | Outcomes of Possible Donors Based on Hospital Characteristics and Detection Site.

		Hospital types		Public vs. Private		Detection Location[a]	
		Type I	Type II	Public	Private	ICU	ER
N (%)		766 (94.6)	44 (5.4)	714 (88.1)	96 (11.9)	694 (85.6)	65 (8.1)
Possible Donors	Improvement (%)	234 (30.5)	9 (20.5)	222 (31.1)	21 (21.9)	220 (31.7)	13 (20.0)
	Circulatory Death (%)	230 (30.0)	17 (38.6)	220 (30.8)	27 (28.1)	208 (30.0)	21 (32.3)
	Brain Death (%)	297 (38.8)	18 (40.9)	268 (37.5)	47 (49.0)	261 (37.6)	31 (47.7)
Brain Dead Potential Donors	Eligible (%)[b]	192 (64.6)	11 (61.1)	175 (65.3)	28 (59.6)	162 (62.1)	25 (80.6)
	Ineligible (%)[b]	105 (35.4)	7 (38.9)	93 (34.7)	19 (40.4)	99 (37.9)	6 (19.4)
Eligible Donors	No Viable Organ (%)[c]	33 (17.2)	2 (18.2)	31 (17.7)	4 (14.3)	25 (15.4)	3 (12.0)
	Refuse to Donate (%)[c]	58 (30.2)	4 (36.4)	54 (30.9)	8 (28.6)	57 (35.2)	3 (12.0)
	Actual Donor (%)[c]	97 (50.5)	5 (45.5)	86 (49.1)	16 (57.1)	78 (48.1)	17 (68.0)

[a]: *51 (6.3%) from other hospital wards.*

[b]: *Percentages are reported among brain-dead potential donors, not overall possible donors in each category*

[c]: *Percentages are reported among eligible donors, not overall possible donors in each category. Unfortunately, data on the follow-up of 8 possible donors were not recorded. Seven of them were from Type I Public hospitals, and 1 was from Type I private hospital. Additionally, 7 of them were detected in the ICU, and 1 in the ED.*

Analysis of Donation Process Outcomes

Type I vs. Type II Hospitals

The conversion rate in type I hospitals was 50.5% which was not statistically different from type II hospitals (45.5%) (P-Value: 0.74, RR: 1.11, CI: 0.57–2.15). The AD/BD ratio was 32.7% in type I hospitals and 27.8% in type II hospitals, with no significant difference (P-Value: 0.66, RR: 1.18, CI: 0.55–2.52). The EDR was 36.4% in type I and 31.4% in type II hospitals, with no significant difference observed (P-Value: 0.55, RR: 1.15, CI: 0.7–1.91). The OLR was not significantly different between two types, Type I 17.2% and Type II 18.2% (P-Value: 0.93, RR: 0.94, CI: 0.26–3.43). In type I hospitals, from 155 approached families 97 (62.6%) families consented to donation. In type II hospitals, the consent rate was 55.6% from 9 interviewed families. However, statistical analysis indicated no significant difference (P-Value: 0.67, RR: 1.12, CI:0.62–2.04), (**Figures 1**, **4A**).

Public vs. Private Hospitals

Public hospitals conversion rate was 49.1% which in comparison with 57.1% rate of private hospitals was not significantly different (P-Value: 0.43, RR: 0.86, CI: 0.6–1.22). The difference between the AD/BD ratio of public hospitals (32.1%) and private hospitals (34%) was not meaningful (P-Value: 0.79, RR: 0.94, CI: 0.61–1.45). The OLR was 17.7% in public hospitals while this ratio was 14.3% in private hospitals which did not show considerable difference. (P-Value: 0.65, RR: 1.24, CI: 0.47–3.24). There was no significant difference in the EDR between public hospitals (35.9%) and private hospitals (37.8%) (P-Value: 0.74, RR: 0.94, CI: 0.69–1.29). The difference of public hospitals consent rate (61.4%) and private hospitals (66.7%) was not statically significant as well (P-Value: 0.62, RR: 0.92, CI: 0.67–1.25), (**Figures 2**, **4B**).

ICU vs. ED

The conversion rate in patients referred from EDs was 68%, which showed a nearly significant difference compared to the conversion rate of 48.1% in ICU-referred patients (P-Value: 0.065, RR: 0.7, CI: 0.51–0.96). The AD/BD ratio in EDs was 54.8%, which was significantly higher than the ratio of 29.9% in ICUs (P-Value: 0.005, RR: 0.54, CI: 0.37–0.78). Another ratio that demonstrated a statistically difference between ICU and ED was the EDR which was 48.1% in EDs and 34.5% in ICUs (P-Value: 0.05, RR: 0.71, CI: 0.52–0.97). The consent rate also showed a meaningful difference, with a rate of 85% in EDs and 57.8% in ICUs (P-Value: 0.02, RR: 0.68, CI: 0.53–0.85). The only ratio that showed no significant changes between these two referral sites was the OLR that was 13% in EDs, and 15.4% in ICUs (P-Value: 0.65, RR: 1.28, CI: 0.41–3.94), (**Figures 3**, **4C**).

Follow-Up Duration

The follow-up duration, showed no influence on the evaluated ratios except for the EDR (P-Value<0.01, OR: 0.91, CI: 0.86–0.96). The evaluation indicated that the chance of eligible death decreases with each day of increase in follow-up duration. Regarding the other ratios, including conversion rate (P-Value: 0.51, OR: 0.97, CI: 0.9–1.05), OLR (P-Value: 0.29, OR: 1.04, CI: 0.96–1.14), consent rate (P-Value: 0.63, OR: 1.03, CI: 0.92–1.13), and the AD/BD ratio (P-Value: 0.39, OR: 0.97, CI: 0.9–1.008), there were no significant associations observed with follow-up duration (**Figure 4D**).

Hospital Size

The results showed no significant relationship between hospital size and conversion rate (P-Value: 0.49, OR: 1.002, CI: 0.99–1.00), OLR (P-Value: 0.70, OR: 0.99, CI: 0.99–1.005), and consent rate (P-Value: 0.49, OR: 1.002, CI: 0.99–1.007). However, there were near significant changes for the EDR (P-Value: 0.07, OR: 1.003, CI: 1.00–1.005) and the AD/BD ratio (P-Value: 0.06, OR: 1.004, CI: 1.00–1.008). The statistics indicated that with an increasing number of hospital beds, these ratios increased. Although these changes were not significant, there was a trend suggesting a potential impact of hospital size (**Figure 4E**).

DISCUSSION

Our findings indicate that, although being a public hospital and a type I hospital are associated with a higher number of

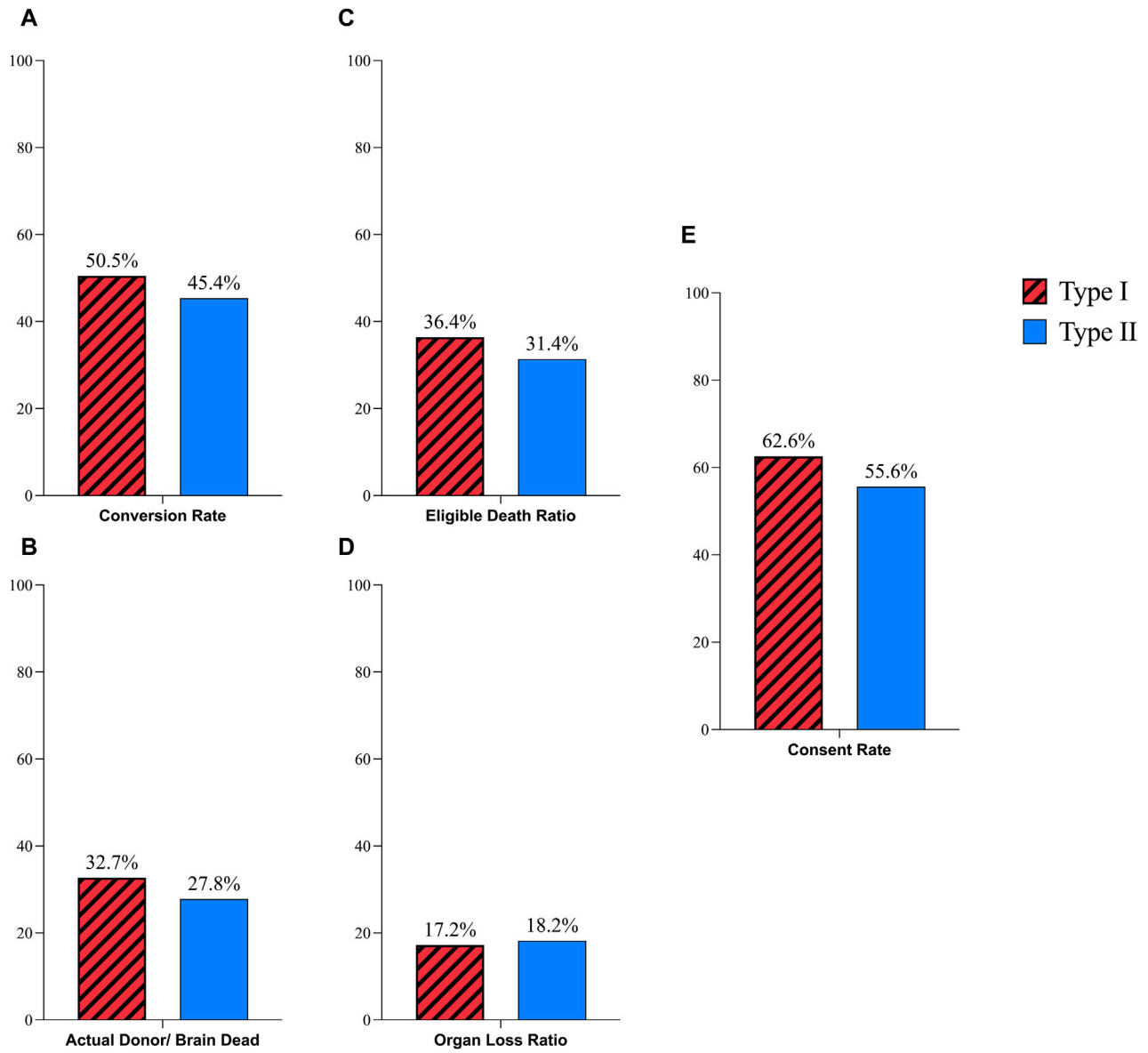


FIGURE 1 | Comparison of donation process in Type I and Type II hospitals; **(A)** Coversion Rate; **(B)** Actual Donor/Brain Dead Ratio; **(C)** Eligible Death Ratio; **(D)** Organ Loss Ratio; **(E)** Consent Rate.

potential donors, they do not have an impact on the success of any stage in the donation process in this OPN. Accordingly, the likelihood of a potential donor progressing to become an actual donor is equal regardless of these characteristics. Furthermore, our study reveals that referring possible donors from ED, improves the donation process. This finding highlights the importance of early involvement of the OPN. We also did not observe any relationship between hospital size and the success of donation. This is promising, as it suggests that smaller hospitals, despite having fewer potential donors and possibly less familiarity with the donation process, still offer an equal chance of donation for potential donors.

Studies suggested identification of potential donors from ED instead of ICU leads to expansion of donor pool [16, 17]. A previous study concluded that identifying potential donors in the ED not only increases the number of potential and actual donors but also leads to a higher ratio of organs donated per donor (3.79) compared to ICU (3.16) [18]. Another study, found a lower refusal rate among potential donors referred from the ED (33.5% vs. 42.7%) [19]. A subsequent systematic review confirmed that the chances of becoming actual donors are higher among patients referred from the ED [20]. Consistent with previous studies, our findings, demonstrate not only a significantly higher consent rate in the ED but also a higher rate of eligible deaths, a higher ratio of actual donors to brain-dead patients and a higher conversion rate.

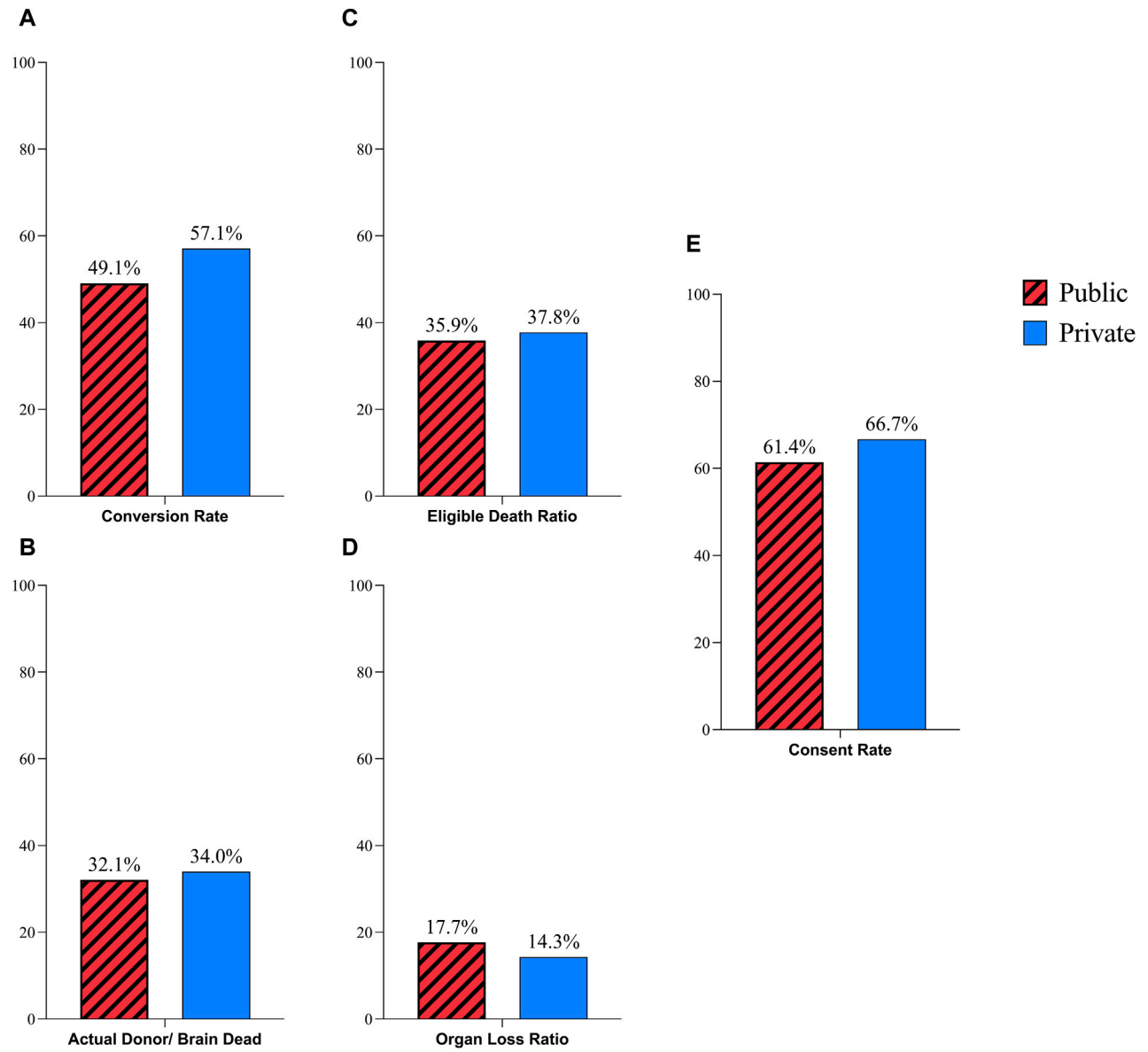


FIGURE 2 | Comparison of donation process in public and private hospitals; **(A)** Coversion Rate; **(B)** Actual Donor/Brain Dead Ratio; **(C)** Eligible Death Ratio; **(D)** Organ Loss Ratio; **(E)** Consent Rate.

We speculate that the higher consent rate in the ED could be attributed to earlier efforts to establish a better relationship with the families. Importantly, we found no difference in the organ loss ratio. This lack of difference is reasonable since patients referred from the ED would be transferred to the ICU, and the management would continue in a similar manner. In conclusion, we strongly recommend considering organ donation and referral to organ procurement organizations in emergency departments.

The majority of possible donors require neurosurgical and trauma care. Therefore, it was expected that hospitals with neurosurgery/trauma departments would have a higher number of potential donors. This assumption has been supported by various studies, including the present paper. Neurosurgery department have been associated with an expansion of the pool of possible donors [21] and trauma center hospitals have shown higher numbers of both eligible and actual donors [13, 14]. Hence, it is crucial not to overlook other hospitals. It is essential to improve the donation process in all hospitals, irrespective of the presence of trauma/neurosurgery care. Furthermore, we expected that with efficient donation policies, there should be an equal chance of donation for potential donors in different hospitals. Contrary to our expectations, previous studies have shown a higher conversion

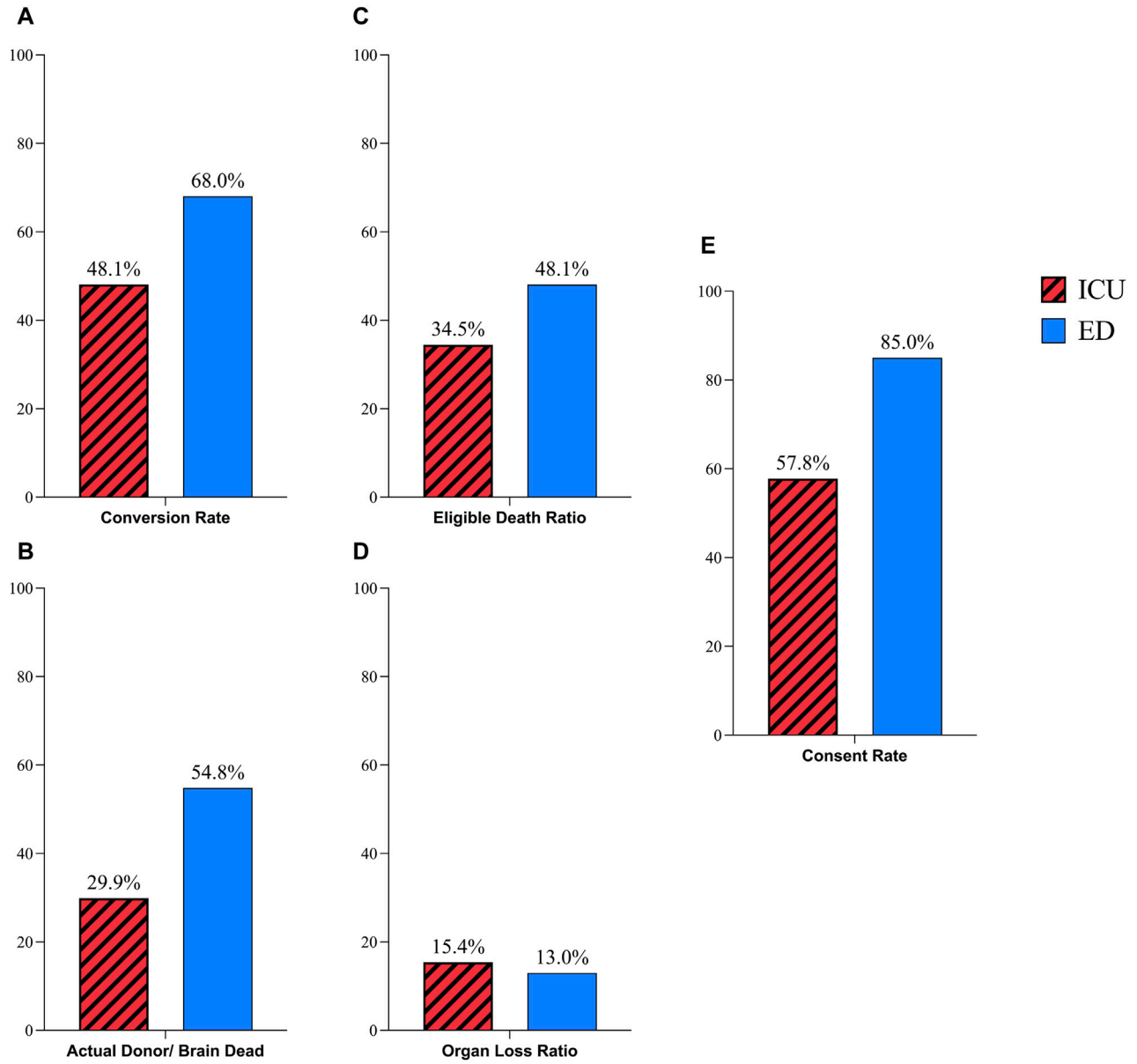


FIGURE 3 | Comparison of donation process in ICU and ED referred possible donors; **(A)** Coversion Rate; **(B)** Actual Donor/Brain Dead Ratio; **(C)** Eligible Death Ratio; **(D)** Organ Loss Ratio; **(E)** Consent Rate.

rate in trauma centers [22–24] as well as higher consent rates [24]. The presence of trauma surgeons has also been found to increase the conversion rate [25]. Unexpectedly, Rios Diaz et al. found a higher conversion rate in non-trauma centers [26]. Since none of the hospitals evaluated in our study had solely a trauma or neurosurgery department, we were compelled to assess the effect of the existence of both departments together. While we confirmed a higher number of possible, potential, eligible, and actual donors in type I hospitals, our findings demonstrate no significant difference in the success of the donation process. We speculate that our methodology, which involved detecting possible donors through twice-daily calls, closely following the condition of possible donors, and handling further steps with the assistance of our coordinators once the patient was declared brain dead, may have contributed to similar success rates in hospitals regardless of the presence of neurosurgery/trauma care. However, this is only a suggestion and should be further assessed in future studies.

In Iran, the lower cost of care in public hospitals results in more admission. Subsequently, it is expected that public hospitals would have a higher number of potential donors. While there are few studies comparing organ donation between public and private hospitals in other countries, an assessment of kidney donation rates in South Africa showed a higher rate of donation

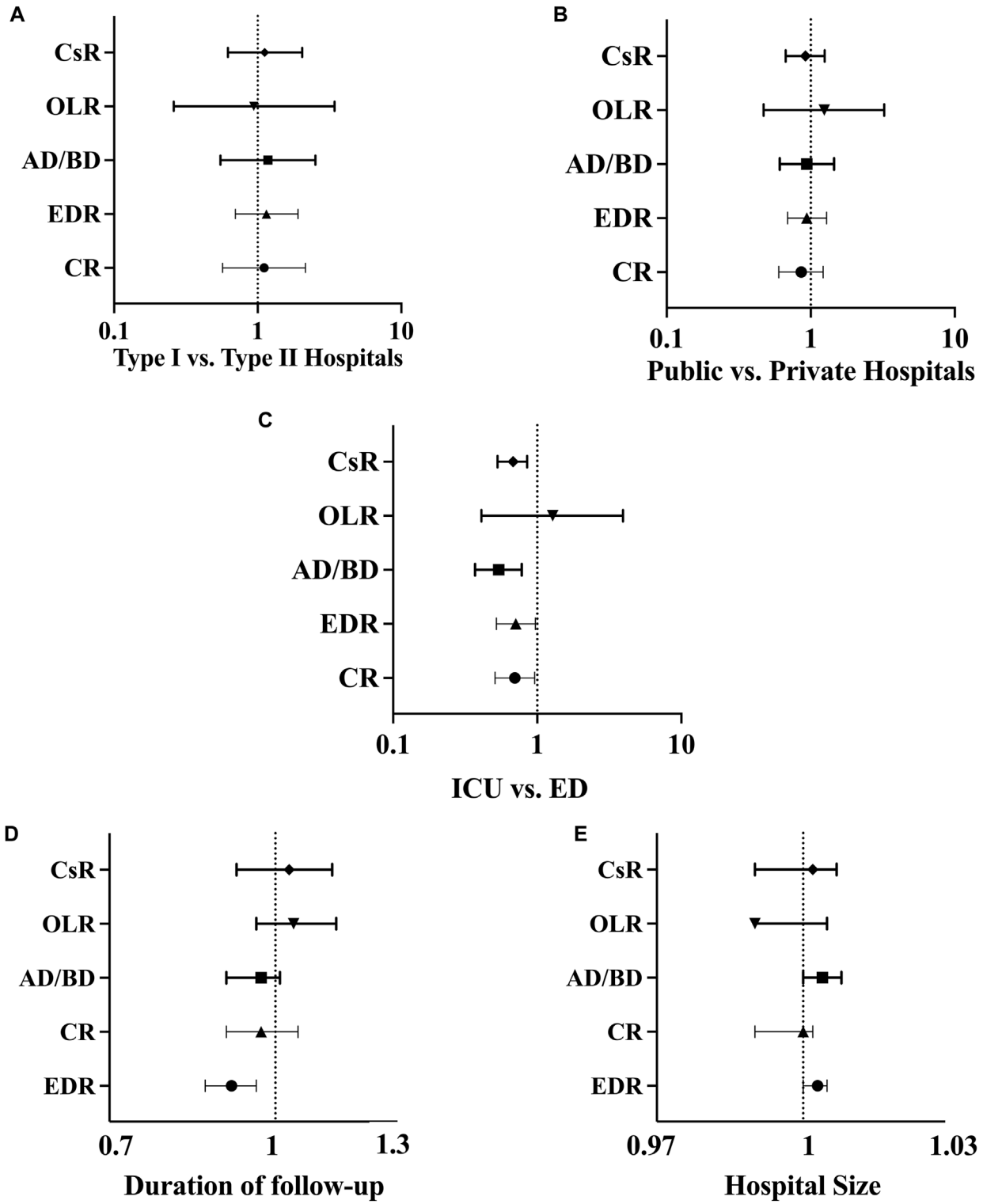


FIGURE 4 | Forest plot for univariable analysis: **(A)** Comparison of donation process in type I and type II hospitals; **(B)** Comparison of donation process in public and private hospitals; **(C)** Comparison of donation process in ICU and ED referred possible donors; **(D)** Analysis of the impact of follow-up duration on different outcomes; **(E)** Analysis of the impact of hospital size on different outcomes. Abbreviations: CR, conversion rate; AD/BD, actual donor/brain dead; EDR, eligible death ratio; OLR, organ loss ratio; CsR, consent rate; ICU, intensive care unit; ED, emergency department.

in private hospitals [27], while the consent rate was higher in public hospitals [28]. Another study conducted in the United States found no difference in the conversion rate based on hospital ownership [26]. We argue that even with a smaller number of potential donors in private hospitals, the donation process should be of the same quality. Our evaluation found no difference in the rates of donation, consent, eligible deaths, or organ loss. We hypothesize that our method of identification and management of possible donors may have contributed to this promising finding.

Larger hospitals often have a higher rate of admission and increased availability of resources and equipment. It is expected that these advantages would lead to a higher number of potential donors, which was supported by our study and Roggenkamp et al. [13]. Lynch et al. obtained similar results for the number of eligible deaths [29]. However, a higher number of potential donors does not necessarily translate to a better success of donation. Our analysis revealed no relationship between the number of ICU, neurosurgery and neurology ward beds with the consent rate, conversion rate, or the ratio of eligible deaths. Similar conclusions were drawn in Webster et al.'s evaluation of the effects of pediatric intensive care unit size on donation [14]. Contrary to our desirable findings, some studies found higher conversion rates [24, 26] and higher consent rates [24] in smaller hospitals. Conversely, Domingo's et al. found higher conversion rates in larger hospitals [30]. Again, we found the alternation of donation success with hospital characteristics, an undesirable outcome. We suggest improving policies to increase organ donation rates regardless of hospital characteristics.

As mentioned, contrary to our findings, numerous previous studies have reported the influence of hospital characteristics on the donation process. While the underlying reason for this favorable outcome requires further investigation, we assume that our method of twice-daily calls for the detection of possible donors and further follow-up resulted in the homogenization of the donation process in different hospitals. Our method differs from the donation models utilized in countries with high donation rates such as Spain [31], the United Kingdom [32], and Croatia [33, 34]. In these models, transplant coordinators or specialist nurses operate at the hospital level to identify possible donors, educate hospital staff, interview potential donor families, and manage other steps of the donation process. These methods are highly dependent on the coordination team within each hospital. Conversely, in the model utilized in our OPN, all these activities are mainly performed by the OPN with the cooperation of the medical team at hospitals (physicians and nurses). While comparing these models is not the purpose of this paper, our model appears to be efficient with lower costs than the mentioned methods, particularly in possible donor identification. However, further investigation is necessary to better understand these differences.

Additionally, when evaluating our OPN data for 2022 compared to 2009, we observed an increase in the utilization rate (utilized donor/actual donor) from 85% to 94% [35] Furthermore, although unpublished, over the 19-year activity period of this OPN, we have noted a rise in the overall consent rate from 30% to 85%, attributed to enhancements in our donation methods, including greater involvement of donation coordinators. While promising, further investigation is necessary to evaluate our model, particularly the efficacy of the twice-daily calls method in detecting potential donors.

Lastly, it's noteworthy that various etiologies can lead to brain death, but not all cases are considered eligible. Death resulting from trauma has generally been associated with a higher rate of donation. While our investigation showed a near significant difference only in the eligible death ratio and not in the conversion rate, several studies have reported otherwise. In two previous studies, trauma-related cases having the highest conversion rates compared to other etiologies [22, 30].

Our study had some limitations. Donation is a complex process. Although we attempted to evaluate some of the hospital-related factors, many factors did not consider including cultural and religious factors. In our study, we only assessed donation process, using our twice-daily calls methodology for possible donor identification. Therefore, our assumption of superiority of this method is only a hypothesis, and future studies needed to compare this method with other models. For example, the presence of key donation professionals in the hospital, which we do not have.

In conclusion, we strongly recommend an early approach of identifying potential organ donors in emergency departments, which has the potential to significantly improve referrals to organ procurement organizations. Additionally, we emphasize the importance of implementing effective policies for the possible donor identification, closely monitoring their condition, and providing supervision over their management. By doing so, we believe that every potential donor in different hospitals should have an equal chance of donation. In total, while many studies have mentioned the early involvement of the donation team, we believe that our approach, leading to the early engagement of the organ donation team, has been instrumental in ensuring a consistent quality of the donation process across hospitals connected to our OPN. Furthermore, we conclude that the referral of possible donors from ED significantly enhances the donation. Therefore, it is essential for hospitals to consider training ED nurses and physicians to improve the identification of possible donors.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by the Ethic Committee of National Research Institute of Tuberculosis and Lung Diseases. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

Conceptualization: AH, SN, and FG; data curation: SS and MH; formal analysis: AH, MI, and BM; visualization: MM, AH, and SS; writing first draft: AH and FG; writing–review and editing: all authors. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

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Clinical Outcomes and Quality of Life of Patients Receiving Multi-Solid-Organ Transplants in Childhood Are Excellent: Results From a 20-Year Cohort Study

*Alicia Paessler[1], Hannah Maple[2], Miriam Cortes[3], Jacob Simmonds[1], Yincent Tse[4], Maduri Raja[1,5], Mordi Muorah[5], Nicos Kessaris[1,2] and Jelena Stojanovic[1,6]**

[1]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, [2]Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom, [3]King's College Hospital NHS Foundation Trust, London, United Kingdom, [4]Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, [5]Birmingham Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom, [6]UCL Institute of Child Health, London, United Kingdom

Advances in medicine allow children with previously fatal conditions to survive longer and present as transplant candidates; some requiring multiple solid-organ transplants (MSOT). There is limited data on clinical outcomes and no data on quality of life (QoL). In this mixed methods cohort study clinical outcomes from the NHSBT registry were analysed for all patients who received a kidney and one other solid-organ transplant as a child between 2000 and 2021 in the UK. QoL was measured using the PedsQL 3.0 Transplant Module questionnaire. 92 children met the inclusion criteria: heart/heart-lung and kidney (n = 15), liver and kidney (n = 72), pancreas and kidney (n = 4) and multivisceral (n = 1). Results showed excellent patient and graft survival, comparable to single-organ transplants. Allograft survival and rejection were significantly better in patients with combined liver and kidney transplants compared to patients with sequential liver and kidney transplants. QoL was excellent with a mean score of 74%. Key findings included a significant improvement in QoL post-transplant. This is the first study to look at clinical and QoL outcomes in MSOT recipients. The results indicate excellent long-term outcomes. All children born with conditions leading to end-stage disease in multiple solid-organs should be assessed as transplant candidates.

Keywords: paediatric, multi-organ transplant, kidney transplant, liver transplant, heart transplant

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***Correspondence**
Jelena Stojanovic,
jelena.stojanovic@gosh.nhs.uk

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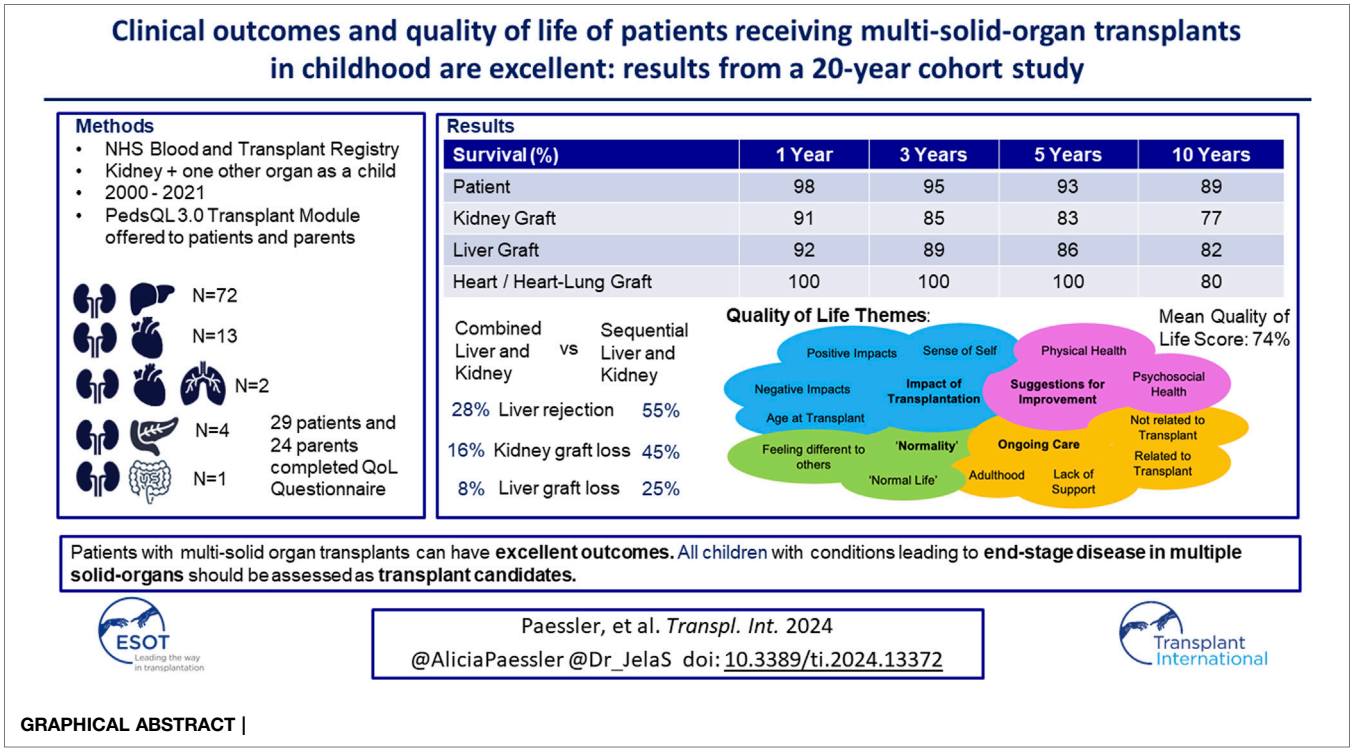
Abbreviations: CLKT, Combined Liver and Kidney Transplant; ESLD, End Stage Liver Disease; EDTA, European Dialysis and Transplantation Association; ELTR, European Liver Transplant Registry; ERA, European Renal Association; ESPN, European Society for Paediatric Nephrology; H/HLKT, Heart/Heart-lung and kidney transplant; SPSS, IBM Statistical Package for Social Sciences; ITOTR, International Thoracic Organ Transplant Registry; KT, Kidney Transplant; LT, Liver Transplant; MSOT, Multi-solid-organ-transplant; NHSBT, National Health Service Blood and Transplant; NYHA, New York Heart Association; QoL, Quality of Life; SLKT, Sequential Liver and Kidney Transplant; UK, United Kingdom; UKTRUnited Kingdom Transplant Registry; UNOS, United Network for Organ Sharing.



GRAPHICAL ABSTRACT |

INTRODUCTION

Advances in modern medicine mean that more babies born with complex health conditions survive into childhood, resulting in an increasing number requiring multiple different solid organ transplants (MSOT) (for example, there were only 2 such transplants in the year 2000 in the UK, and 15 years later there was as many as 8 in 1 year [1]). These patients have unique healthcare needs that have not yet sufficiently been explored. Some of these children will have metabolic conditions, and present at an earlier age, bringing challenges in finding size-matched grafts but also in creating adequate vascular anastomosis and achieving abdominal closure for those receiving a graft from an adult. Some children with single-organ transplants go on to need a second organ, (thereby making them MSOT candidates) and for these children sensitisation from their prior transplants can be a significant issue. Caring for a child with one transplanted organ is challenging enough, so it follows that children with MSOT can provide extra challenges for patients and healthcare professionals in both paediatric, and subsequently adult settings.

Despite the increasing number of children requiring MSOT, there is still no large-scale registry data published on their long-term outcomes nor data on how these patients do once they reach adulthood [2–11]. Within the existing limited evidence, there is an ongoing debate as to whether liver and kidney transplants have better outcomes if they are done combined or sequentially. There is a suggested immunological advantage of combined transplants with data showing that the presence of a liver graft from the same donor has an immunological protective effect, with various possible explanations [3, 12–15]. However, some studies report a higher rate of complications and mortality in the first year post-combined liver and kidney transplant (CLKT) when compared to patients undergoing sequential liver and kidney transplants (SLKT), isolated liver transplants (LT) or isolated kidney transplant (KT) [2, 3]. At present, there is no clear consensus favouring one over another.

Furthermore, there is no available data on quality of life (QoL) outcomes for these children. QoL is a crucial aspect of patient's outcomes; studies have shown increased stress, anxiety and a poorer QoL is correlated with medication non-adherence [16–18]. Medication non-adherence, particularly in adolescents, is a widely reported issue that can lead to more hospitalizations, graft loss and poorer health outcomes [19] so it is key to explore this issue further.

This study is a mixed-methods cohort study that is the first registry study analysis on children with MSOT and to our knowledge, the first one to investigate their QoL. Moreover, it's one of the largest cohorts of MSOT patients reported and the only one to follow these patients into adulthood. The aim was the following:

To review the long-term clinical outcomes and gain a better understanding of the quality of life of all patients receiving more than one different solid organ transplant during childhood between 2000 and 2021 in the UK.

MATERIALS AND METHODS

Those who had received a kidney, plus a minimum of one other solid-organ transplant (either combined or sequentially) in the United Kingdom (UK) before their 18th birthday were eligible for inclusion. The timeframe selected was January 2000 to May 2021. All clinical outcome data was requested and provided by NHS Blood and Transplant (NHSBT) from the UK Transplant registry (UKTR) which includes extensive data on all patients that are listed for transplant, all donors and all transplant outcomes. Informed consent for data collection is obtained from recipients and donor next of kin by NHSBT at the time of listing for transplant/donation. All patient follow-up data was based upon their status on the registry in December 2021. The full details of the UKTR dataset and the variables collected can be viewed online [1]. Throughout this manuscript when abbreviating types of transplants we have described simultaneous transplants as combined (e.g., combined liver and kidney transplant (CLKT)) with multiple different single-organ transplants as sequential transplants (e.g., sequential liver and kidney transplant (SLKT)). We have done this to easier be able to differentiate between the two.

All surviving patients and their families were contacted either via a phone call or at their clinic appointments. They were contacted a maximum of two times and were given an information sheet to allow them to make an informed choice on whether they wanted to consent for the QoL arm of the study. Both patients and parents were asked to complete the PedsQL 3·0 Transplant Module questionnaire either online or on paper [20], with the parent copy of the questionnaire asking parents how they thought their child's QoL was. The questionnaire assesses how often different aspects of their life are impacted by their transplants, including categories on medication burden, physical appearance, worries, fitting in with their peers etc. Parent copies were given to parents of patients <18 years old and to parents of adult patients where possible. Scores were out of 100 and higher scores indicate a better QoL. Prior to data collection, the authors deemed a score >70 to suggest good QoL to improve understanding of the scores for readers of the manuscript. However, the original tool does not have any validated score cut-offs so this is specific to this study and has not been validated. The questionnaire has age-appropriate versions for 2–4, 5–7, 8–12, 13–18, and >18 years old. Participants were given the opportunity to add any additional comments to the questionnaires about their QoL in a free-text section at the end. Questionnaires were fully anonymised.

IBM Statistical Package for Social Sciences (SPSS) Version 28 [21] was used for all statistical analyses. Patient and graft survival was estimated using Kaplan-Meier analysis and log-rank testing was used to assess comparisons. Multivariable linear regression analysis was carried out where possible. Regression analysis was carried out with the following variables: type of transplant, age at transplant, dialysis status pre-transplant, donor type and underlying disease. P-values, with a threshold of significance of $p < 0{\cdot}05$, are displayed as a measure of significance. In the QoL arm of the study, patients were also compared based on age at transplantation by the following groups: <4, 5–7, 8–12, 13–18 years old at time of transplantation. For QoL data, both statistically significant differences and clinically significant differences were reported using Minimally Important Difference values of 0.5 the standard deviation [22]. When data was used for multiple comparisons Bonferroni corrections were implemented. Free-text responses were analysed through thematic analysis [23] to further explore the quantitative data on quality of life in more detail, and add depth to our data on quality of life in MSOT-recipients. Two co-authors read through all the raw data independently to familiarise themselves with the data. Initial codes were identified in the data and then these were grouped into themes. These themes were then compared between the two authors and reviewed and revised. During this process further sub-themes were then identified from the initial codes identified from the raw data.

This study required full ethics approval from the NHS Health Research Authority which was approved under IRAS project ID number 297707 in June 2021. The study was completed in full accordance with ethics approval requirements.

RESULTS

Demographics and Background Information

In total, 92 children had MSOT including a kidney, in the UK during the study period. The transplant types, basic demographics and transplant details can be seen in **Table 1**.

Underlying medical conditions can be seen in **Supplementary Material S1**.

Clinical Outcomes

The median follow-up times post-transplant for the different transplant types can be seen in **Table 2**. In the SLKT group there was a median of 2 years between liver and kidney transplants, in the H/HLKT group there was a median of 9.5 years between the heart/heart-lung and kidney transplant.

Clinical Outcomes: Allograft Function

Serum creatinine levels remained stable at 3 months, one and 5 years post-KT (mean 82 ± 54, 82 ± 69, and 93 ± 44 μmol/L respectively). There was no statistically significant difference between the transplant types. However, when comparing those with kidney and liver transplants, the serum creatinine was significantly lower at 5 years post-transplant for patients in whom both organs had come from the same donor (i.e., combined transplant from one deceased donor or sequential transplants from the same living donor) (82 μmol/L vs. 104 μmol/L, $p = 0{\cdot}02$).

For patients undergoing H/HLT, prior to transplant the majority (66% n = 6) were classified as New York Heart Association (NYHA) Heart Failure Class IV [24]. At 10 years post-transplant, 100% of patients were classified as NYHA Heart Failure Class I [24]. At 10 years post-H/HLT, patients had an average of seven hospital admissions post-transplant.

Patients had a median of five and four (CLKT and SLKT respectively) hospital admissions in the first 5 years post-

TABLE 1 | Sex distribution, ethnicities and median ages at time of transplantation organ donor demographics, graft types, HLA match types, and median waiting list times across the different transplant types. Kidney match type is categorised as per NHS Blood and Transplant with favourable including one of the following HLA mismatches: 000, 100, 010 or 110. Letters within the table signify a significant difference (p < 0·05) between variables containing the same letter.

		Total n = 92	Liver and kidney (n = 72)		Heart and kidney (n = 15)		Pancreas and kidney n = 4	Multivisceral n = 1
			Combined n = 53	Sequential n = 19	Combined n = 1	Sequential n = 14		
Sex (%)	Male	52 (57)	33 (62)	9 (47)	0 (0)	9 (64)	1 (25)	0 (0)
	Female	40 (43)	20 (38)	10 (53)	1 (100)	5 (36)	3 (75)	1 (100)
Ethnicity (%)	Asian	14 (15)	9 (17)	3 (16)	0 (0)	2 (14)	0 (0)	0 (0)
	Black	1 (1)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)
	White	70 (76)	42 (79)	12 (63)	1 (100)	11 (79)	4 (100)	0 (0)
	Other	7 (8)	2 (4)	4 (21)	0 (0)	0 (0)	0 (0)	1 (100)
Median age at time of transplant in years (range)	Kidney	8 (1–17)	7 (1–16)	5 (1–16)	11	13·5 (5–17)	16 (15–17)	12
	Liver	6 (0–19)	7 (1–16)	2 (0–17)	-	-	-	-
	Heart	4 (0–12)	-	-	11	3 (0–12)	-	-
	Heart-Lung	4·5 (4–5)	-	-	-	4.5 (4–5)	-	-
	Pancreas	16 (15–17)	-	-	-	-	16 (15–17)	-
	Multivisceral	12	-	-	-	-	-	12
Kidney Donor Type (%)	DBD	76 (82)	52 (98)	8 (42)	1 (100)	7 (50)	4 (100)	1 (100)
	Living Related	16 (18)	1 (2)	11 (58)	0 (0)	7 (50)	0 (0)	0 (0)
Liver Donor Type (%)	DBD	64 (89)	52 (98)	12 (63)	-	-	-	-
	DCD	1 (1)	0 (0)	1 (6)	-	-	-	-
	Living Related	7 (10)	1 (2)	6 (31)	-	-	-	-
Median Donor Age (range)	Kidney	31 (5–54)	25 (5–49)	34 (12–52)	9	45 (30–54)	27·5 (14–45)	24
	Liver	24·5 (5–57)	25 (5–49)	28 (6–57)	-	-	-	-
	Heart	9 (0–39)	-	-	9	7 (0–39)	-	-
	Heart-Lung	4 (2–6)	-	-	-	4 (2–6)	-	-
	Pancreas	27·5 (14–45)	-	-	-	-	27·5 (14–45)	-
	Multivisceral	24	-	-	-	-	-	24
Kidney Match Type (%)	Favourable	20 (22)	4 (8)	9 (47)	0 (0)	6 (43)	1 (25)	0 (0)
	Non-Favourable	72 (78)	49 (92)	10 (53)	1 (100)	8 (57)	3 (75)	1 (100)
Liver Graft Type (%)	Reduced	14 (19)	6 (12)	8 (42)	-	-	-	-
	Split	38 (53)	32 (60)	6 (32)	-	-	-	-
	Whole	20 (28)	15 (28)	5 (26)	-	-	-	-
Pre-emptive Kidney Transplant (%)	Yes	59 (64)	27 (51) b,c	2 (10) b	1 (100)	2 (15) c	0 (0)	1 (100)
	No	33 (36)	25 (49)	17 (90)	0 (0)	12 (85)	4 (100)	0 (0)
Median Days Spent on the Waiting List (range)	Kidney	210 (13–2,287)	109 (13–1,430) a	504 (39–1,552) a	Not Reported	145 (30–2,287)	219 (175–2,287)	178
	Liver	Not reported	109 (13–1,430)	Not Reported	-	-	-	-
	Heart	111 (1–347)	-	-	Not Reported	111 (1–347)	-	-
	Heart-Lung	510 (99–921)	-	-	-	510 (99–921)	-	-
	Pancreas	219 (175–2,287)	-	-	-	-	219 (175–2,287)	-
	Multivisceral	178	-	-	-	-	-	178

DBD, Donation after brainstem death; DCD, donation after circulatory determination of death.

transplant and their lifestyle activity score significantly improved post-transplant, where pre-transplant only 5% of patients were able to carry out normal activity without restriction and post-transplant this increased to 79% (p < 0·01).

Clinical Outcomes: Rejection

In the first 5 years post-transplant, 7 patients (7%) had experienced episodes of kidney rejection. These occurred in 9% (n = 3) of CLKT patients, 9% (n = 1) of SLKT patients and 20% (n = 3) of heart/heart-lung and kidney transplant (H/HLKT) patients. 14 patients (19%) had experienced episodes of liver rejection, which was significantly higher in SLKT patients (n = 5, 36% vs. n = 9, 10%, p = 0.01) in the first 5 years post-transplant. 4 patients (27%) had experienced episodes of heart rejection at 5 years post-transplant. Multivariable analysis did not find any variables that significantly impacted episodes of any graft rejection.

Clinical Outcomes: Graft Survival

Patients with grafts from the same donor were less likely to lose their kidney grafts than patients with grafts from different donors (p < 0·01). Similarly, CLKT patients were less likely to lose their liver graft than SLKT patients (p < 0·01). The causes of graft loss can be seen in **Supplementary Material S1**.

TABLE 2 | Median follow up times post-transplant across the different transplant types.

	Total (n = 92)	Liver and kidney (n = 72)		Heart and kidney (n = 15)		Pancreas and kidney (n = 4)	Multivisceral (n = 1)
		CLKT (n = 53)	SLKT (n = 19)	CHKT (n = 1)	SHKT (n = 14)		
Median Follow up Time (years) Post-Kidney Transplant (Range)	8·4 (0–22·5)	8·8 (0·2–22·5)	7·3 (0–18·6)	9·8	7·6 (0·9–15·6)	6·5 (0–16·4)	1·0
Median Follow up Time (years) Post-Liver Transplant (Range)	8·7 (0·1–26·9)	8·8 (0·2–22·5)	7·3 (0·1–26·9)	-	-	-	-
Median Follow up Time (years) Post-Heart Transplant (Range)	14·6 (3·0–29·6)	-	-	9·8	14·2 (3·0–29·6)	-	-
Median Follow up Time (years) Post-Heart-Lung Transplant (Range)	23·2 (21·9–24·4)	-	-	-	23.2 (21.9–24.4)	-	-
Median Follow up Time (years) Post-Pancreas Transplant (Range)	6·5 (0–16·4)	-	-	-	-	6·5 (0–16·4)	-
Median Follow up Time (years) Post-Multivisceral Transplant (Range)	1·0	-	-	-	-	-	1·0

CLKT, Combined Liver and Kidney Transplant; SLKT, Sequential Liver and Kidney Transplant; CHKT, Combined Heart and Kidney Transplant; SHKT, Sequential Heart and Kidney Transplant.

TABLE 3 | Graft and death-censored graft survival at 1, 3, 5, and 10 years post-transplant for different transplant types. Letters within the table signify a significant difference ($p < 0·05$) between variables containing the same letter.

		Total (n = 92)	Liver and kidney (n = 72)		Heart/Heart-lung and kidney (n = 15)	Pancreas and kidney (n = 4)	Multi-visceral (n = 1)
			CLKT (n = 53)	SLKT (n = 19)			
Kidney Graft Survival (%)	1 year	91	91	94	93	50	100
	3 years	85	87	89	93	50	0
	5 years	83	85	83	86	50	0
	10 years	77	81	83	47	50	0
Death Censored Kidney Graft Survival (%)	1 year	91	92	94	93	50	100
	3 years	88	91	89	93	50	0
	5 years	86	89	89	86	50	0
	10 years	82	85	89	62	50	0
Liver Graft Survival (%)	1 year	92	96 a	79 a	-	-	100
	3 years	89	92 b	79 b	-	-	0
	5 years	89	92 c	79 c	-	-	0
	10 years	86	92 d	68 d	-	-	0
Death Censored Liver Graft Survival (%)	1 year	93	98 e	79 e	-	-	100
	3 years	92	96 f	79 f	-	-	0
	5 years	92	96 g	79 g	-	-	0
	10 years	89	96 h	68 h	-	-	0
Heart/ Heart-Lung Graft Survival (%)	1 year	100	-	-	100	-	-
	3 years	100	-	-	100	-	-
	5 years	100	-	-	100	-	-
	10 years	80	-	-	80	-	-
Death Censored Heart/ Heart-Lung Graft Survival (%)	1 year	100	-	-	100	-	-
	3 years	100	-	-	100	-	-
	5 years	100	-	-	100	-	-
	10 years	87	-	-	87	-	-
Pancreas Graft Survival (%)	1 year	75	-	-	-	75	-
	3 years	75	-	-	-	75	-
	5 years	50	-	-	-	50	-
	10 years	50	-	-	-	50	-
Multi-visceral Graft Survival (%)	1 year	100	-	-	-	-	100
	3 years	0	-	-	-	-	0
	5 years	0	-	-	-	-	0
	10 years	0	-	-	-	-	0

CLKT = Combined Liver and Kidney Transplant, SLKT = Sequential Liver and Kidney Transplant.

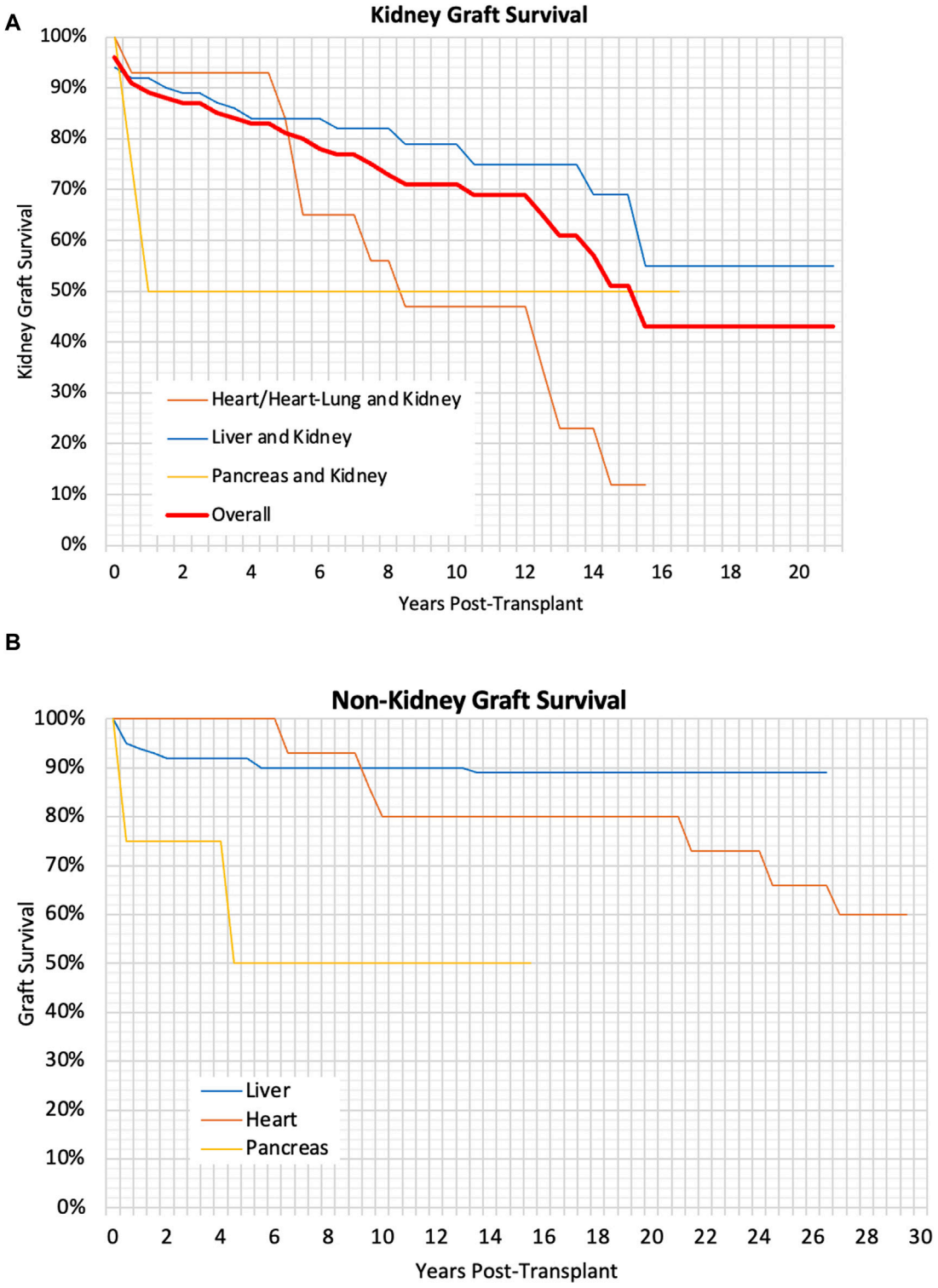


FIGURE 1 | (A) Kaplan Meier Graph showing the kidney graft survival for different types of transplants, $p < 0.01$, **(B)** Kaplan Meier Graph showing the graft survival of liver, heart and pancreas grafts, $p < 0.01$.

Liver graft survival was found to be significantly better in CLKT patients compared to SLKT patients ($p < 0{\cdot}01$). There was no significant difference in kidney graft survival between the CLKT and SLKT group, however kidney graft survival was significantly better in liver and kidney patients compared to heart/heart-lung and kidney patients ($p < 0{\cdot}01$). However once

TABLE 4 | Patient survival at 1, 3, 5, and 10 years post-transplant for different transplant types.

		Total (n = 92)	Liver and kidney (n = 72)		Heart/Heart-lung and kidney (n = 15)	Pancreas and kidney (n = 4)	Multi-visceral (n = 1)
			CLKT (n = 53)	SLKT (n = 19)			
Patient Survival Post-Kidney Transplant (%)	1 year	98	96	100	100	100	100
	3 years	95	93	100	100	100	0
	5 years	93	93	93	100	100	0
	10 years	89	93	85	71	100	0
Patient Survival Post-Liver Transplant (%)	1 year	96	96	95	-	-	100
	3 years	93	93	95	-	-	0
	5 years	93	93	95	-	-	0
	10 years	92	93	90	-	-	0
Patient Survival Post-Heart/Heart-Lung Transplant (%)	1 year	100	-	-	100	-	-
	3 years	100	-	-	100	-	-
	5 years	100	-	-	100	-	-
	10 years	87	-	-	87	-	-
Patient Survival Post-Pancreas Transplant (%)	1 year	100	-	-	-	100	-
	3 years	100	-	-	-	100	-
	5 years	100	-	-	-	100	-
	10 years	100	-	-	-	100	-
Patient Survival Post-Multivisceral Transplant (%)	1 year	100	-	-	-	-	100
	3 years	0	-	-	-	-	0
	5 years	0	-	-	-	-	0
	10 years	0	-	-	-	-	0

CLKT, Combined Liver and Kidney Transplant; SLKT, Sequential Liver and Kidney Transplant.

death-censored this difference was no longer significant. Multivariable analysis did not find any other variables which impacted graft survival. There was no significant difference in graft survival for children transplanted at different ages (p = 0.55). Graft survival can be seen in **Table 3** and Kaplan-Meier curves for graft survival can be seen in **Figures 1A, B**.

Clinical Outcomes: Patient Survival

Overall, 14 patients died during the study period, this was not significantly different between the transplant types. Causes of death can be seen in **Supplementary Material S1**.

There was no significant difference in the patient Kaplan-Meier survival rates and multivariable analysis found no variables that significantly impacted these. There was no significant difference in patient survival for children transplanted at different ages (p = 0.55). The patient survival can be seen in **Table 4** and the Kaplan-Meier survival curves can be seen in **Figures 2A, B**.

Quality of Life

Out of the 78 surviving patients, 46 were identified through their local transplant centre. Of these, we were able to contact and consent 37 to the QoL arm of the study. Finally, Thirty-one families returned their questionnaires which included 29 patients and 24 parents. The distribution across the different transplant types was representative of the number of patients of each transplant type in the clinical arm of the study (20 CLKT patients, 8 SLKT patients, 8 HKT patients). The median age of the patients at the time of participation was 16 years (ranging between 4 and 32 years old). 21 were still under the age of 18 and 10 had become adults. The median time since transplantation was 7 years (range 0·3–17·5 years). Validity of the questionnaire results were analysed using Cronbach's coefficient alpha and can be seen in **Supplementary Material S1**.

Overall patient and parent scores can be seen in **Table 5** as well as by the different age categories at the time of response in **Figures 3A, B**. Minimally important difference values for each category, that are used to determine clinical significance of changes in each category are also listed in **Table 5**. Overall, patient self-reports had higher QoL scores than parent-proxy QoL scores, however this was not statistically significant. (p = 0.44).

Patients who were transplanted at a younger age had a significantly better QoL (both statistically significant and clinically significant) across every category ($p < 0·01$) when compared to those transplanted at an older age (Total mean QoL score of 79.5, 78.6, 73.4, and 56.0 for patients transplanted at age <4, 5–7, 8–12, and 13–18 respectively). Patient QoL significantly decreased with age in relation to medication burden, pain, worry and communication (p = 0·02, 0·02, 0·01, and 0·03 respectively) as displayed in **Figures 3A, B**. However, there was no difference in overall QoL between the different transplant types (p = 0.94) nor by time since transplantation (p = 0.39). These differences were also apparent when testing for clinical significance.

These trends were explored further with thematic analysis of the additional comments left by patients and parents. The analysis produced four overarching themes with 12 sub-themes. Themes and sub-themes can be seen in **Figure 4** and the data including participant quotes can be seen in **Supplementary Material S2**.

The first main theme explored the impact of transplantation. Receiving a MSOT had a significant impact of patients' sense of self', with some describing themselves as "a completely different

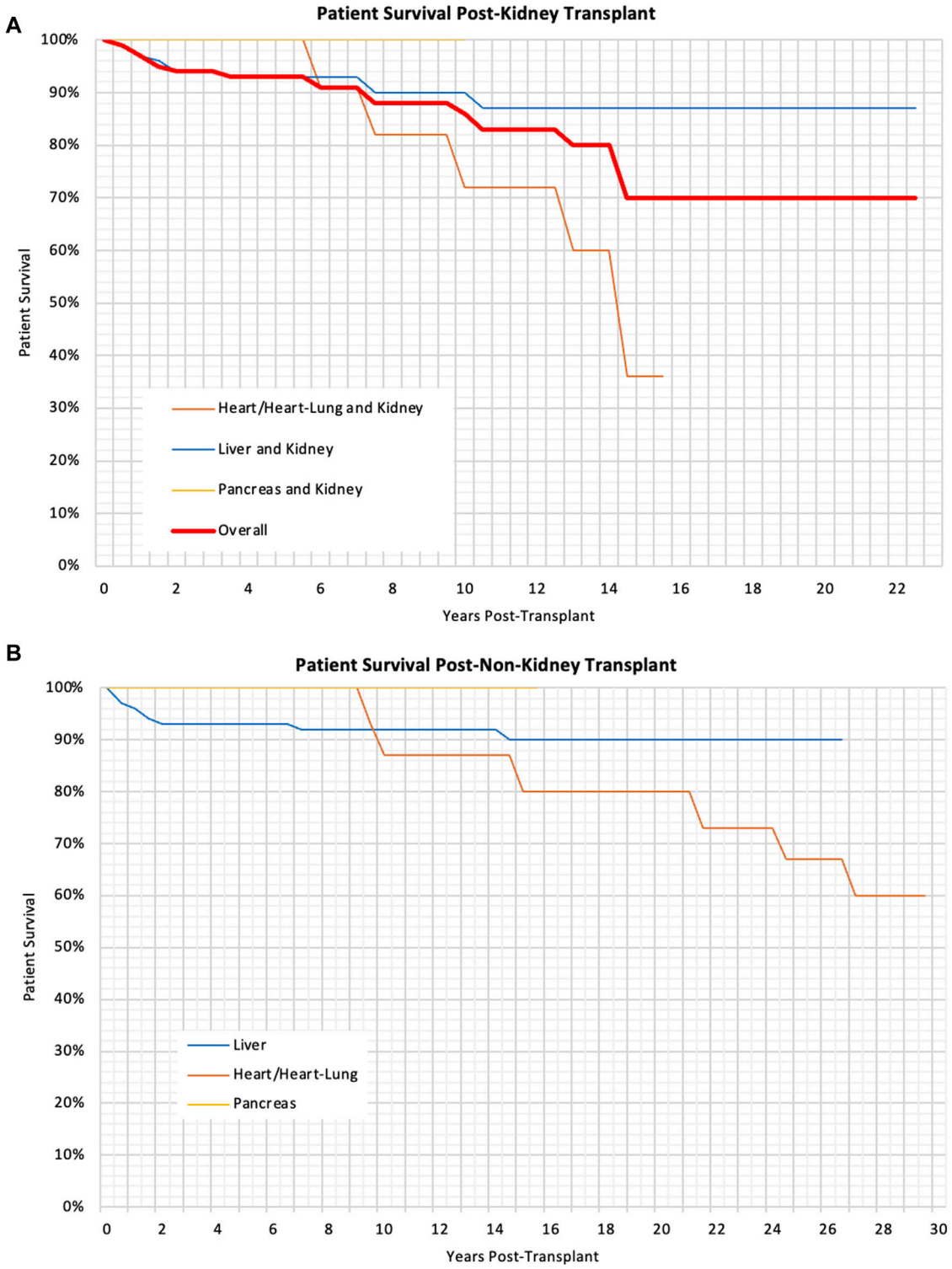


FIGURE 2 | (A) Kaplan Meier Graph showing the patient survival post-kidney transplant for different types of transplants, $p < 0.01$ **(B)** Kaplan Meier Graph showing the patient survival following liver, heart and pancreas, $p = 0.03$.

person" (Patient 6) pre- and post-transplant. Many positive impacts of transplantation were also discussed, with participants saying that their "Quality of life improved tremendously" (Parent 10). Sub-themes included feelings of gratitude, absence of fear or anxiety, feelings of empowerment and an improvement in physical symptoms. Naturally, negative

TABLE 5 | Patient and Parent reported quality of life scores across all categories with 95% Confidence Intervals and minimally important difference values.

	Patient mean	Patient 95% CI	Minimally important difference (0.5 SD)	Parent mean	Parent 95% CI	Minimally important difference (0.5 SD)
About My Medicines I	79·9	73·6–86·2	9.0	79·9	77·9–81·9	9.0
About My Medicines II	88·2	82·6–93·7	7.9	84·1	76·7–91·5	9.3
My Transplant and Others	62·8	55·2–70·5	10.9	58·9	48·8–69	12.7
Pain and Hurt	76·8	68·3–85·3	12.2	72·2	62·2–82·2	12.5
Worry	71·1	63·7–78·4	10.5	66·9	55·2–78·6	14.7
Treatment Anxiety	66·3	55·3–77·3	15.6	53·9	37·4–70·4	20.6
How I Look	69·9	61·9–78	11.4	72·2	60·5–84	14.7
Communication	65·4	54·3–76·5	15.7	68·8	54·8–82·7	17.4
Total	**73·7**	**68·2–79·2**	**7.8**	**70·1**	**62·7–77·4**	**9.2**

SD, standard deviation.
Bold values represent the overall results across the whole questionnaire.

impacts of transplantation were also explored which included physical consequences such as vulnerability to infections, as well as the impact on mental health. The age at transplantation was often referred to, with some participants feeling that being transplanted at a younger age was beneficial either due to the lack of memories of the transplant itself or because it was always a part of normal life whilst they were growing up. Conversely, some commented that being transplanted young was more challenging with one parent saying "the trauma of becoming so poorly and to need so much intervention at such a young age is underestimated" (Parent 31).

The second theme was about 'Normality' and what our patient's experience of "normality was. Naturally, the idea of "normalcy" is very abstract and will mean something different to every person and is something that many adolescents seek irrespective of underlying health conditions. Healthcare professionals should be careful not to try to define "normality" and should not reinforce "normalcy" as a binary concept that separates children with underlying health conditions from others. However, patients and parents did widely report their experience with seeking "normality" and how this changed post-transplant. Feeling different to others was challenging for many patients, however was seen as a positive thing in others. This partially related to physical differences, but also through missing out on life experiences during childhood due to illness. There was also some reference to a "normal life" and what that looked like post-transplant, with some stating that their life had become much more "normal" post-transplant.

The third theme related to ongoing care post-transplant. The challenges of transitioning into adulthood was deemed especially important. Participants described that the transition to adult services was "very difficult" (Parent 6), with less perceived support than the paediatric setting. They also described concerns about equal employment opportunities in the workplace. Concerns about the future appeared to become more prevalent as MSOT recipients grew older, with concerns about the implications of their transplant status. Furthermore, there was a number of comments made about the lack of psychosocial support post-transplant and how this remained a key issue impacting QoL.

Finally, there were also many suggestions for how transplant services could be improved, not only with further support for physical symptoms, but also more support for mental health. There were suggestions for both formal support and the potential value of peer support for the psychosocial health of MSOT recipients.

DISCUSSION

The results from this study have shown that patients who receive MSOT during childhood can have excellent long-term physical and quality of life outcomes with the right support from the multi-disciplinary team.

Overall, the graft survival, across all types of patients, particularly when death censored, is comparable to other studies looking at CLKT/SLKT and HKT outcomes [2, 5, 9, 25] and is similar if not better, than after single organ transplants as per the United Network for Organ Sharing (UNOS), European Society of Paediatric Nephrology/ European Renal Association/ European Dialysis and Transplantation Association (ESPN/ERA/EDTA), European Liver Transplant Registry (ELTR) and International Thoracic Organ Transplant Registry (ITOTR) registry data [8, 26–28]. For example, our kidney graft survival was 91% and 83% at 1 and 5 years, and the UNOS single-kidney graft survival was 95%–97% and 78%–88% across the same time periods. For liver transplants, our graft survival was 92% and 89% at 1 and 5 years, while UNOS single-liver graft survival was 86%–92% and 79%–87%. Our heart graft survival was 100% both at 1 and 5 years, compared to 87%–96% and 75%–84% from UNOS data for single-heart graft survival [28]. One possible reason for the excellent liver graft outcomes is that at least 40% of these children did not have end stage liver disease (ESLD) prior to transplant, but the liver was replaced for other reasons, such as replacing deficient enzyme activity in metabolic conditions. Existing data suggests that children with ESLD have poorer outcomes post-transplant so this may be a contributing factor to the positive outcomes in this study [29]. Another possible explanation for the improved graft survival in MSOT recipients is that these patients may have extra follow-ups with more than one specialist team (i.e., both with hepatologists/cardiologists and nephrologists) than children with isolated single-organ transplants. Therefore, any complications or findings that may impact graft survival may be picked up quicker

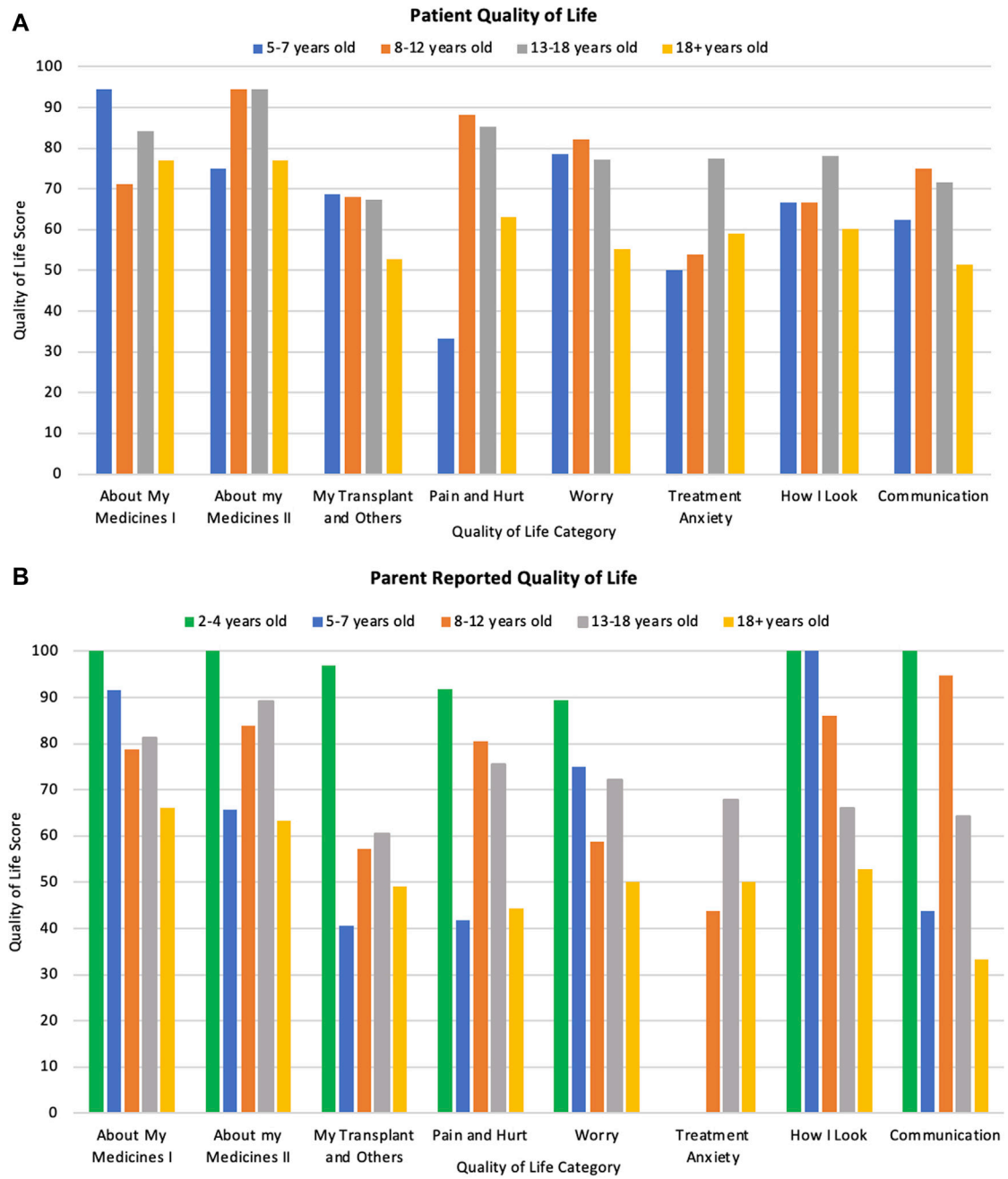


FIGURE 3 | (A) Patient reported quality of life scores across different ages and categories at time of response. **(B)** Parent reported scores of their child's quality of life across different patient ages and categories.

[30]. It is also likely that for these reasons, our patient survival was excellent and equally comparable to single-organ transplant recipients. Renal insufficiency is often cited as a relative contraindication to heart transplantation [31], but our data shows that these patients can still have excellent outcomes and so MSOT should still be carefully considered [11].

In terms of liver and kidney patients, our study suggests that CLKT may be a better option – with better outcomes for both the liver and kidney grafts. Furthermore, patients waited longer for their deceased donor KT in the SLKT group than in the CLKT group, and so were less likely to undergo pre-emptive transplants. This is possibly because multi-organ transplants are prioritised in the UK organ allocation process (thereby favouring the CLKT group), or may be because children receiving a KT after a liver transplant may be sensitised from their previous transplant [32, 33]. Current

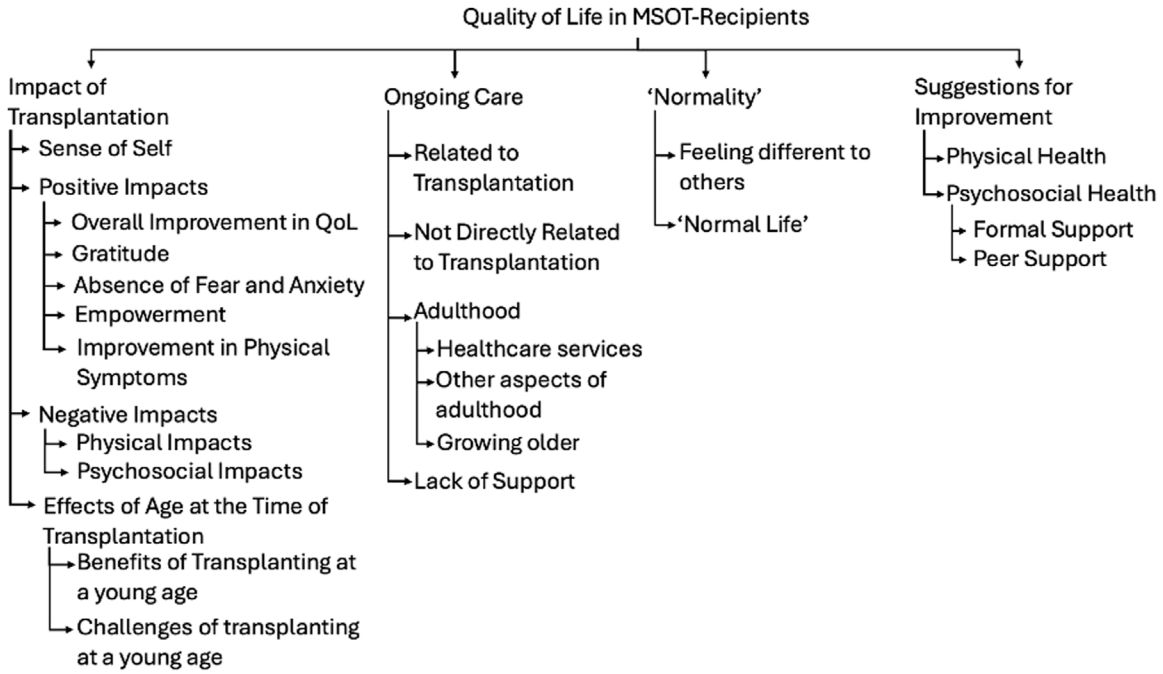


FIGURE 4 | Themes and Sub-themes identified in thematic analysis of free-text responses in quality of life questionnaire.

evidence highlights the improved outcomes after pre-emptive transplantation [34], so this is an important factor to consider when deciding to opt for CLKT or SLKT. We also did not find a difference in the rate of complications or mortality in the first-year post-transplant between the two groups. This is reassuring and suggests that an increased potential for complications or higher mortality in the first year post-transplant should not be the sole reason not to list a child for a CLKT if they are otherwise suitable.

A significant strength in this study is the use of a validated, transplant-specific to collect mixed methods data on quality of life; something which is relatively under investigated and therefore poorly quantified in all areas of paediatric transplantation.

One of our main findings is that children who are transplanted at a younger age have a significantly better QoL despite the fact that age at transplantation did not affect clinical outcomes. Our qualitative data indicates that this may be due to a lack of memory of the transplant itself, or of life before it was deemed a necessity. These children are likely to grow up with the identity of being a transplant recipient already embedded in their sense of self. Conversely older children may recall a time before they were unwell and must grow accustomed to their transplant recipient status from a place of prior 'normality'. Similarly, a study looking at QoL in paediatric LT recipients found older age at transplantation to be a predictor for poorer QoL [35]. We also found that QoL was worse in older patients, particularly with respects to medication burden and worries. Patients described that as they became older and more mature, they thought more about the implications of their health conditions, and they noticed greater differences between themselves and others. Increased worry and anxiety around the future may have significant implications on mental health and also on medication adherence. Although adherence was not formally investigated in this study, the About My Medicines I section of the questionnaire does explore patients' medication burden which showed that that adolescents struggled more with their medication burden than younger patients, putting them at higher risk of non-adherence. A key contributing factor to non-adherence is transition to adult services [36] which can be challenging, and some of our patients reported struggling with this. While our data shows better QoL in those transplanted at an earlier age, the clinical application of this finding is somewhat limited by our relatively small sample size. However, clinicians should be aware of this finding when assessing their patients who were transplanted at an older age.

The need for greater mental health support was very clearly identified within this study. Whilst it is well known that mental health issues are increasing in children for numerous reasons [37, 38], our cohort poses unique mental health needs that require a specialized and multidisciplinary approach, with equal focus on these and physical outcomes. Whilst participants did indicate the need for formal mental health support, peer support was also raised as an appropriate alternative. Such suggestions should be considered as part of standard care for MSOT recipients, particularly for adolescents as part of transition programs to protect the most vulnerable cohort of patients.

Although this study is limited by its sample size and the homogenous nature of the participants, it remains one of the largest cohort studies of MSOT to have been performed. However, all clinical data used has come from the UKTR, which is a reliable source that contains clinical data on every eligible patient, who was subsequently included in the analysis. Furthermore, this cohort has a long follow-up period and includes a large number of children reaching adulthood, and therefore provides high quality data to assess long-term outcomes. One of the possible limitations with our QoL data is that only <40% of patients and only surviving patients and families were surveyed. It is possible that patients who unfortunately died post-transplant or patients that did not participate in the QoL arm of the study had a very different QoL experience when compared to those who were able to participate.

Whilst it is encouraging to see that patients undergoing MSOT in childhood can have equally good outcomes as children requiring a single organ, it is important to note that single organ transplants are not a suitable option for these patients. A more worthwhile comparison would be to compare this cohort with the outcomes of patients who require MSOT but do not undergo transplantation, however such data is not readily available. We would also encourage prospective research in this field, starting prior to transplantation with participants completing annual QoL questionnaires both pre- and post-transplant to further identify trends and new issues in QoL.

CONCLUSION

This is the largest study presenting data on the outcomes of recipients of MSOT followed up over two decades. It is the first to look at all organ combinations and quality of life outcomes. It demonstrates that patients undergoing MSOT in childhood have excellent outcomes in terms of graft function, graft and patient survival, and QoL. These outcomes are all comparable to those undergoing single-organ transplants in the literature. Both liver and kidney graft survival and rates of rejection were found to be better in patients undergoing CLKT when compared to SLKT in this cohort of patients. QoL can be excellent with the support of the multi-disciplinary team which is crucial throughout patients' transplant journeys. The evidence in this study is supportive of children with the need for multiple organ replacement being considered for multi-organ transplantation.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by the NHS Health Research Authority Ethics Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/ next of kin.

AUTHOR CONTRIBUTIONS

JS co-ordinated this study and completed the application for registry data. AP, HM, and JS completed the ethics applications. MC, YT, JS, MM, and MR, served as PIs at other centres. AP conducted the literature review and analysed the quantitative data. AP and HM analysed the qualitative data. AP wrote the initial draft and coordinated the submission of the manuscript. All authors reviewed the manuscript and the data prior to submission. JS supervised the study. 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.2024.13372/full#supplementary-material

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ORIGINAL RESEARCH
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Longitudinal Trajectories of Estimated Glomerular Filtration Rate in a European Population of Living Kidney Donors

Manuela Almeida[1,2,3]*†, *Pedro Reis Pereira*[1,2,3], *José Silvano*[1,2,3], *Catarina Ribeiro*[1,2,3], *Sofia Pedroso*[1,2,3], *Sandra Tafulo*[2,4], *La Salete Martins*[1,2,3], *Miguel Silva Ramos*[5] and *Jorge Malheiro*[1,2,3]

[1]Department of Nephrology, Unidade Local de Saúde de Santo António (ULSdSA), Porto, Portugal, [2]UMIB - Unit for Multidisciplinary Research in Biomedicine, ICBAS - School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal, [3]ITR - Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal, [4]Instituto Português do Sangue e da Transplantação, Porto, Portugal, [5]Department of Urology, Unidade Local de Saúde de Santo António (ULSdSA), Porto, Portugal

A living donor (LD) kidney transplant is the best treatment for kidney failure, but LDs safety is paramount. We sought to evaluate our LDs cohort's longitudinal changes in estimated glomerular filtration rate (eGFR). We retrospectively studied 320 LDs submitted to nephrectomy between 1998 and 2020. The primary outcome was the eGFR change until 15 years (y) post-donation. Subgroup analysis considered distinct donor characteristics and kidney function reduction rate (%KFRR) post-donation [–($eGFR_{6\ months(M)}$–$eGFR_{pre\text{-}donation}$)/$eGFR_{pre\text{-}donation}$*100]. Donors had a mean age of 47.3 ± 10.5 years, 71% female. Overall, LDs presented an average eGFR change 6 M onward of +0.35 mL/min/1.73 m^2/year. The period with the highest increase was 6 M–2 Y, with a mean eGFR change of +0.85L/min/1.73 m^2/year. Recovery plateaued at 10 years. Normal weight donors presented significantly better recovery of eGFR +0.59 mL/min/1.73 m^2/year, compared to obese donors –0.18L/min/1.73 m^2/year (p = 0.020). Noteworthy, these results only hold for the first 5 years. The subgroup with a lower KFRR (<26.2%) had a significantly higher decrease in eGFR overall of –0.21 mL/min/1.73 m^2/year compared to the groups with higher KFRR (p < 0.001). These differences only hold for 6 M–2 Y. Moreover, an eGFR<50 mL/min/1.73 m^2 was a rare event, with ≤5% prevalence in the 2–15 Y span, correlating with eGFR pre-donation. Our data show that eGFR recovery is significant and may last until 10 years post-donation. However, some subgroups presented more ominous kidney function trajectories.

Keywords: kidney transplant, living donor, estimated glomerular filtration rate, living donor characteristics, estimated glomerular filtration rate trajectories

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***Correspondence**
Manuela Almeida,
manuelaalmeida.nefrologia@chporto.min-saude.pt,
manuela.almeida10@gmail.com

†ORCID:
Manuela Almeida
orcid.org/0000-0002-0312-3685

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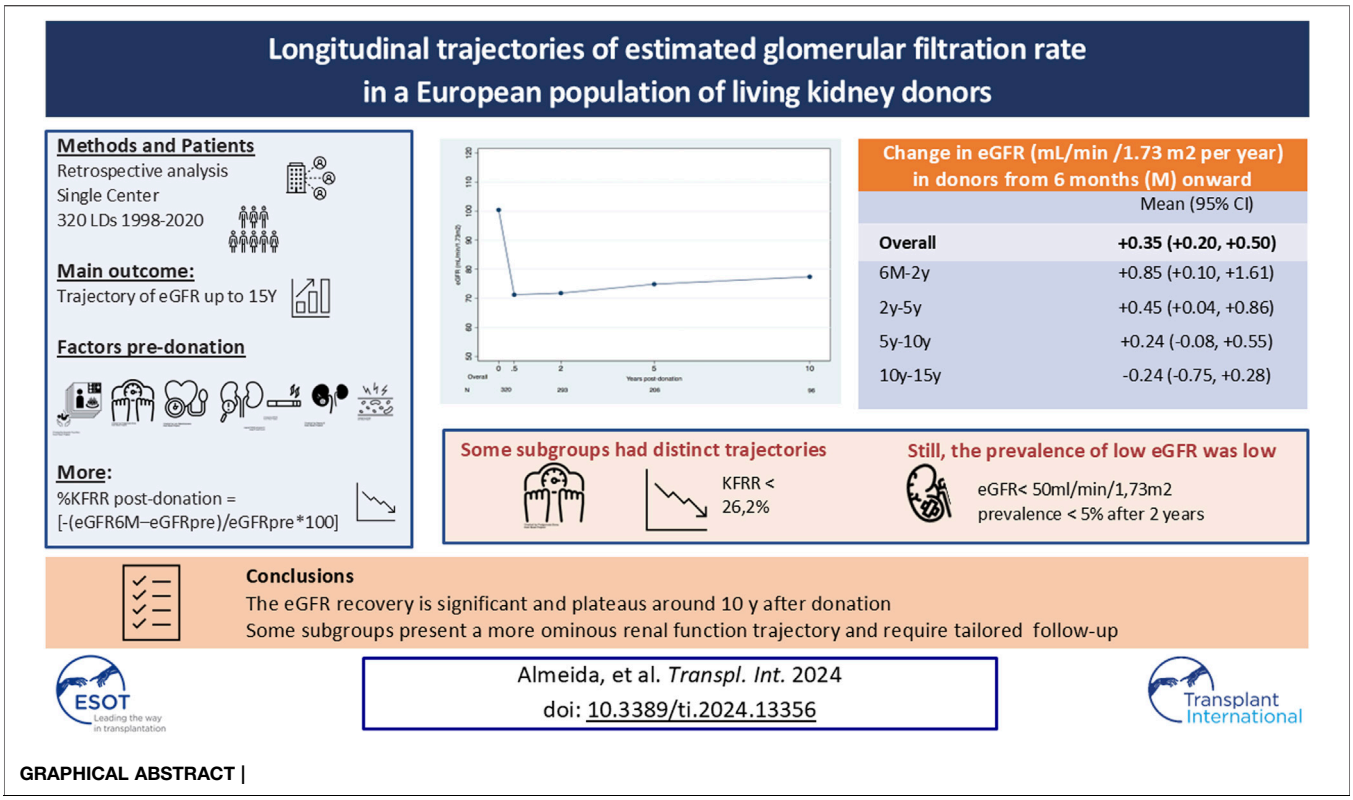
INTRODUCTION

A living donor (LD) kidney transplant (KT) is the best treatment for end-stage renal disease (ESRD) [1–3]. LDKT increases organ availability, decreases time on the waiting list, allows preemptive transplantation, and improves graft and patient survival with lower healthcare costs [1–5]. Although the perceived risks for the donors are considered low and ethically acceptable [3], two landmark studies showed an increased risk of ESRD in donors compared with matched



GRAPHICAL ABSTRACT |

healthy non-donors, albeit the absolute risk was minimal [6, 7]. Subgroups with a higher risk of ESRD have been identified [8, 9], but post-donation kidney function evolution and the mechanisms involved in the hyperfiltration after donation are less well characterized [10–14]. Furthermore, due to organ scarcity, we are increasingly accepting donors with borderline abnormalities that were previously declined [15]. Long-term follow-up data are scarce.

For guiding clinical practice, it would be desirable to foresee the evolution of kidney function after nephrectomy in each LD and the meaningful identification of markers that could identify individuals at higher risk in whom preventive measures of chronic kidney disease (CKD) and ESRD [16] could be sought more stringently. The 2017 Kidney Disease Improving Global Outcomes (KDIGO) Workgroup published extensive clinical practice guidelines for evaluating LD candidates [16]. They recommend that transplant programs provide each candidate with individualized quantitative estimates of short-term and long-term risks from the donation and a personalized follow-up plan [16]. However, the document does not provide precise instructions on how to do that.

We sought to retrospectively describe the estimated glomerular filtration rate (eGFR) change in our cohort of LDs and evaluate if it changes differently according to baseline donor characteristics and the kidney function reduction rate (KFRR) 6 months post-donation. We also investigated the prevalence of low eGFR (<50 mL/min/1.73 m^2) in different donor subgroups and proteinuria after donation. We hypothesize that identifying different patterns of eGFR change after donation could signal groups of LDs that would benefit from a better risk assessment and customized preventive care.

PATIENTS AND METHODS

We retrospectively reviewed the clinical data of all adult LDs submitted to nephrectomy at our center between January 1998 and January 2020 (n = 364). Inclusion criteria were serum creatinine (Scr) evaluation at 6 months and at least 3 Scr evaluations at follow-up (31 LKDs without Scr evaluations at 6 months and 13 without at least 3 evaluations at follow-up were excluded from the analysis, further details of non-included donors are available as **Supplementary Material**). The remaining 320 LKDs defined our studied cohort.

The Institutional Review Board at Unidade Local de Saúde de Santo António (ULSdSA) approved this retrospective observational study, which was conducted according to the Helsinki Declaration.

Donor Variables

Following international guidelines [16, 17], all donors were subjected to a standard evaluation protocol. Baseline demographic, anthropometric, analytical, and clinical data were collected from the LDs. Hypertension was defined by blood pressure in the consultation >140/90 mmHg, ABPM >135/85 mmHg, and past hypertension or antihypertensive medication. Uncontrolled hypertension or evidence of end-organ damage were criteria of exclusion.

TABLE 1 | Baseline characteristics of the study cohort.

	n = 320
Age (years), Mean ± SD	47.3 ± 10.5
Age (years), n (%)	
<40	81 (25)
40–55	154 (48)
≥55	85 (27)
Sex F:M, n (%)	227 (71):93(29)
BMI kg/m^2, Mean ± SD	25.3 ± 3.3
BMI kg/m^2, n (%)	
<25	155 (48)
25–30	132 (41)
≥30	33 (10)
Smoking habits, n (%)	48 (15)
Hypertension, n (%)	51 (16)
Dyslipidemia, n (%)	44 (14)
ProtU 0.15–0.5 g/g, n (%)	96 (30)
Pre-donation SCr mg/dL, Mean ± SD	0.75 ± 0.16
Pre- donation eGFR mL/min/1.73 m^2, Mean ± SD	100.4 ± 14.6
Pre- donation eGFR mL/min/1.73 m^2, n (%)	
<80	29 (9)
80–90	48 (15)
≥90	243 (76)
Number of SCr measurements, Median (IQR) [min. max.]	7 (5–11) [3.16]
% kidney function reduction rate (FKRR) post-donation*, Median (IQR)	31.9 (22.6–38.1)
% KFRR post-donation, n (%)	
<26.2	106 (33)
26.2–36.1	107 (33)
>36.1	107 (33)

**KFRR post-donation = [–(eGFR6M-eGFRpre-donation)/eGFRpre-donation*100].*
SD, standard deviation; n, number; F, female: M, male; BMI, Body Mass Index; ProtU, protein/creatinine ratio in the urine; ProtU 0.15–0.5 g/g, a ratio protein/creatinine of 0.15–0.5 g/g in a urinary sample; SCr, Serum creatinine; eGFR, estimated glomerular filtration rate; IQR, interquartile range; KFRR, kidney function reduction rate.

TABLE 2 | Change in eGFR (mL/min/1.73 m^2/year) in 320 donors from 6 months onward.

	Mean (95% CI)
Overall	+0.35 (+0.20, +0.50)
Linear spline model	
6M–2y	+0.85 (+0.10, +1.61)
2y–5y	+0.45 (+0.04, +0.86)
5y–10y	+0.24 (–0.08, +0.55)
10y–15y	–0.24 (–0.75, +0.28)

CI, confidence interval; M, months; y, years; eGFR, estimated glomerular filtration rate.

Potential donors with a history of malignancy, obesity, or diabetes were excluded. Serum creatinine-based CKD-Epidemiology Collaboration (CKD-EPI equation) [18] was used to predict eGFR. Although a lower limit of eGFR was not established by Unit protocol, potential donors with eGFR below 80 mL/min/1.73 m^2 were usually discarded. Upon urinary analysis, proteinuria was defined by a random urine protein/creatinine ratio of 0.15–0.5 g/g [19] and was confirmed by determination using a 24-h urinary sample. Donors with confirmed proteinuria over 300 mg/day were discarded [20, 21]. The final approval for kidney donation was reviewed in a multidisciplinary meeting, and ethical approval was mandatory.

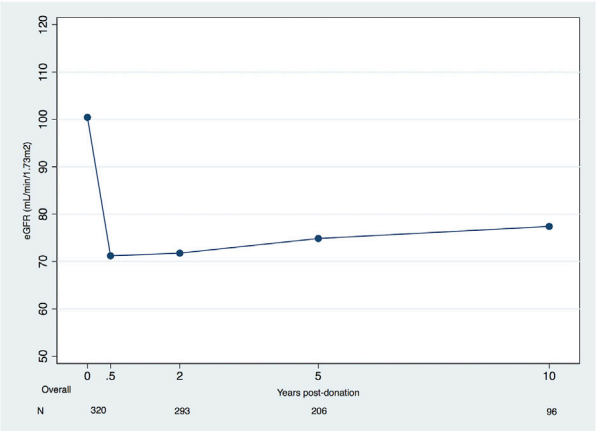


FIGURE 1 | Mean eGFR (mL/min/1.73 m^2) in living kidney donors pre-donation and during post-donation follow-up (eGFR, estimated glomerular filtration rate).

The date of nephrectomy was defined as the beginning of follow-up. All donors have lifetime annual follow-up appointments.

Outcomes

The primary outcome was the change in eGFR until 15 years post-donation (ml/min/1.73m^2/per year), using all available eGFR measurements from 6 months after the nephrectomy onward. Donors were followed from the nephrectomy date until one of the following occurred: death, ESRD, attaining 15-year follow-up, or end-of-study period (31 December 2022). We performed additional analyses to examine the effects of various characteristics on the progression of eGFR over time in living kidney donors presenting at the time of donation that could be associated with the recovery of kidney function after donation [22–25], including demographic and clinical data. Further, the kidney function reduction rate (%KFRR) post-donation [$-(eGFR_{6months(M)post\text{-}donation} - eGFR_{pre\text{-}donation})/eGFR_{pre\text{-}donation}*100$] in the remnant kidney in the first 6 months after donation was considered in the analysis, bearing in mind it was a variable available only after donation.

Statistical Analysis

Continuous data were described using mean and standard deviation (SD) or median (interquartile range [IQR]), and categorical data were expressed as numbers (and percentages). Categorical data were compared using Pearson chi-square test or Fisher exact test, and continuous variables were compared with Student's t-test or Mann–Whitney U-test.

Subgroup analysis considered the following donor characteristics: age, sex, obesity, diagnosis of hypertension, smoking habits, proteinuria, and pre-donation eGFR category; these same variables were included in the multivariable model. Differently, %KFRR post-donation as an independent predictor

TABLE 3 | Changes in eGFR (mL/min/1.73 m^2/year) in living kidney donors (n = 320) by subgroup over different periods during follow-up from 6 weeks onward (univariate analysis).

	Overall	Linear spline model			
		6M–2y	2y–5y	5y–10y	10–15y
Age (years)					
<40	+0.39 (+0.11, +0.68)^A	+0.09 (−1.44, 1.62)^A	+0.97 (+0.14, +1.80)^A	+0.10 (−0.51, 0.72)^A	−0.04 (−0.94, +0.87)^A
40–55	+0.34 (+0.13, +0.55)^A	+1.03 (−0.05, +2.11)^A	+0.36 (−0.22, +0.95)^A	+0.30 (−0.14, +0.74)^A	−0.41 (−1.14, +0.32)^A
≥ 55	+0.52 (+0.21, +0.82)^A	+1.39 (−0.07, +2.84)^A	+0.33 (−0.46, +1.13)^A	+0.47 (−0.20, +1.14)^A	+0.12 (−1.08, +1.32)^A
p	*0.642*	*0.457*	*0.445*	*0.73*	*0.698*
Sex					
Male	+0.54 (+0.25, +0.82)	+0.08 (−1.34, +1.50)	+0.79 (+0.00, +1.58)	+0.36 (−0.25, +0.98)	+0.86 (−0.14, +1.85)
Female	+0.28 (+0.10, +0.45)	+1.16 (+0.27, +2.04)	+0.34 (−0.14, +0.82)	+0.20 (−0.17, +0.56)	−0.65 (−1.24, −0.05)
p	*0.124*	*0.209*	*0.335*	*0.653*	***0.011***
BMI (kg/m^2)*					
<25	+0.50 (+0.28, +0.71)^A	+0.46 (−0.62, +1.54)^A	+0.96 (+0.37, +1.54)^A	+0.17 (−0.30, +0.64)^A	+0.01 (−0.85, +0.86)^A
25–30	+0.32 (+0.10, +0.54)^A	+2.23 (+1.06, +3.41)^B	−0.29 (−0.92, +0.34)^B	+0.50 (+0.05, +0.96)^A	−0.49 (−1.20, +0.22)^A
≥30	−0.01 (−0.50, +0.47)^A	−2.52 (−4.82, −0.22)^C	+1.28 (+0.02, +2.55)^A	−0.51 (−1.60, +0.58)^A	+0.08 (−1.44, +1.60)^A
p	*0.143*	***0.001***	***0.007***	*0.205*	*0.616*
Hypertension					
No	+0.33 (+0.17, +0.49)	+0.95 (+0.12, +1.77)	+0.35 (−0.10, +0.79)	+0.30 (−0.04, +0.64)	−0.37 (−0.91, +0.18)
Yes	+0.53 (+0.13, +0.93)	+0.42 (−1.47, +2.31)	+1.05 (+0.03, +2.08)	−0.09 (−0.97, +0.79)	+0.83 (−0.69, +2.35)
p	*0.365*	*0.616*	*0.215*	*0.413*	*0.148*
Smoking habits					
No	+0.32 (+0.15, +0.48)	+1.26 (+0.45, +2.08)	+0.22 (−0.23, +0.66)	+0.28 (−0.05, +0.62)	−0.44 (−1.00, +0.13)
Yes	+0.58 (+0.19, +0.97)	−1.52 (−3.48, +0.43)	+1.92 (+0.84, +3.00)	+0.02 (−0.84, +0.87)	+0.65 (−0.57, +1.87)
p	*0.213*	***0.01***	***0.004***	*0.567*	*0.114*
Dyslipidemia					
No	+0.33 (+0.17, +0.49)	+0.82 (+0.00, +1.63)	+0.46 (+0.02, +0.91)	+0.22 (−0.12, +0.55)	−0.31 (−0.87, +0.24)
Yes	+0.50 (+0.08, +0.92)	+1.20 (−0.79, +3.20)	+0.41 (−0.70, +1.52)	+0.42 (−0.49, +1.32)	+0.21 (−1.22, +1.63)
p	*0.459*	*0.724*	*0.928*	*0.682*	*0.504*
ProtU 0.15–0.5 g/g					
No	+0.32 (+0.15, +0.49)	+1.20 (+0.30, +2.11)	+0.22 (−0.26, +0.71)	+0.30 (−0.05, +0.65)	−0.26 (−0.83, +0.30)
Yes	+0.44 (+0.14, 0.75)	+0.06 (−1.31, +1.42)	+1.01 (+0.25, +1.77)	+0.05 (−0.67, +0.77)	−0.17 (−1.42, +1.09)
p	*0.502*	*0.17*	*0.086*	*0.541*	*0.891*
Pre-donationeGFR*(mL/min/1.73 m^2)					
<80	−0.06 (−0.61, +0.48)^A	+2.84 (+0.31, +5.37)^A	−0.06 (−1.58, +1.46)^A	−0.88 (−2.08, +0.32)^A	−0.75 (−2.23, +0.73)^A
80–90	+0.47 (+0.10, +0.85)^A	+2.15 (+0.24, +4.06)^A	−0.43 (−1.48, +0.62)^A	+0.48 (−0.32, +1.27)^A	+1.38 (+0.15, +2.61)^B
≥90	+0.38 (+0.21, +0.55)^A	+0.37 (−0.49, +1.24)^A	+0.70 (+0.24, +1.16)^A	+0.32 (−0.03, +0.68)^A	−0.54 (−1.15, +0.07)^A
p	*0.256*	*0.07*	*0.122*	*0.146*	***0.018***
%KFRR post-donation*, **					
<26.2	−0.12 (−0.34, +0.10)^B	−2.89 (−4.19, −1.59)^A	+0.59 (−0.08, +1.26)^A	−0.01 (−0.48, +0.46)^A	−0.24 (−0.90, +0.43)^A
26.2–36.1	+0.62 (+0.36, +0.87)^A	+1.54 (+0.24, +2.83)^B	+0.88 (+0.17, +1.59)^A	+0.25 (−0.30, +0.80)^A	−0.29 (−1.36, +0.79)^A
>36.1	+0.75 (+0.48, +1.02)^A	+3.77 (+2.50, +5.04)^C	+0.05 (−0.66, +0.76)^A	+0.61 (+0.02, +1.20)^A	−0.56 (−1.67, +0.55)^A
p	***<0.001***	***<0.001***	*0.262*	*0.273*	*0.885*

**In variables with 3 or more groups, each box will present letters A to C (superscript). It should be concluded that subgroups that share the same letters in the same box are non-significantly different.*

***KFRR post-donation = [−(eGFR6M-eGFRpre-donation)/eGFRpre-donation*100].*

y, years; M, months; BMI, body mass index; ProtU, protein/creatinine ratio in the urine; eGFR, estimated glomerular filtration rate; KFRR, kidney function reduction rate.

p *values are depicted in italics; statistically significant* p *values (<.05) are shown in bold.*

was evaluated separately, adjusted to the aforementioned donor characteristics pre-donation.

Donor eGFR change between 6 months and 15 years post-donation was assessed by univariate and multivariable linear mixed regression model that imputed subject-specific random effects (intercept and slope defined as eGFR at 6-month and time in years, respectively) on an unstructured covariance matrix. The Bonferroni test was used to correct multiple significance tests. The dependent variable was all eGFR measurements, and the independent variables were entered as 2-way interaction terms between them and the time (in years) variable. Additionally, distinct temporal trends of eGFR change were sought by imputing time as a linear spline with knots at 2, 5, and 10 years.

Statistical calculations were performed using STATA/MP, version 15.1 (Stata Corp, College Station, TX, United States). A 2-sided *P*-value <0.05 was considered as statistically significant.

RESULTS

Baseline Characteristics

The baseline characteristics for our study cohort are summarized in **Table 1**. The mean age of the population was 47.3 ± 10.5 years, and most were female (71%). The representation in the race of donors was nearly exclusively Caucasian. Most donors were either overweight

TABLE 4 | Changes in eGFR (mL/min/1.73 m^2/year) in living kidney donors (n = 320) by subgroup over different periods during follow-up from 6 months onward (multivariable analysis).

	Overall	Linear spline model			
		6mo–2y	2y–5y	5y–10y	10–15y
Age* (years)					
<40	+0.36 (+0.07, +0.65)^{A}	+0.66 (−0.94, 2.26)^{A}	+0.69 (−0.18, +1.56)^{A}	+0.05 (−0.61, +0.71)^{A}	+0.08 (−1.03, +1.18)^{A}
40–55	+0.41 (+0.21, +0.62)^{A}	+1.18 (+0.08, +2.27)^{A}	+0.42 (−0.17, +1.01)^{A}	+0.36 (+0.08, +0.81)^{A}	−0.47 (−1.31, +0.38)^{A}
≥55	+0.44 (+0.12, +0.75)^{A}	+0.96 (−0.59, +2.51)^{A}	+0.45 (−0.39, +1.30)^{A}	+0.40 (−0.34, +1.14)^{A}	+0.07 (−1.51, +1.36)^{A}
p	*0.932*	*0.87*	*0.879*	*0.706*	*0.727*
Sex					
Male	+0.61 (+0.31, +0.91)	+0.57 (−0.91, +2.05)	+0.60 (−0.23, +1.43)	+0.68 (−0.01, +1.37)	+0.53 (−0.93, +2.00)
Female	+0.33 (+0.16, +0.50)	+1.15 (+0.24, +2.06)	+0.46 (−0.03, +0.95)	+0.15 (−0.25, +0.55)	−0.52 (−1.24, +0.21)
p	*0.128*	*0.522*	*0.787*	*0.222*	*0.242*
BMI* (kg/m^2)					
<25	+0.59 (+0.37, +0.80)^{B}	+0.67 (−0.44, +1.77) ^{AB}	+0.97 (+0.36, +1.57)^{B}	+0.32 (−0.17, +0.81)^{A}	−0.11 (−1.14, +0.91)^{A}
25–30	+0.35 (−0.14, +0.56) ^{AB}	+2.17 (+0.98, +3.36)^{B}	−0.17 (−0.81, +0.46)^{A}	+0.49 (+0.02, +0.95)^{A}	−0.26 (−1.01, +0.48)^{A}
≥30	−0.18 (−0.68, +0.31)^{A}	−2.47 (−4.92, −0.03)^{A}	+1.18 (−0.17, +2.53) ^{AB}	−0.64 (−1.82, +0.54)^{A}	−0.62 (−2.39, +1.16)^{A}
p	***0.02***	***0.002***	***0.021***	*0.214*	*0.897*
Hypertension					
No	+0.37 (+0.21, +0.53)	+1.07 (+0.23, +1.90)	+0.34 (−0.11, +0.80)	+0.37 (+0.01, +0.73)	−0.22 (−0.88, +0.44)
Yes	+0.60 (+0.19, +1.01)	+0.58 (−1.48, +2.64)	+1.36 (+0.23, +2.48)	−0.12 (−1.08, +0.83)	−0.29 (−2.17, +1.59)
p	*0.313*	*0.672*	*0.11*	*0.361*	*0.946*
Smoking					
No	+0.41 (+0.25, +0.56)	+1.31 (+0.48, +2.14)	+0.30 (−0.15, +0.75)	+0.40 (+0.04, +0.75)	−0.30 (−1.01, +0.42)
Yes	+0.40 (−0.01, +0.82)	−0.86 (−2.93, +1.20)	+1.66 (+0.48, +2.83)	−0.31 (−1.32, +0.70)	+0.16 (−1.47, +1.78)
p	*0.985*	*0.059*	***0.039***	*0.211*	*0.648*
Dyslipidemia					
No	+0.37 (+0.22, +0.53)	+0.92 (+0.10, +1.75)	+0.51 (+0.06, +0.95)	+0.27 (−0.08, +0.62)	−0.30 (−0.96, +0.36)
Yes	+0.61 (+0.19, +1.04)	+1.45 (−0.72, +3.62)	+0.43 (−0.78, +1.64)	+0.46 (−0.52, +1.43)	+0.24 (−1.54, +2.03)
p	*0.311*	*0.661*	*0.904*	*0.725*	*0.585*
ProtU					
0.15–0.5 g/g	+0.39 (+0.23, +0.55)	+1.28 (+0.38, +2.20)	+0.32 (−0.16, +0.81)	+0.37 (+0.01, +0.72)	−0.24 (−0.88, +0.41)
No	+0.46 (+0.16, 0.76)	+0.19 (−1.19, +1.56)	+0.99 (+0.22, +1.75)	+0.08 (−0.65, +0.82)	−0.21 (−1.61, +1.18)
Yes	*0.674*	*0.193*	*0.152*	*0.504*	*0.975*
p					
Predonation eGFR*(mL/min/1.73m^2)					
<80	−0.09 (−0.63, +0.44)^{A}	+2.85 (+0.24, +5.46)^{A}	+0.14 (−1.41, +1.69)^{A}	−1.16 (−2.39, +0.06)^{B}	−0.44 (−2.03, +1.15) ^{AB}
80–90	+0.52 (+0.16, +0.88)^{A}	+2.32 (+0.34, +4.29)^{A}	−0.33 (−1.41, +0.75)^{A}	+0.51 (−0.31, +1.32)^{A}	+1.62 (+0.23, +3.01)^{B}
≥90	+0.43 (+0.27, +0.60)^{A}	+0.54 (−0.34, +1.41)^{A}	+0.70 (+0.23, +1.17)^{A}	+0.40 (+0.04, +0.77)^{A}	−0.58 (−1.33, +0.18)^{A}
p	*0.141*	*0.105*	*0.217*	***0.049***	***0.028***

**In variables with 3 or more groups, each box will present letters A to C (superscript). It should be concluded that subgroups that share the same letters in the same box are non-significantly different.*
y, years; M, months; BMI, body mass index; ProtU, protein/creatinine ratio in the urine; eGFR, estimated glomerular filtration rate.
p *values are depicted in italics; statistically significant,* p *values (<.05) are shown in bold.*

(41%) or obese (10%). Fifteen percent had smoking habits, 14% had dyslipidemia, and 16% had hypertension. Pre-donation mean eGFR was 100.4 ± 14.6 mL/min/1.73 m^2. 76% of the cohort had eGFR >90 mL/min/1.73 m^2, and 29 donors (9%) had eGFR <80 mL/min/1.73 m^2. Ninety-six donors (30%) had proteinuria.

At follow-up, after discharge, the donors had a median number of SCr measurements of 7 (IQR 5–11), performed, per protocol, at 6 months, 1 year after donation, and then yearly.

Evolution of Renal Function After Donation

The median percentage of KFRR was 31.9 (IQR 22.6–38.1)%, One-third of the cohort had a reduction rate of less than 26.2%, one-third between 26.2% and 36.1%, and one-third greater than 36.1% (**Table 1**).

Overall, after the first 6 months, our cohort's eGFR increased, on average, +0.35 mL/min/1.73 m^2/year (95% confidence interval (CI), +0.20 to +0.50). Using the linear spline model results, the average changes of eGFR were, respectively, from 6 months to 2 years, 2–5 years, 5–10 years, and 10–15 years, +0.85 mL/min/1.73 m^2/year (95% CI, +0.10 to +1.61), +0.45L/min/1.73 m^2/year (95% CI, +0.04 to +0.86), +0.24 mL/min/1.73 m^2/year (95% CI, −0.08 to +0.55) and −0.24 mL/min/1.73 m^2/year (95% CI, −0.75 to +0.28) (**Table 2**). A plateau was achieved around 10 years (**Figure 1**).

Donor Subgroup Analysis

Overall, there were no significant differences in the evolution of renal function after donation based on donor characteristics such as age, sex, hypertension, dyslipidemia, and presence of proteinuria (**Tables 3**, **4**).

We found a non signficant trend when comparing pre-donation eGFR subgroups. The donors with lower eGFR pre-donation (<80 mL/min/1.73 m^2) presented a negative eGFR change overall of −0.09 (95% CI, −0.63 to+0.44)mL/min/1.73 m^2 vs. a positive shift in around 0.5 mL/min/1.73 m^2 in

TABLE 5 | Changes in eGFR (mL/min/1.73 m^2/year) in living kidney donors (n = 320) by % of KFRR post-donation donor group over different periods during follow-up from 6 months onward (multivariable analysis), adjusted to pre-donation variables previous analyzed: donor age, sex, BMI group: <25, 25–30, ≥30 kg/m^2, diagnosis of hypertension, smoking habits, dyslipidemia, presence of proteinuria and eGFR group <80, 80–90 and ≥90 m/min/1.73 m^2.

	Overall	Linear spline model			
		6M–2y	2y–5y	5y–10y	10–15y
%KFRR post-donation*,**					
<26.2	−0.21 (−0.42, +0.01)^B	−2.71 (−4.04, −1.39)^A	+0.35 (−0.34, +1.03)^A	+0.03 (−0.47, +0.53)^A	−0.36 (−1.14, +0.42)^A
26.2–36.1	+0.53 (+0.28, +0.78)^A	+1.50 (+0.20, +2.80)^B	+0.79 (+0.08, +1.51)^A	+0.09 (−0.48, +0.66)^A	−0.49 (−1.77, +0.80)^A
>36.1	+0.65 (+0.39, +0.92)^A	+3.66 (+2.38, +4.94)^C	+0.04 (−0.67, +0.76)^A	+0.43 (−0.19, +1.05)^A	−0.61 (−1.84, +0.61)^A
p	***<0.001***	***<0.001***	*0.339*	*0.595*	*0.941*

**In variables with 3 or more groups, each box will present letters A to C (superscript). It should be concluded that subgroups that share the same letters in the same box are non-significantly different.*

***KFRR post-donation = [−(eGFR6M-eGFRpre-donation)/eGFRpre-donation*100].*

y, years; M, months; BMI, body mass index; ProtU, protein/creatinine ratio in the urine; eGFR, estimated glomerular filtration rate; KFRR, kidney function reduction rate post-donation.

p *values are depicted in italics; statistically significant,* p *values (<.05) are shown in bold.*

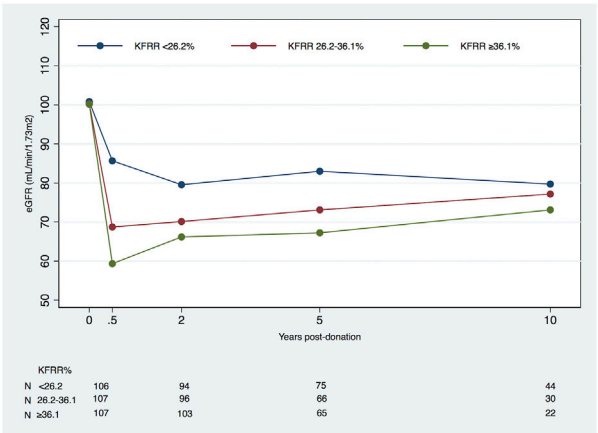


FIGURE 2 | Mean eGFR (mL/min/1.73 m^2) in living kidney donors by kidney function reduction rate (KFRR*) percentage subgroups at 6 months, starting at pre-donation and during post-donation follow-up (eGFR, estimated glomerular filtration rate). *KFRR post-donation = [−(eGFR6M-eGFRpre-donation)/eGFRpre-donation*100].

the subgroups with ≥80 mL/min/1.73 m^2 pre-donation (**Table 4**). Moreover, when analyzing eGFR variations by timespans, the subgroup with lower eGFR pre-donation presented a significant decline in eGFR in the period between 5 and 10 years of −1.16 (95% CI, −2.39 to +0.06) mL/min/1.73 m^2/year, when compared to the other subgroups: +0.51 (95% CI, −0.31 to +1.32) mL/min/1.73 m^2/year in the subgroup with pre-donation eGFR 80–90 mL/min/1.73 m^2, vs. +0.40 (95% CI, +0.04 to +0.77) mL/min/1.73 m^2/year in those with ≥90 mL/min/1.73 m^2 pre-donation, $p = 0.049$. The lower function subgroup was associated with a more precocious increase in eGFR. The group with the highest eGFR pre-donation presented a more stable behavior, resembling the overall cohort, except for the last period of 10–15 years.

Pre-donation obesity was associated with a significantly greater decline of eGFR in the cohort over the entire period compared to normal weight donors (**Table 4**). Obese donors had a decrease of eGFR of −0.18 (95% CI −0.68 to +0.31) mL/min/1.73 m^2/year, while the second group had an increase of +0.59 (95% CI +0.37, +0.80) mL/min/1.73 m^2/year ($p = 0.02$). This difference was more apparent in the earlier periods post-donation (6 months–5 years), with varying directions. Initially, at 6 months to 2 years, obese donors experienced significantly higher decline of eGFR of −2.47 (95% CI, −4.92 to −0.03) mL/min/1.73 m^2/year, $p = 0.002$. However, in the 2–5 year period, they showed a temporary recovery of eGFR of +1.18 (95% CI, −0.17 to +2.53) mL/min/1.73 m^2/year.

We carried out a separate analysis of %KFRR at 6 months post-donation, adjusted to the LD pre-donation factors (**Table 5**). The subgroup with a lower percentage of KFRR (<26.2%) had a significantly negative change in eGFR overall compared to the groups with higher loss rates of −0.21 (95% CI, −0.42 to +0.01) mL/min/1.73 m^2/year vs. +0.53 (95% CI, +0.28 to +0.78) in the intermedium group and +0.65 (95% CI, +0.39 to +0.92) mL/min/1.73 m^2/year in the group with KFRR >36.1%, $p < 0.001$. In the linear spline model, these differences only hold for 6 months to 2 years, where the three subgroups of kidney function recovery had significantly different eGFR changes (**Figure 2**).

Table 6 presents the observed eGFR values in our cohort, categorized by different subgroups, before and after donation at 6 months, 2, 5, 10, and 15 years.

Low eGFR and Proteinuria in LKD During Follow-Up

Table 7 depicts the eGFR category (ml/min/1.73 m^2) for our cohort of LDs based on the last available SCr measurement. Notably, no donor reached eGFR <15 mL/min/1.73 m^2, and only six reached CKD stages 3b and 4.

We analyzed the prevalence of low eGFR by time frames after donation. We considered several cutoffs (**Table 8**). When we used eGFR <60 mL/min/1.73 m^2, according to KDIGO definition of CKD [26], the prevalence of low eGFR during follow-up diminished from 25% at 6 months to 13% at 10 years. This was not an unexpected finding. We have observed a steady increase in eGFR from 6 months post-donation up to 10 years after donation. No donor had eGFR <30 mL/min/1.73 m^2, and

TABLE 6 | Mean eGFR (mL/min per 1.73 m^2) in living kidney donors by subgroup using the CKD-EPI equation, pre-donation, and post-donation at 6 months, 2 years, 5 and 10 years.

	Pre-donation	6M	2y	5y	10y
N	320	320	293	206	96
Overall	100.4 (14.6)	71.2 (16.3)	71.8 (14.9)	74.9 (16.1)	77.4 (14.8)
Age (years)					
<40	112.1 (12.8)^A	81.6 (15.8)^A	81.7 (14.7)^A	86.7 (13.2)^A	83.9 (11.4)^A
40–55	99.1 (14.1)^B	70.1 (15.7)^B	70.7 (13.0)^B	73.9 (14.8)^B	77.7 (15.3)^A
≥ 55	91.8 (10.3)^C	63.3 (12.3)^C	65.1 (13.8)^C	64.9 (13.6)^C	68.3 (13.4)^B
p	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***0.001***
Sex					
Male	99.3 (14.3)	70.3 (18.0)	69.4 (15.9)	73.5 (16.5)	75.2 (17.5)
Female	100.9 (14.8)	71.6 (15.5)	72.6 (14.4)	75.4 (16.0)	78.1 (13.9)
p	*0.363*	*0.596*	*0.099*	*0.459*	*0.406*
BMI (kg/m^2)					
<25	102.4 (15.0)^A	73.5 (16.8)^A	73.4 (15.7)^A	78.4 (16.5)^A	78.7 (13.9)^A
25–30	99.0 (14.0)^A	67.8 (13.8)^B	70.5 (13.3)^A	70.5 (13.4)^B	76.0 (14.4)^A
≥30	97.2 (14.6)^A	74.2 (20.6)^B	69.4 (16.2)^A	75.0 (20.1)^A	80.7 (22.8)^A
p	*0.060*	***0.007***	*0.187*	***0.004***	*0.583*
Hypertension					
No	101.7 (14.6)	72.1 (16.4)	72.8 (14.9)	76.0 (16.2)	78.1 (14.6)
Yes	93.6 (12.6)	66.4 (15.0)	66.4 (13.9)	69.1 (14.1)	71.7 (15.7)
p	***<0.001***	***0.022***	***0.007***	***0.025***	*0.176*
Smoking habits					
No	99.3 (14.4)	70.3 (15.8)	71.4 (14.9)	74.0 (16.0)	77.0 (14.9)
Yes	106.5 (14.4)	76.6 (18.1)	74.1 (14.7)	79.8 (16.0)	79.7 (14.7)
p	***0.002***	***0.013***	*0.256*	*0.069*	*0.552*
Dyslipidemia					
No	102.0 (13.8)	72.6 (16.2)	73.1 (14.7)	76.3 (15.6)	77.8 (14.4)
Yes	90.8 (16.0)	62.7 (14.5)	64.0 (13.7)	65.1 (16.1)	74.7 (18.0)
p	***<0.001***	***<0.001***	***<0.001***	***<0.001***	*0.523*
ProtU 0.15–0.5 g/g					
No	100.0 (13.9)	70.9 (15.7)	71.5 (14.8)	73.4 (15.0)	77.0 (15.4)
Yes	101.5 (16.2)	72.0 (17.6)	72.2 (15.1)	78.2 (18.0)	79.5 (11.5)
p	*0.375*	*0.573*	*0.714*	*0.051*	*0.546*
Predonation eGFR*(mL/min/1.73m^2)					
<80	71.6 (6.7)^A	52.7 (10.8)^A	56.1 (12.2)^A	59.3 (17.7)^A	60.5 (9.4)^A
80–90	85.7 (3.0)^B	62.3 (12.1)^B	63.6 (12.2)^A	63.6 (12.5)^A	71.8 (17.2)^{AB}
≥90	106.8 (9.6)^C	75.2 (15.3)^C	75.3 (13.8)^B	78.3 (14.8)^B	80.1 (13.4)^B
p	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***
%KFRR post-donation*,**					
<26.2	100.8 (16.9)^A	85.7 (16.1)^A	79.6 (15.9)^A	84.0 (16.8)^A	79.7 (15.0)^A
26.2–36.1	100.3 (14.1)^A	68.7 (10.5)^B	70.1 (12.8)^B	73.1 (14.1)^B	77.2 (14.9)^A
>36.1	100.2 (12.7)^A	59.3 (8.6)^C	66.2 (12.6)^B	67.2 (12.7)^B	73.1 (14.0)^A
p	*0.941*	***<0.001***	***<0.001***	***<0.001***	*0.234*

**In variables with 3 or more groups, each box will present letters A to C (superscript). It should be concluded that subgroups that share the same letters in the same box are non-significantly different.*

***KFRR post-donation = [–(eGFR6M-eGFRpre-donation)/eGFRpre-donation*100].*

Y, years; M, months; BMI, body mass index; ProtU, protein/creatinine ratio in the urine; eGFR, estimated glomerular filtration rate; FKRR, kidney function reduction rate post-donation; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration equation.

p *values are depicted in italics; statistically significant,* p *values (<.05) are shown in bold.*

only one percent had eGFR <40 mL/min/1.73 m^2. We selected the cutoff of 50 mL/min/1.73 m^2, as we believe that it defines a more meaningful CKD status, to analyze the prevalence of low eGFR by subgroup over different periods during follow-up (**Table 9**). The prevalence of low eGFR remained overall low after 6 months, ≤5%. Older LDs (≥55 years) had a significantly higher prevalence of low eGFR from 6 months until 5 years of follow-up (13% for those ≥55 years vs. 3% for those 40–55 years and none in the younger group, $p = 0.005$), not thereafter. The same holds for donors with lower eGFR pre-donation. Those with higher KFRR (>36.1%) had a higher prevalence of lower eGFR at 6 months of 19% vs. 6% in the intermedium group and 0% in the group with KFRR <26.2%, $p < 0.001$. No difference in prevalence of lower eGFR was observed between KFRR subgroups thereafter.

These findings were accompanied by a non-significant rise in proteinuria after donation (**Table 10**). In fact, the prevalence of proteinuria decreased from 30% pre-donation to 10% 6 months after donation, and that prevalence remained stable afterward.

DISCUSSION

In this cohort of 320 LDs, we found reassuring results about the evolution of long-term eGFR in LDs. Overall, the donors

TABLE 7 | eGFR (ml/mi/1.73 m^2) category for donors based on the last available SCr measurement, using the CKD-EPI equation.

eGFR (ml/min/1.73 m^2)	n = 320 n (%)
<15	0
15–30	2 (1)
30–45	4 (1)
45–60	55 (17)
60–90	205 (64)
≥90	54 (17)

Scr, serum creatinine; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration equation.

TABLE 8 | Prevalence of low eGFR (ml/min/1.73 m^2) using the CKD-EPI equation, in living kidney donors during follow-up n (%).

	Predonation	6 M	2y	5y	10y
N	320	320	293	206	96
<60	0	79 (25)	68 (23)	38 (18)	12 (13)
<55	0	44 (14)	31 (11)	16 (8)	5 (5)
<50	**0**	**26 (8)**	**13 (4)**	**10 (5)**	**2 (2)**
<45	0	8 (3)	3 (1)	4 (2)	2 (2)
<40	0	3 (1)	2 (1)	2 (1)	1 (1)
<35	0	0	2 (1)	0	0
<30	0	0	0	0	0

M, months; y, years; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration equation.
Bold is used to indicate the cutoff for defining a low estimated glomerular filtration rate in the cohort.

presented an average change in eGFR 6 months onward of +0.35 (95% CI, +0.20 to +0.50) mL/min/1.73 m^2 per year. The period with the higher increase was from 6 months to 2 years with a mean increase of eGFR of +0.85 (95% CI +0.10 to +1.61) mL/min/1.73 m^2 per year, and the recovery after donation plateaued at 10 years, after which the calculated mean change in eGFR is −0.24 (95% CI, −0.75 to +0.28) mL/min/1.73 m^2 per year. To the best of our knowledge, this time span of 10–15 years post-donation trajectories have not been previously reported. As we hypothesized, when subgroups of donors were analyzed, we identified different kidney function recovery patterns. Obese LDs had a statistically significant overall worse recovery of eGFR compared to normal weight donors. The recovery trajectory of kidney function in obese donors showed a biphasic pattern at earlier timespans after donation, up to 5 years. The intermediate group of eGFR pre-donation has a better recovery than the extreme function groups. LDs with a lower %KFRR at 6 M (<26.2%) compared to eGFR pre-donation presented a significantly higher decrease of eGFR in the overall period compared to the other two groups. Still, the differences between groups only hold for the time frame of 6 M to 2 years. Moreover, an eGFR <50 mL/min/1.73 m^2 was a rare event, and the proteinuria prevalence did not increase during the follow-up.

A substantial nephron loss is expected in the aging kidneys [27]. Renal function decline was well-characterized in several general and healthy populations [28–30]. Studies in the healthy Swedish population have demonstrated that the mean decline in GFR was 4 mL/min/1.73 m^2 per decade up to 50 years of age and then decreased annually by 1 mL/min [29, 30]. In a large series of healthy potential LDs, Fenton et al. [28] found the measured GFR (mGFR) had a linear decline after 35 years of 6.6–7.7 mL/min/1.73 m^2/decade. In the long term (10–15Y), our cohort's mean change in eGFR stayed below these references.

Increases in GFR long-term after donation have been described for years [31, 32], but most studies lack detailed data about GFR trajectories. Matas et al. [32] found that the increase in eGFR continued until at least 20 years post-donation in their study of 2002 predominantly white donors.

Kasiske et al. [14], in a prospective observational study, compared 205 living donor candidates and 203 healthy controls with serially measured iohexol GFR. Between 6 M and 9 years, the mean change in mGFR was significantly different among donors +0.02 (95% CI, −0.16 to −20) mL/min/1.73 m^2/year vs. −1.26 (95% CI, −1.52 to −1.00) mL/min/1.73 m^2/year in controls. Lam et al. [10], in a retrospective cohort study of LDs in Alberta, in 2002–2016, matched 604 donors to 2,414 healthy non-donors from the general population. Overall, from 6 weeks onwards, the eGFR increased by 0.35 mL/min/1.73 m^2 per year (95% CI, +0.21 to +0.48) in donors and significantly decreased by −0.85 mL/min/1.73 m^2 per year (95% CI, −0.94 to −0.75) in the matched non-donors [10]. Our data is largely in line with these observations.

After nephrectomy, there is compensatory hyperfiltration in the remaining kidney, such that while a donor immediately loses approximately 50% of the kidney mass, the net reduction in GFR early after the donation is only approximately 30% [16]. The mechanisms of compensatory hyperfiltration are not clear yet. In a remarkable long-term study of glomerular hemodynamics after kidney donation [12], it was noted that adaptive hyperfiltration after donor nephrectomy was attributable to hyperperfusion and hypertrophy of the remaining glomeruli, without glomerular hypertension in most donors, and these changes were sustained throughout the late post-donation period, without significant albuminuria [12]. Nevertheless, there is concern that adaptive hyperfiltration might result in faster progression of kidney disease in certain groups of donors with less functional reserve, such as those older, obese, or hypertensive [12].

Van de Weijden et al. [33], in a cohort of 1024 donors, found that individuals with a more pronounced increase in single-kidney GFR at 3 months after donation had better long-term kidney function, independent of pre-donation GFR and age. The authors hypothesized that an early increase in eGFR may reflect a more physiologic adaptation mechanism to an acute reduction in renal mass and a better renal functional reserve. These results could help personalize LD follow-up [33].

Our results were surprising when we evaluated the impact of the percentage of KFRR at 6M in the trajectories of eGFR over time. The individuals with less KFRR (<26.2%) in the first 6 months had a significantly higher decrease of eGFR in the overall period compared to the other subgroups. However, the significant differences between the three subgroups only held from 6 months to 2 years. Distinctly, it was not a predictive

TABLE 9 | Prevalence of eGFR<50 mL/min/1.73 m^2, in living kidney donors by subgroup over different time periods during follow-up from 6 months onward n (%), using the CKD-EPI equation.

	Predonation	6M	2y	5y	10y
n	320	320	293	206	96
Overall	0	26 (8)	13 (4)	10 (5)	2 (2)
Age (years)	—				
<40		1 (4)	1 (4)	0	0
40–55		14 (9)	4 (3)	3 (3)	1 (2)
≥ 55		11 (13)	8 (10)	7 (13)	1 (5)
p		***0.009***	***0.025***	***0.005***	*0.446*
Sex	—				
Male		9 (10)	6 (7)	3 (5)	2 (8)
Female		17 (7)	7 (3)	7 (5)	0
p		*0.515*	*0.127*	*0.729*	*0.061*
BMI (kg/m^2)	—				
<25		12 (8)	8 (6)	4 (4)	1 (3)
25–30		11 (8)	2 (2)	5 (6)	0
≥30		3 (9)	3 (10)	1 (5)	1 (14)
p		*0.956*	*0.063*	*0.894*	*0.064*
Hypertension	—				
No		18 (7)	9 (4)	6 (3)	1 (1)
Yes		8 (16)	4 (9)	4 (12)	1 (9)
p		***0.031***	*0.138*	*0.057*	*0.217*
Smoking	—				
No		24 (9)	13 (5)	10 (6)	2 (2)
Yes		2 (4)	0	0	0
p		*0.394*	*0.227*	*0.364*	*1*
Dyslipidemia	—				
No		17 (6)	7 (3)	6 (3)	1 (1)
Yes		9 (20)	6 (14)	4 (15)	1 (9)
p		***0.001***	***0.001***	***0.025***	*0.217*
ProtU 0.15–0.5 g/g	—				
No		19 (8)	9 (4)	9 (6)	2 (2)
Yes		7 (7)	4 (4)	1 (2)	0
p		*0.721*	*1*	*0.287*	*1*
Pre-donation eGFR (mL/min/1.73m^2)	—				
<80		14 (48)	8 (31)	5 (36)	1 (14)
80–90		9 (19)	3 (7)	3 (10)	1 (7)
≥90		3 (1)	2 (1)	2 (1)	0
p		***<0.001***	***<0.001***	***<0.001***	*0.051*
%KFRR post-donation	—				
<26.2		0	2 (2)	2 (3)	1 (2)
26.2–36.1		6 (6)	3 (3)	3 (5)	0
>36.1		20 (19)	8 (8)	5 (8)	1 (5)
p		***<0.001***	*0.162*	*0.395*	*0.711*

**KFRR post-onation = [–(eGFR6M-eGFRpre-donation)/eGFRpre-donation*100].*

y, years; M, months; BMI, body mass index; ProtU, protein/creatinine ratio in the urine; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration equation; KFRR, kidney function reduction rate post-donation.

p *values are depicted in italics; statistically significant,* p *values (<.05) are shown in bold.*

factor of long-term renal function in our cohort, and we could not support the hypothesis of Weijden et al. [33].

Lower pre-donation eGFR has been associated with lower post-donation eGFR and a higher risk of ESRD [34, 35]. Tan et al. [11], in a retrospective cohort of 174 Southeast Asian LKDs, described that pre-nephrectomy eGFR was a good predictor of post-donation eGFR, especially in the short term (<6 M). Still, it was limited to <5 years and did not necessarily translate into a long-term (>5 Y) reduction in post-donation eGFR. In our cohort, we could not correlate better pre-donation eGFR with improved recovery of post-donation eGFR. We could hypothesize, as studied by Chakkera et al. [36], that adaptation reserves for increasing filtration after nephrectomy may be limited in donors with a high eGFR.

Several studies reported worse outcomes in obese LDs, including an increased risk of ESRD [8, 9, 34], although it is not a contraindication for donation [16]. Ibrahim et al. [35], in a white LDs population, showed that each increase of 1 unit in BMI pre-donation was associated with a 3%–10% higher risk of proteinuria and reduced GFR. In our study, obese donors at the time of donation experienced significantly worse overall eGFR change from 6 months onward compared to normal-weight donors. However, these differences only hold for the initial

TABLE 10 | Prevalence of proteinuria in living kidney donors pre-donation and over different periods during follow-up.

	Time				
	Pre-donation	**6M**	**2y**	**5y**	**10y**
n	302	283	251	172	78
Median (IQR)	0.11 (0.07–0.16)	0.08 (0.06–0.11)	0.07 (0.06–0.10)	0.08 (0.06–0.11)	0.07 (0.06–0.10)
≥0.15 g/g n (%)	96 (30)	30 (11)	19 (8)	18 (10)	6 (8)

n, number; %, percentage; IQR, interquartile range; g/g, protein g/creatinine g in a random urinary sample; M, months; Y, years.

time frames (6 M–5 Y). Some of these donors, with preexisting obesity-related hyperfiltration, may have a diminished capacity to undergo further adaptive hyperfiltration after nephrectomy compared to a normal-weight donor [37]. Our cohort results clearly red-flagged this population and deserve further investigation concerning the mechanisms involved and potential preventive primary or secondary measures that might be indicated [38].

In our cohort, we did not find significantly different trajectories of eGFR when considering donor age, sex, hypertension, dyslipidemia, and the presence of proteinuria pre-donation. The aging healthy kidney is associated with lower renal function and blunted adaptative capacity [30]. Our cohort of older donors has not been associated with worse outcomes for their recipients [21]. A comprehensive evaluation of an older LD could be a good strategy for many LDs pairs.

LDs diagnosed with hypertension pre-donation did not present a distinctive slope of eGFR after donation. Hypertension represents a leading cause of cardiovascular morbidity and mortality. It is associated with CKD and the risk of ESRD in the general population and is a frequently reported cause of ESRD in living donors [39]. Furthermore, it can reduce the renal reserve and limit the expected post-donation compensation [40]. Our results could be explained by our thorough practice in selecting these donors. Sanchez et al. [23], in a population of LDs, found that the risks for the different clinical outcomes, including eGFR < 60, 45, or 30 mL/min/1.72 m^2 or ESRD, between those with and without hypertension at the time of donation were not different. A different issue, the effect of hypertension after donation on the eGFR trajectories, is beyond the scope of this work.

The proportion of LDs with low eGFR, defined as eGFR <50 mL/min/1.73 m^2 was overall small, 5% or less after the 6 months, decreased with the follow-up time, which is expected with progressive improvement in kidney function, suggesting that the decline in eGFR was not progressive in the majority of LDs. The results on the prevalence of proteinuria in the follow-up period support this theory, pointing away from the hypothesis of hyperfiltration after a donation from the remnant nephron [38], which focused on the role of glomerular hypertension in the remaining nephrons as the main pathway for progressive renal damage and consequent glomerular leakage of proteins.

Our study has several limitations. First, donors were evaluated retrospectively, and unobserved confounders may have introduced bias. Second, we have not assessed a non-donor control group, although we can compare our results with studies of the evolution of eGFR with aging in healthy European populations [28–30]. Third, our cohort consisted almost exclusively of Caucasian patients, limiting the generalization of our results. In addition, eGFR using estimation equations to assess kidney function has limitations, but it is the common practice in most transplant centers and agrees with the International Guidelines [16]. In addition, an added value of our study cohort is its larger size and the availability of serial SCr measurements. Nevertheless, longer follow-up studies must be required; prospective studies are necessary to allow a cause-effect analysis of the parameters studied. Furthermore, the influence of *de novo* comorbidities such as hypertension and diabetes were not evaluated as modifiers of the evolution of kidney function after donation.

CONCLUSION

Our data show that eGFR post-donation recovery is significant and may last until 10 years post-donation. Moreover, an eGFR <50 mL/min1.73 m^2 was a rare observation, having a prevalence of 5% or less in the 2–15 years span. These observations confirm that in a carefully selected cohort of donors, the occurrence of a significant kidney function loss or accelerated decline is exceptional. However, some subgroups of donors presented a more ominous kidney function trajectory pattern, pointing to the necessity of tailored follow-up.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by Ref.: 147-21 (119-DEFI/122-CE) ULSdSA. 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

MA, PR, and JM: Research design, data acquisition, data analysis, and paper writing. JS, CR, SP, and ST were engaged in the data acquisition and analysis. MS and LM were involved in the research design and data analysis. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.13356/full#supplementary-material

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ORIGINAL RESEARCH
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Comparison of Kidney Graft Function and Survival in an Emulated Trial With Living Donors and Brain-Dead Donors

Emilie Savoye[1†], Gaëlle Santin[1†], Camille Legeai[1†], François Kerbaul[1†], François Gaillard[2†], Myriam Pastural[1†] and the CRISTAL Registry Study Group[‡]*

[1]Direction Prélèvement Greffe Organes-Tissus, Agence de la Biomédecine, Saint-Denis La Plaine, France, [2]Service de Transplantation, Néphrologie et Immunologie Clinique, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France

Living donation (LD) transplantation is the preferred treatment for kidney failure as compared to donation after brain death (DBD), but age may play a role. We compared the 1-year estimated glomerular filtration rate (eGFR) after kidney transplantation for recipients of LD and DBD stratified by recipient and donor age between 2015 and 2018 in a matched cohort. The strength of the association between donation type and 1-year eGFR differed by recipient age ($P_{interaction}$ < 0.0001). For LD recipients aged 40–54 years versus same-aged DBD recipients, the adjusted odds ratio (aOR) for eGFR ≥60 mL/min/1.73 m^2 was 1.48 (95% CI: 1.16–1.90). For DBD recipients aged ≥ 60 years, the aOR was 0.18 (95% CI: 0.12–0.29) versus DBD recipients aged 40–54 years but was 0.91 (95% CI: 0.67–1.24) versus LD recipients aged ≥60 years. In the matched cohort, 4-year graft and patient survival differed by donor age and type. As compared with DBD grafts, LD grafts increased the proportion of recipients with 1-year eGFR ≥60 mL/min/1.73 m^2. Recipients aged ≥60 years benefited most from LD transplantation, even if the donor was aged ≥60 years. For younger recipients, large age differences between donor and recipient could also be addressed with a paired exchange program.

Keywords: living donation, kidney function posttransplant, emulation target trial, age, brain-dead donor

***Correspondence**
Myriam Pastural,
myriam.pastural@biomedecine.fr

†ORCID:
Emilie Savoye
orcid.org/0000-0002-9098-0203
Gaëlle Santin
orcid.org/0000-0003-4279-8893
Camille Legeai
orcid.org/0000-0001-7752-1144
François Kerbaul
orcid.org/0000-0003-4552-1267
François Gaillard
orcid.org/0000-0002-7248-8418
Myriam Pastural
orcid.org/0000-0003-2488-6718

[‡]A full listing of the members of the CRISTAL Registry Study Group is provided in the Supplementary List S1

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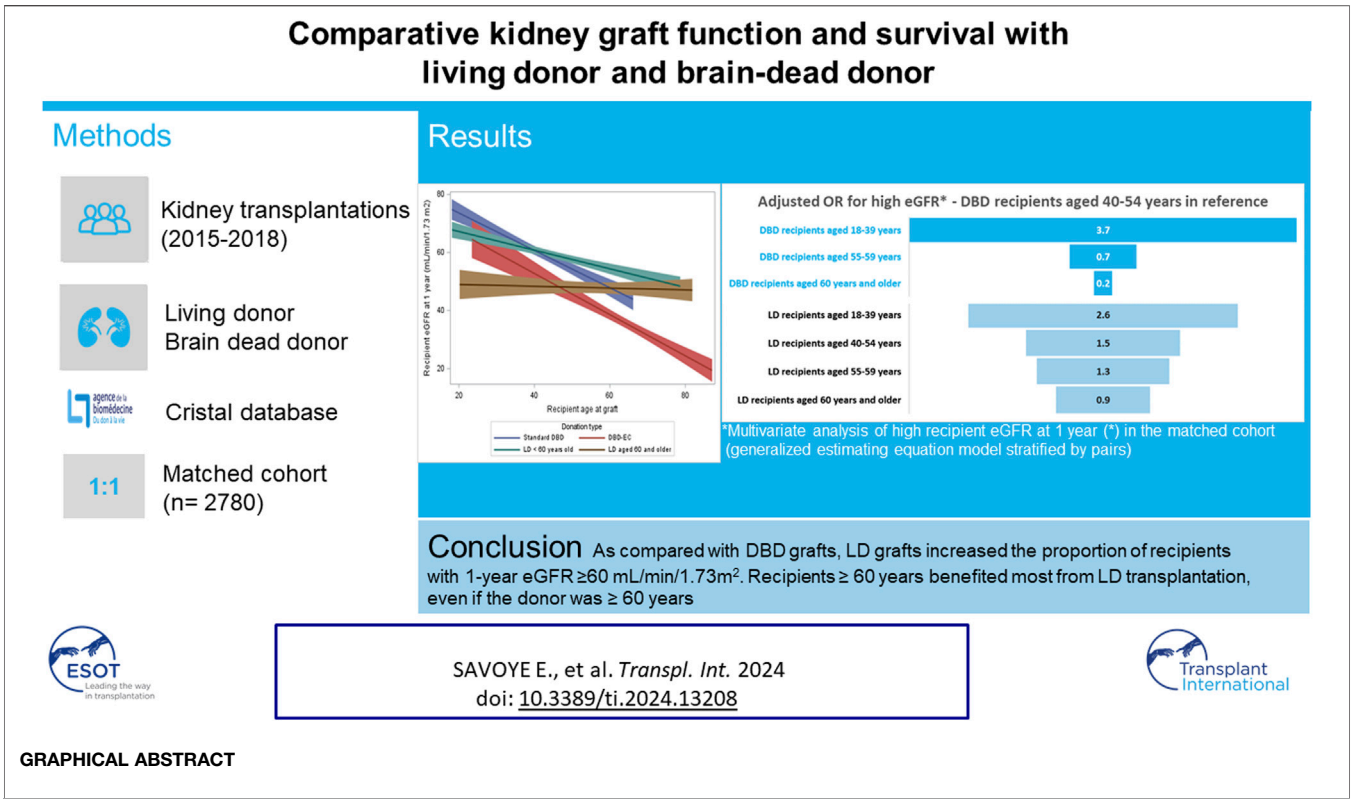
INTRODUCTION

Graft and patient survival with living donation (LD) is better than donation after brain death (DBD) [1–6]. Data from a UK transplant registry showed that all-cause mortality was lower for recipients of older LD kidneys (aged ≥60 years) than standard-criteria DBD (DBD-SC), but graft and overall survival were lower for LD recipients with older living donors rather than younger (aged < 60 years) [7]. DBD and LD transplantations have significant differences that may affect post-transplantation survival. One of the major advantages of LD transplantation is that it allows for pre-emptive transplantation. The age and immunological profile of LD recipients may also differ from those of DBD recipients.

At first glance, a short cold ischemia time and very good health of the donor seem to result in higher eGFR after LD than DBD transplantation. Alternatively, these expected benefits of LD over DBD may be counterbalanced by the better age and immunological matching between the donor and

Abbreviations: LD, living donation; DBD, donation after brain death; DBD-EC, donation after brain death with expanded criteria; KT, kidney transplantation; eGFR, estimated glomerular filtration rate from plasma creatinine; HLA, human leukocyte antigen; cPRA, calculated panel-reactive antibodies; BMI, body mass index; ESRD, end-stage renal disease.



GRAPHICAL ABSTRACT

recipient in DBD than in genetically and emotionally related LD. Altogether, LD and DBD have different graft access procedures and clinical characteristics that may affect the outcomes of kidney transplantation (KT) independent of the donation type [1].

From our annual medical and scientific report [8], for 44% of LD recipients, the eGFR at 1 year was >60 mL/min as compared with 51% for DBD-SC recipients. This unfavorable outcome for LD prompted us to conduct this study.

In the context of the various pros and cons for each of the two strategies, we compared the impact of DBD and LD on eGFR at 1 year after transplantation using propensity score (PS) matching to attempt to mimic a randomized trial [9]. Because age is an important element in the choice of donor and eGFR interpretation, we conducted several sensitivity analyses to explore this confounding factor. We analyzed eGFR with DBD and LD by recipient age and donor subgroup, namely, standard criteria and expanded criteria. Secondary outcomes were graft and patient survival at 4 years.

MATERIALS AND METHODS

Patients

We included all LD and DBD first single-organ kidney transplants performed in metropolitan France from 2015 to 2018. We excluded transplants with human leukocyte antigen (HLA) or ABO incompatibility, pediatric recipients, recipients who died in the first week after the transplant, and those with missing data for 1-year eGFR.

Outcome Measures

The primary outcome was an eGFR estimated with the chronic kidney disease (CKD)-EPI equation [10] of ≥60 mL/min/1.73 m^2 or over at 1 year after KT, which corresponds to a normal or mild loss of kidney function according to the international classification of CKD stages. Recipients with graft failure <1 year after KT (n = 113) were classified in the group with eGFR <60 mL/min/1.73 m^2, as were those who died <1 year after KT (n = 42), because death is most often pooled with graft failure in graft failure analysis. When eGFR was measured <9 months or >21 months after the KT or was > 150 mL/min/1.73 m^2, 1-year eGFR was considered missing (data missing for 8% of LD and 7% of DBD transplants, detailed in **Figure 1**). Two additional 1-year eGFR thresholds were explored: 45 mL/min/1.73 m^2, which corresponds to normal or mild to moderate loss of kidney function (CKD stage 1 to 3a), and 80 mL/min/1.73 m^2, which we considered as normal kidney function since too few patients in the current study had a 1-year eGFR of ≥ 90 mL/min/1.73 m^2 (CKD stage 1).

Secondary outcomes were 4-year graft and patient survival.

Study Variables

Our main studied variables were type of donation (DBD or LD) and recipient age.

We also considered other recipient characteristics at KT: blood group, sex, cardiovascular comorbidities, end-stage renal disease (ESRD) cause, duration of dialysis before KT, BMI, and immunization level assessed by calculated panel-reactive antibodies (cPRA) (0%, 1%–84%, 85%–100%).

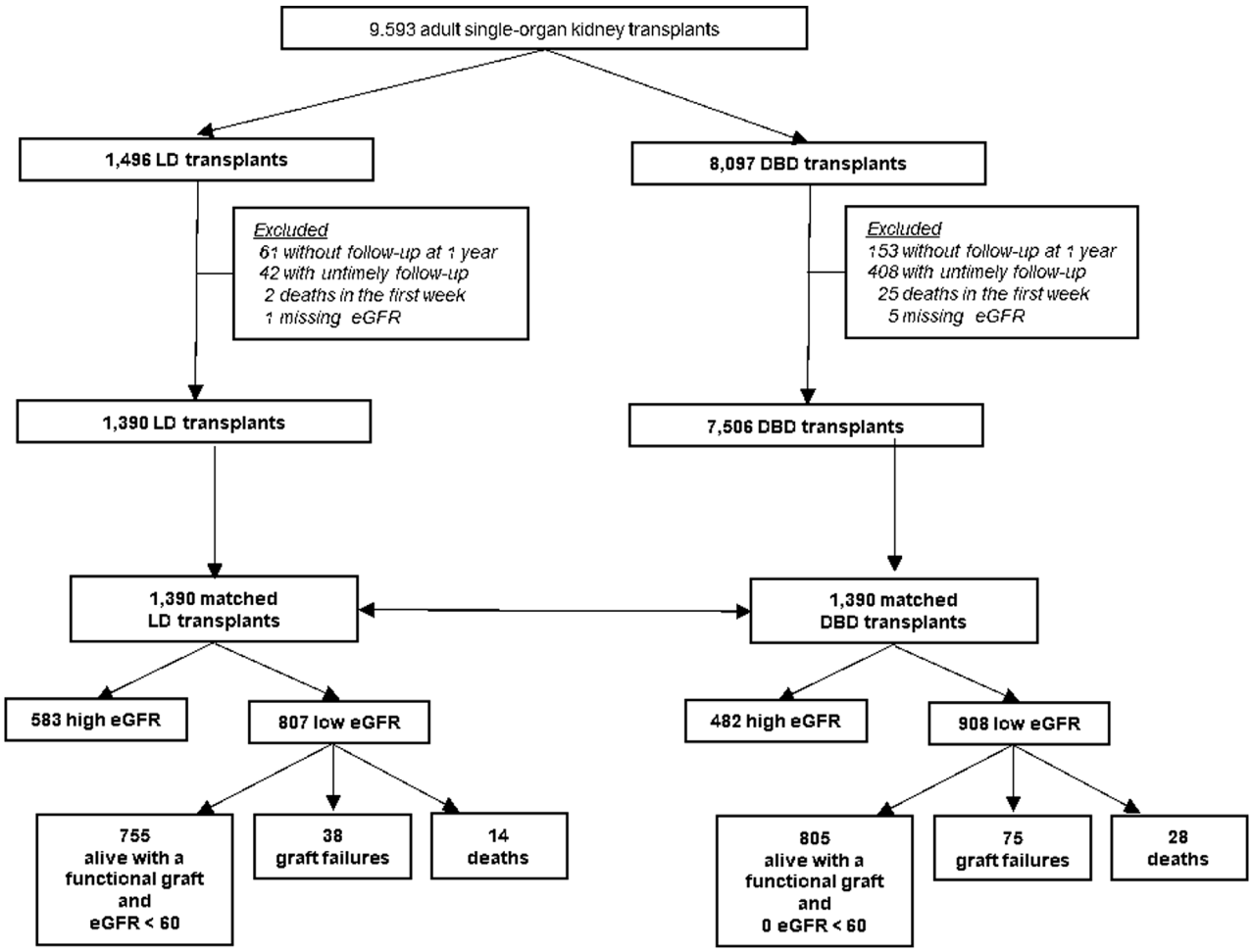


FIGURE 1 | Enrollment and outcomes. eGFR: glomerular filtration rate estimated with the CKD-EPI formula mL/min/1.73 m^2, LD, living donation; DBD, donation after brain death.

Four of these variables were continuous and were categorized. Age cut-offs were chosen according to French kidney allocation rules. BMI, duration of dialysis, and immunization rate cut-offs were chosen according to clinical relevance and statistical criteria (association between outcomes and continuous variables analyzed graphically with restricted cubic splines).

Data Collection

Data were retrieved from the French national transplant registry, CRISTAL. The French biomedicine agency (*Agence de la Biomédecine*) is a public institution supported by the French ministry of health. One of its missions is to manage organ and tissue procurement and transplantation in France. For this purpose, the CRISTAL registry prospectively collects demographic, clinical, and laboratory data for all organ transplant recipients and donors as well as transplant outcomes in France. The CRISTAL registry has full coverage of all French transplant units. Data are recorded at registration (placement on a waitlist), procurement, and transplantation and annually thereafter. Data collection is mandatory, and research technicians double-check its completeness and accuracy. In accordance with French law, research studies based on this national registry are part of transplant assessment and do not require additional institutional review board approval. The database has been reported to the French National Commission on Computing and Liberty.

Statistical Analysis

Characteristics of recipients and donors are described with mean (SD), median (inter-quartile ranges) for continuous variables, or number (percentage) for categorical variables. Missing data (always <5% for items with missing values) were imputed to the least risky and most frequent category when possible; relevant items were the recipient's body mass index (BMI; 0.3%), duration of dialysis (0.8%), cardiovascular comorbidities (4.0%), and presence of diabetes (2.4%) as well as the donor's eGFR (2.7%).

Propensity Score (PS) Matching

Because recipients were not randomly assigned to one of the two donor groups (LD or DBD), we followed the recommendations

TABLE 1 | Baseline characteristics of kidney transplantations by donation after brain death (DBD) and living donation (LD) for the overall study cohort and the matched cohort.

		Overall study cohort			Matched cohort		
		DBD 7,506 N (%)	**LD 1,390 N (%)**	**Standardized difference**	**DBD 1,390 N (%)**	**LD 1,390 N (%)**	**Standardized difference**
Recipient characteristics							
Recipient body mass index (kg/m^2)	Underweight (<18.5 kg/m^2)	289 (3.9)	69 (5)	0.16	70 (5)	69 (5)	<0.1
	Normal (18.5–24 kg/m^2)	3,154 (42)	686 (49.4)		645 (46.4)	686 (49.4)	
	Overweight (≥25 kg/m^2)	4,063 (54.1)	635 (45.7)		675 (48.6)	635 (45.7)	
Recipient sex	Male	4,762 (63.4)	934 (67.2)	<0.1	917 (66)	934 (67.2)	<0.1
	Female	2,744 (36.6)	456 (32.8)		473 (34)	456 (32.8)	
Recipient blood group	A	3,338 (44.5)	589 (42.4)	<0.1	616 (44.3)	589 (42.4)	<0.1
	AB	34 (4.6)	61 (4.4)		60 (4.3)	61 (4.4)	
	B	792 (10.6)	173 (12.4)		166 (11.9)	173 (12.4)	
	O	3,032 (40.4)	567 (40.8)		548 (39.4)	567 (40.8)	
Cause of ESRD	Chronic glomerulonephritis	1,547 (20.6)	389 (28)	0.27	320 (23)	389 (28)	0.15
	Diabetes (type I or II)	817 (10.9)	96 (6.9)		81 (5.8)	96 (6.9)	
	Kidney malformation or hereditary nephropathy	311 (4.1)	94 (6.8)		84 (6)	94 (6.8)	
	Chronic interstitial nephropathy	745 (9.9)	142 (10.2)		169 (12.2)	142 (10.2)	
	Nephroangiosclerosis	813 (10.8)	91 (6.6)		112 (8.1)	91 (6.6)	
	PKD	1,261 (16.8)	240 (17.3)		267 (19.2)	240 (17.3)	
	Others	2,012 (26.8)	338 (24.2)		357 (25.7)	338 (24.2)	
cPRA	0%	4,357 (58)	885 (63.7)	0.23	883 (63.5)	885 (63.7)	<0.1
	1%–84%	2,551 (34)	465 (33.5)		469 (33.7)	465 (33.5)	
	85%–100%	598 (8)	40 (2.9)		38 (2.7)	40 (2.9)	
Recipient age	18–39 years	1,292 (17.2)	422 (30.4)	0.45	418 (30.1)	422 (30.4)	<0.1
	40–54 years	2,175 (29)	485 (34.9)		488 (35.1)	485 (34.9)	
	55–59 years	938 (12.5)	162 (11.7)		165 (11.9)	162 (11.7)	
	≥60 years	3,101 (41.3)	321 (23.1)		319 (22.9)	321 (23.1)	
Cardiovascular comorbidities	No	6,352 (84.6)	1,250 (89.9)	0.16	1,245 (89.6)	1,250 (89.9)	<0.1
	Yes	1,154 (15.4)	140 (10.1)		145 (10.4)	140 (10.1)	
Recipient diabetes	No	6,034 (80.4)	1,201 (86.4)	0.16	1,212 (87.2)	1,201 (86.4)	<0.1
	Yes	1,472 (19.6)	189 (13.6)		178 (12.8)	189 (13.6)	

(Continued on following page)

TABLE 1 | (*Continued*) Baseline characteristics of kidney transplantations by donation after brain death (DBD) and living donation (LD) for the overall study cohort and the matched cohort.

		Overall study cohort			Matched cohort		
		DBD 7,506 N (%)	**LD 1,390 N (%)**	**Standardized difference**	**DBD 1,390 N (%)**	**LD 1,390 N (%)**	**Standardized difference**
Duration of dialysis before transplantation	Preemptive transplantation	890 (11.9)	576 (41.4)	0.99	575 (41.4)	576 (41.4)	<0.1
	<3 years	3,636 (48.4)	718 (51.7)		719 (51.7)	718 (51.7)	
	≥3 years	2,980 (39.7)	96 (6.9)		96 (6.9)	96 (6.9)	
Time on waitlist	<1 year	2,263 (30.2)	908 (65.3)	0.81	544 (39.2)	908 (65.3)	0.54
	Between 1 and 3 years	3,171 (42.3)	394 (28.3)		657 (47.3)	394 (28.3)	
	>3 years	2,070 (27.6)	88 (6.3)		188 (13.5)	88 (6.3)	
Donor characteristics							
Donor age	<39 years	1,157 (15.4)	240 (17.3)	0.51	385 (27.7)	240 (17.3)	0.34
	40–54 years	1,927 (25.7)	605 (43.5)		427 (30.7)	605 (43.5)	
	55–59 years	841 (11.2)	192 (13.8)		154 (11.1)	192 (13.8)	
	≥60 years	3,581 (47.7)	353 (25.4)		424 (30.5)	353 (25.4)	
Donor hypertension	No	4,833 (64.4)	1,304 (93.8)	0.78	1,040 (74.8)	1,304 (93.8)	0.54
	Yes	2,673 (35.6)	86 (6.2)		350 (25.2)	86 (6.2)	
Donor eGFR at procurement	≥60 mL/min/1.73 m^2	5,099 (67.9)	1,382 (99.4)	0.94	951 (68.4)	1,382 (99.4)	0.93
	<60 mL/min/1.73 m^2	2,407 (32.1)	8 (0.6)		439 (31.6)	8 (0.6)	
Transplant characteristics							
Cold ischemia time, hr		15.9 (5.9)	3.6 (4.1)	2.43	15.4 (5.8)	3.6 (4.1)	2.35
HLA A-B mismatches		1.6 (0.5)	1.2 (0.6)	0.71	1.6 (0.5)	1.2 (0.6)	0.75
HLA DR-DQ mismatches		0.9 (0.6)	1 (0.7)	<0.1	0.9 (0.7)	1 (0.7)	0.12
Delta donor age–recipient age	<–3.5 years	1,277 (17)	412 (29.6)	0.39	287 (20.6)	412 (29.6)	0.34
	3.5–0 years	1,659 (22.1)	272 (19.6)		324 (23.3)	272 (19.6)	
	0–7 years	2,720 (36.2)	306 (22)		488 (35.1)	306 (22)	
	>7 years	1,850 (24.6)	400 (28.8)		291 (20.9)	400 (28.8)	

Note: Continuous variables are presented in italic as means (standard deviation); dichotomous variables as n (%).

BMI, body mass index; ESRD, end-stage renal disease; PKD, polycystic kidney disease; cPRA, calculated panel-reactive antibodies; eGFR, glomerular filtration rate estimated with the CKD-EPI formula (mL/min/1.73 m^2); HLA, human leukocyte antigen; LD: living donation; DBD, donation after brain death.

for emulating a target trial by constructing a PS to reduce selection bias [9]. The specification, emulation, and description of this target trial are described in **Supplementary Table S1**, **Supplementary Text S1**. The aim of the PS matching was to constitute a group of recipients with the same probability of receiving a kidney from LD and from DBD at the time of transplantation. We chose matching for the PS [11], that is, 1) estimating the probability of treatment (here the type of donation) from a multivariate logistic regression model according to recipients' characteristics at KT, which may differ because of medical practices that vary by type of graft (in terms of age, sex, blood type, BMI, duration of dialysis, cardiovascular

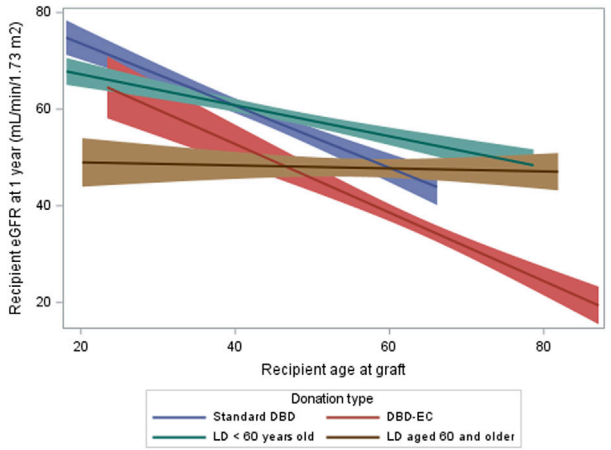


FIGURE 2 | Recipient eGFR at 1 year by type of donation and recipient age in the matched cohort. eGFR, glomerular filtration rate estimated with the CKD-EPI formula (mL/min/1.73 m^2); LD, living donation; DBD, donation after brain death.

comorbidities, diabetes, and cPRA); and 2) using a greedy matching algorithm (caliper width 0.2, without replacement) to match one LD recipient to one DBD recipient with the same probability of LD treatment. The PS for the matching process included recipient age, duration of dialysis before transplantation, blood group, sex, and cPRA (**Supplementary Table S2**; **Supplementary Figure S1**).

Imbalance in each baseline covariate was defined as a standardized difference >0.2 and was computed for each recipient characteristic included in the PS, donor characteristic (age, hypertension, and eGFR at procurement), and KT characteristics (cold ischemia time, HLA A-B mismatches, HLA DR-DQ mismatches, and delta donor age–recipient age) to describe the potential differences between the two populations.

Association Between 1-Year eGFR and Type of Donor

To study the association between eGFR at 1 year and type of donor (LD or DBD), we used logistic generalized estimating equations taking into account matching. Confounders considered were recipient characteristics at KT (age, sex, blood type, BMI, duration of dialysis, cardiovascular comorbidities, ESRD cause, and immunization in three calculated cPRA classes). Because differences in delta age, HLA mismatches, and cold ischemia time are inherent in receiving a kidney graft from an LD or DBD, these variables were not included in our models. After stepwise selection, only variables with $p < 0.05$ were included in the multivariate final model. Furthermore, we performed an interaction test between donor type and donor age.

Because age is a major determinant of the interpretation of eGFR in both physiological conditions [12] and CKD [13], we conducted sensitivity analyses considering two additional eGFR thresholds at 1 year: 45 and 80 mL/min/1.73 m^2.

We also analyzed eGFR as a continuous variable by recipient age and donor subgroup: DBD with standard criteria (DBD-SC) or expanded criteria (DBD-EC) and LD <60 years old ($LD_{<60y}$) or ≥ 60 years old ($LD_{\geq 60y}$); the latter considered an expanded-criteria LD. DBD-EC is defined by the American Organization of Transplantation and the United Network for Organ Sharing as DBD at age ≥ 60 years or 50–59 years with at least two of the following risk factors: donor hypertension, history of cerebrovascular accident, or terminal serum creatinine level ≥130 μmol/L [14]. Linear regressions by donor subgroup were used to investigate variation between the donor subgroups in the association between 1-year eGFR as a continuous variable and recipient age as a continuous variable.

We performed another sensitivity analysis, categorizing none of the continuous variables. In this analysis, continuous variables (age, BMI, and duration of dialysis) were transformed by using restricted cubic splines to estimate a new PS and to study the association between donation type and 1-year eGFR (**Supplementary Text S2**).

Graft and Recipient Survival by Type of Donor

Graft and recipient survival were studied at 4 years by type of donor in the matched cohort. Survival curves of graft and recipient groups were estimated by the Kaplan-Meier method and compared by the log-rank test.

Statistical analyses were performed with SAS Enterprise Guide 7.15 (SAS Institute, Cary, NC).

RESULTS

Population Characteristics

The cohort included 1,496 LD and 8,097 DBD transplantations (**Figure 1**). Because of missing follow-up at 1 year, untimely follow-up, death during the first week post-KT, or missing eGFR, 591 DBD recipients and 106 LD recipients were excluded. The study included 1,390 LD and 7,506 DBD transplantations.

The LD donors were significantly younger than DBD donors (mean age 51 vs. 57 years; $p < 0.0001$), had higher eGFR at procurement (mean 95 vs. 73 mL/min/1.73 m^2; $p < 0.0001$), and had hypertension less frequently (6.2% vs. 35.6%) (**Table 1**). As compared with DBD transplantations, LD transplantations had significantly shorter cold ischemia time (mean 3.6 vs. 15.9 h; $p < 0.0001$) and more HLA A-B mismatches (mean 1.6 vs. 1.2; $p < 0.0001$). The difference between donor age and recipient age (hereafter called delta age) was higher for LD than DBD recipients (mean 3 vs. 2 years; $p = 0.02$) (**Table 1**; **Supplementary Table S3**).

As compared with DBD recipients, LD recipients were significantly younger (mean age 48 vs. 55 years; $p < 0.0001$) and more often male (67.2% vs. 63.4%), with fewer comorbidities (diabetes: 13.6% vs. 19.6%; cardiovascular comorbidities: 10.1% vs. 15.4%) and lower BMI (mean 25 vs. 26 kg/m^2; $p < 0.0001$). The cause of ESRD for LD recipients was more often chronic glomerulonephritis (28% vs. 20.6% for DBD recipients) and they more frequently had cPRA of 0% (63.7% vs. 58%), a waitlist time <1 year (65.3% vs.

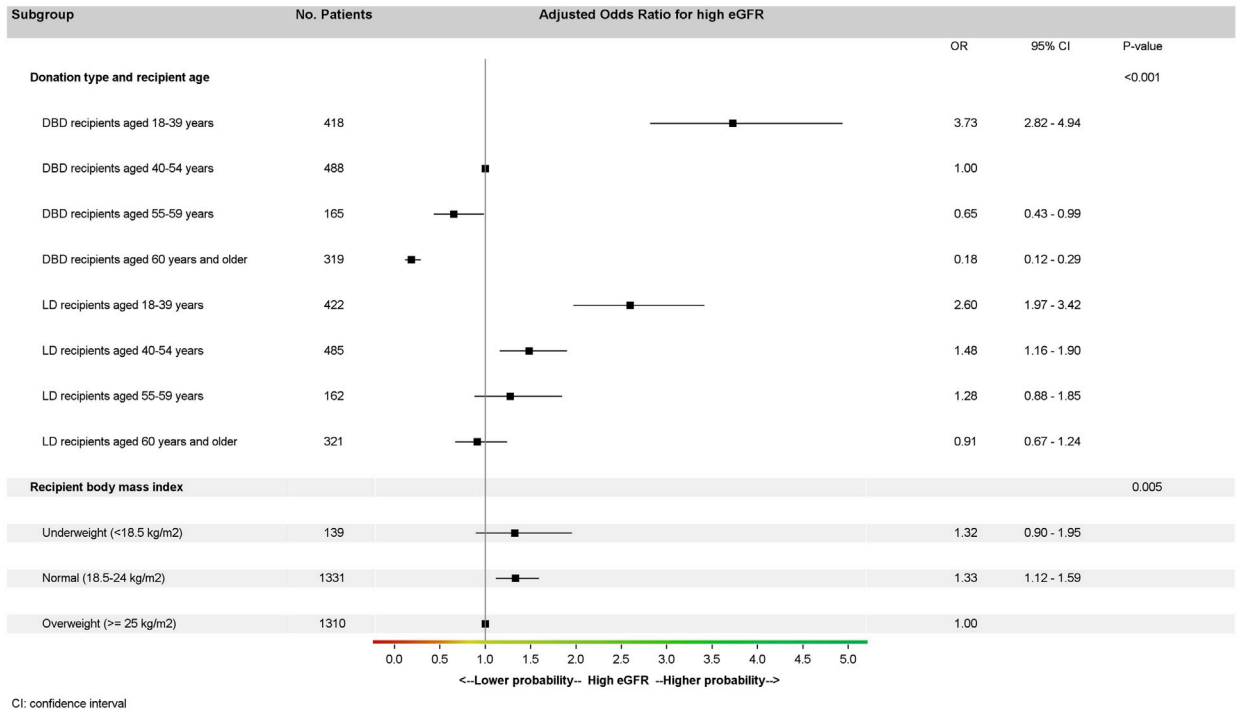


FIGURE 3 | Multivariate analysis of high recipient eGFR at 1 year (*) in the matched cohort (generalized estimating equation model stratified by pairs). (*) High eGFR at 1-year is defined by eGFR ≥ 60 mL/min/1.73 m^2; eGFR, glomerular filtration rate estimated with the CKD-EPI formula mL/min/1.73 m^2; LD, living donation; DBD, donation after brain death.

30.2%), and a preemptive transplantation (41.4% vs. 11.9%) than DBD recipients.

The matching procedure retained 1,390 LD and 1,390 DBD transplantations (**Table 1**). After matching on recipient characteristics, the standardized differences for recipient criteria (except waitlist time) were insignificant.

In the matched cohort, DBD donors were younger than LD donors for recipients aged 18–39 years (mean 32 vs. 47 years; $p < 0.0001$), whereas LD donors were younger than DBD donors for recipients aged ≥60 years (mean 58 vs. 73 years; $p < 0.0001$) (**Supplementary Table S4**).

eGFR at 1 Year After KT

In the matched cohort, about 50% of both DBD-SC and $LD_{<60y}$ recipients had an eGFR ≥60 mL/min/1.73 m^2 at 1 year; this proportion decreased to 22% in older LD recipients and to 9% in DBD-EC recipients (**Supplementary Figure S3**). More precisely, at 1 year, the proportion of recipients with eGFR ≥80 mL/min/1.73 m^2 was highest for DBD-SC recipients (19%); it was 13% for LD recipients <60 years and 2%–4% for LD recipients ≥60 years and DBD-EC recipients. Overall, 14% of DBD-EC recipients and 2%–4% of recipients of other types of donations died or had graft failure at 1 year.

Whatever the recipient's age, the mean 1-year eGFR was about 50 mL/min/1.73 m^2 for LD recipients aged ≥60 years (**Figure 2**). For recipients <40 years, 1-year eGFR was higher for DBD-SC recipients than other recipients. For recipients ≥60 years, 1-year eGFR was higher with all types of LD than with DBD.

In the multivariate model (**Figure 3**) of the matched cohort, high eGFR at 1 year (≥60 mL/min/1.73 m^2) was more frequent for recipients with normal BMI than overweight recipients (OR: 1.33; 95% CI: 1.12–1.99, $p = 0.005$). We found an interaction between donation type and recipient age ($p < 0.0001$). For LD recipients aged 40–54 years versus same-aged DBD recipients, the adjusted odds ratio (aOR) for eGFR ≥60 mL/min/1.73 m^2 was 1.48 (95% CI: 1.16–1.90). For DBD recipients ≥60 years, the aOR was 0.18 (95% CI: 0.12–0.29) versus DBD recipients 40–54 years but was 0.91 (95% CI: 0.67–1.24) versus LD recipients ≥60 years (i.e., 5.1 times higher).

We performed sensitivity analyses on the matched cohort for different eGFR thresholds (45 mL/min/1.73 m^2 and 60 and 80 mL/min/1.73 m^2) (**Figure 4**) in the multivariate model. High eGFR was associated with type of donation regardless of the threshold considered but was more likely for LD recipients with a threshold at 45 mL/min/1.73 m^2 (OR: 2.12; 95% CI: 1.79–2.51, $p < 0.001$) or 60 mL/min/1.73 m^2 (OR: 1.40; 95% CI: 1.19–1.63, $p < 0.001$) and less likely for LD than DBD recipients with a threshold at 80 mL/min/1.73 m^2 (OR: 0.77; 95% CI: 0.60–0.98, $p = 0.03$).

The sensitivity analysis with all continuous variables transformed by using restricted cubic splines revealed a significant interaction between recipient age and type of donor in the association with eGFR ($p < 0.0001$): eGFR was higher for recipients aged under 40 whatever the type of donor and that from the age of 55 eGFR was higher for LD than for DBD recipients (**Supplementary Figure S4**).

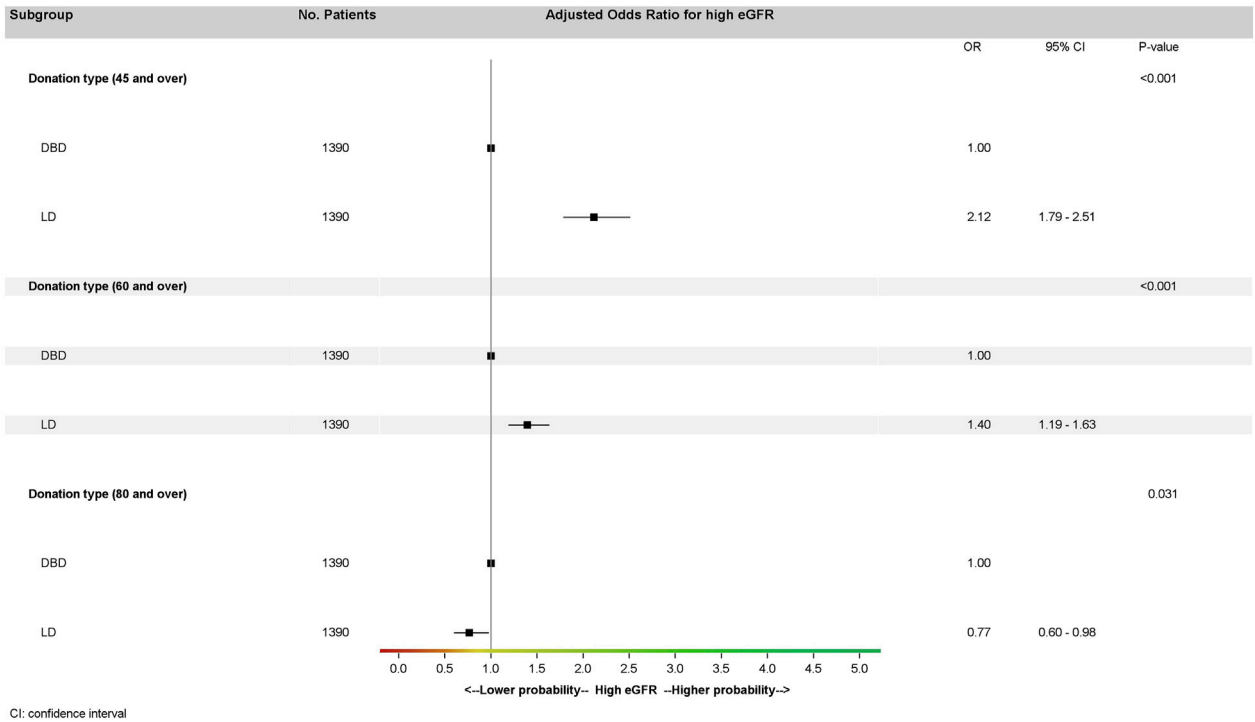


FIGURE 4 | Multivariate analysis of eGFR at 1 year in the matched cohort (generalized estimating equation model stratified by pairs) according to several thresholds by donation type. Donor type odds ratios for high eGFR were adjusted on recipient age and recipient BMI for all three multivariate analyses. High eGFR at 1 year is defined by three different thresholds: eGFR ≥ 45 mL/min/1.73 m^2, eGFR ≥ 60 mL/min/1.73 m^2, and eGFR ≥ 80 mL/min/1.73 m^2. eGFR, glomerular filtration rate estimated with the CKD-EPI formula mL/min/1.73 m^2; LD, living donation; DBD, donation after brain death.

Graft and Recipient Survival by Donor Subgroup

In the matched cohort, 4-year graft survival differed by donor subgroup (**Figure 5**): it was lowest with DBD-EC transplants (76.4%, 95% CI 72.4%–79.9%) versus DBD-SC transplants (91.2%, 95% CI 89.2%–92.9%), $LD_{<60y}$ transplants (91.9%, 95% CI 90.0%–93.4%), and $LD_{\geq 60y}$ transplants (91.6%, 95% CI 88.2%–94.1%). Similar results were found when analyzing 4-year patient survival (**Figure 5**).

DISCUSSION

LD transplantation is the preferred treatment for kidney failure, offering *a priori* superior patient and graft survival as compared with DBD transplantation. However, LD recipients are usually not comparable to DBD recipients, LD recipients typically being younger and having no or less pre-transplant dialysis duration. We attempted to emulate a target trial by creating a PS-matched cohort to investigate eGFR at 1 year after KT for DBD and LD recipients, ensuring comparability between the LD and DBD groups in recipient age, sex, blood group, pretransplant dialysis duration, and cPRA. The eGFR at 1-year post-transplant is widely considered the most relevant marker for predicting graft and patient survival after transplantation and is extensively used in randomized clinical trials [15]. At 1 year after KT, eGFR was significantly higher for LD than DBD recipients. Specifically, the OR for attaining an eGFR ≥45 mL/min/1.73 m^2 was 2.12 times higher and an eGFR ≥60 mL/min/1.73 m^2 was 1.40 times higher for LD than DBD recipients.

However, our study suggests that the superiority of LD over DBD in terms of eGFR is not consistent across all recipient age groups. Among recipients <40 years, the OR for an eGFR ≥60 mL/min/1.73 m^2 did not significantly differ between DBD and LD recipients. For recipients ≥60 years, the OR for an eGFR ≥60 mL/min/1.73 m^2 was 5 times higher for LD than DBD recipients (0.91 vs. 0.18 for younger LD recipients).

Several factors may explain this difference in eGFR between DBD and LD recipients based on recipient age. LD recipients <40 years frequently receive a kidney from an older LD donor, a situation that contrasts with the DBD allocation strategy, which often favors age matching. As a result, younger DBD recipients typically receive kidneys from young DBD donors [16]. This situation is supported by the greater delta donor age–recipient age in the LD than DBD group. In contrast, DBD recipients ≥60 years mainly receive kidneys from donors within the same age group, whereas LD recipients ≥60 years may receive kidneys from younger donors

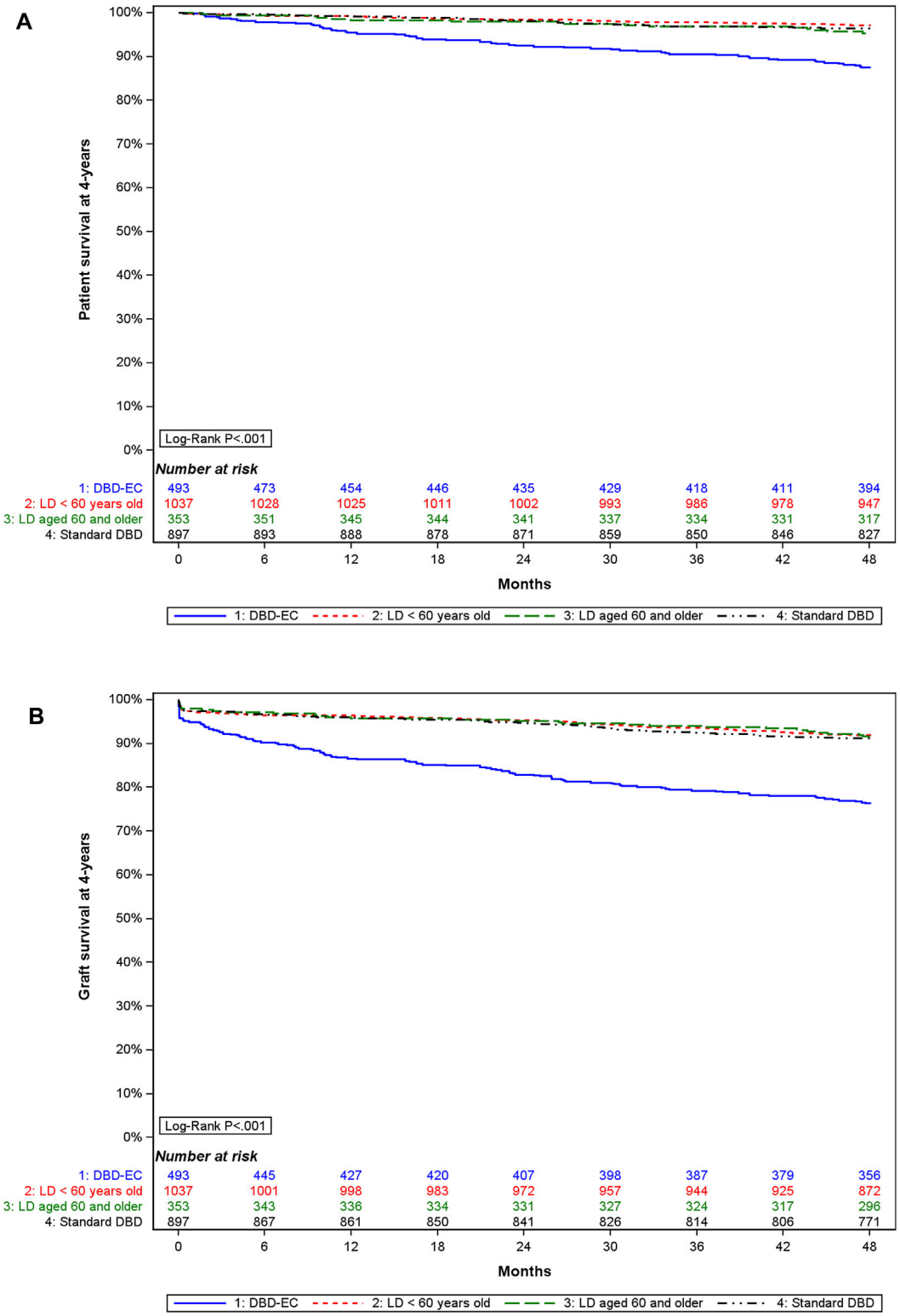


FIGURE 5 | 4-year **(A)** graft survival and **(B)** patient survival by type of donor in the matched cohort.

[16]. Additionally, DBD recipients ≥60 years may receive kidneys from DBD-EC donors, whereas LD recipients usually have few or no comorbidities. Hypertension and kidney aging are associated with a higher proportion of sclerotic glomeruli and nephron loss, leading to lower eGFR after KT [17–19]. Therefore, kidneys from an older LD donor may result in a lower eGFR than kidneys from a younger DBD donor. Our sensitivity analyses showed that a threshold eGFR of 80 mL/min/1.73 m^2 was more common among DBD than LD recipients, who are often matched with younger donors. In contrast, at 1 year after KT, the mean eGFR was approximately 50 mL/min/1.73 m^2 for recipients from LD donors ≥60 years old, regardless of recipient age.

At 1 year after KT, donor age has been found correlated with renal function as well as long-term graft and patient survival [20–24]. Lim et al. [25] reported an association between donor age, 1-year eGFR, and overall graft loss. However, eGFR <60 mL/min/1.73 m^2 at 1 year with a kidney from an older LD is expected and should not preclude the selection of an LD donor as suitable [26, 27].

In our matched cohort, the analysis of graft and patient survival at 4 years post-KT highlights the inferior outcomes of transplantation from a DBD-EC. Indeed, at 4 years, the graft survival was approximately 15% lower for recipients of a DBD-EC than for other recipients. The graft acceptance criteria are more extensive in France than in the United States [28, 29]. However, graft survival from a DBD-EC donor in France is comparable to literature data and is considered satisfactory as compared with dialysis maintenance [17, 30]. In older patients, long-term results were found better with LD than DBD-SC or DBD-EC and suggested the use of LD transplants in older patients whenever possible [18]. However, in Japan, the age of the oldest LD is high (70–89 years) and outcomes were found to be poor in terms of graft survival and eGFR for older recipients from very old LD donors [31]. In the same way, from UK registry data, all-cause mortality was greater for recipients of older LD (donor age ≥70 years) than DBD-SC and was equivalent to that for DBD-EC recipients [7].

Our study has some limitations. It was conducted in France, where national practices for DBD allocation and organ acceptance differ from those in other countries. Different allocation scores and stricter kidney acceptance criteria in other regions may yield different results between DBD and LD recipients. The particular strength of our work lies in its methodology, effectively used in other studies [32, 33], emulating a target trial that is not feasible in the real world. This method allows for defining all the conditions required for the target trial and precisely describing the deviations from it. However, some important factors may not have been taken into account in our PS. Furthermore, we excluded recipients without timely follow-up or who died in the first week before matching. Because they represented less than 10% of the target population and their distribution was not different between LD and DBD recipients, we considered the resulting selection bias to be negligible.

A second limitation is the lack of long-term follow-up. Nevertheless, we needed to begin inclusions in 2015 to have both a homogeneous donor population (sharp increase in age of donors since 2000) and the same kidney allocation system throughout the cohort (the current kidney allocation system was implemented in 2015).

A third limitation could be our choice to conduct stepwise regressions based on *p*-value and involving multiple comparisons; we opted for this choice because of our sample tail that allowed for a high number of degrees of freedom. Furthermore, we opted to categorize all our continuous variables, which implies loss of information and precision [34, 35]. We made this choice after discussion with clinicians who preferred having information directly usable with the references they used in practice. To test the robustness of our results, we conducted a sensitivity analysis performed with Harrell's recommendations and found consistent results.

A final limitation is the use of eGFR at 1 year after KT as a single surrogate marker of graft outcome. Indeed, predicted graft survival based on this surrogate marker is correlated with observed graft survival [36] and this parameter is used in studies testing new treatments [37]. However, graft injuries may develop slowly over time and eGFR at 1 year fails to capture ongoing disease process [38]. In our matched cohort on recipient characteristics, we tested eGFR at 1 year after KT depending on donor type stratified by age. So, we discussed eGFR at 1 year as a marker potentially reflecting nephron loss more than nephron injury that leads to graft failure.

Our study showed that older recipients derive significant benefits from LD transplants, which emphasizes the importance of evaluating living donors ≥60 years old. Conversely, transplants from DBD donors can yield good outcomes for young adult recipients, provided that there is a suitable age and HLA match, along with prompt access to transplantation. Of note, our matched cohort reflects a notably short pre-transplant dialysis period, a characteristic often associated with LD transplants. Paired-exchange programs offer a viable avenue to explore improved age matching, particularly with a significant age gap between the donor and recipient. However, KT for compatible donor-recipient pairs seeking a better match in terms of age should not be delayed too long, and the search for a better match should be carried out early.

Our study is the first published research to use an emulated target trial to compare LD and DBD recipients. These findings offer valuable insights for healthcare professionals, empowering them to make well-informed decisions regarding the suitability of different donor types for specific recipients.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: In accordance with French law, research studies based on Cristal national registry are part of transplant assessment and do not require additional institutional review board approval. The database has been reported to the French National Commission on Computing and Liberty. Requests to access these datasets should be directed to nicolas.chatauret@biomedecine.fr.

ETHICS STATEMENT

In accordance with French law, research studies based on this national registry are part of transplant assessment and do not require additional institutional review board approval.

AUTHOR CONTRIBUTIONS

GS: study concept and design, statistical analysis, interpretation of results, writing of the manuscript. ES: study concept and design, interpretation of results, writing of the manuscript. MP: study concept and design, interpretation of results, writing of the manuscript. FG: study concept and design, interpretation of results, writing of the manuscript. Others: critical revision of the manuscript and final approval of the version to be published.

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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.2024.13208/full#supplementary-material

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Benefits of Living Over Deceased Donor Kidney Transplantation in Elderly Recipients. A Propensity Score Matched Analysis of a Large European Registry Cohort

Néstor Toapanta[1], Jordi Comas[2], Ignacio Revuelta[3], Anna Manonelles[4], Carme Facundo[5], María José Pérez-Saez[6], Anna Vila[7], Emma Arcos[2], Jaume Tort[2], Magali Giral[8], Maarten Naesens[9], Dirk Kuypers[9], Anders Asberg[10,11], Francesc Moreso[1]†, Oriol Bestard[1]*† and the EKITE consortium*

[1]Kidney Transplant Unit, Nephrology Department, Vall d'Hebron University Hospital, Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital Campus, Autonomous University of Barcelona, Barcelona, Spain, [2]Catalan Transplantation Organization, Barcelona, Spain, [3]Kidney Transplant Unit, Nephrology Department, Hospital Clinic, Barcelona, Spain, [4]Kidney Transplant Unit, Nephrology Department, Bellvitge University Hospital, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona University (UB), Barcelona, Spain, [5]Kidney Transplant Unit, Nephrology Department, Fundació Puigvert, Barcelona, Spain, [6]Kidney Transplant Unit, Nephrology Department, Hospital del Mar, Barcelona, Spain, [7]Kidney Transplant Unit, Nephrology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [8]CRTI UMR 1064, Inserm, Université de Nantes, ITUN, CHU Nantes, RTRS Centaure, Nantes, France, [9]Department of Microbiology, Immunology, and Transplantation, KU Leuven, Leuven, Belgium, [10]Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway, [11]Department of Pharmacy, University of Oslo, Oslo, Norway

***Correspondence**
Francesc Moreso,
francescjosep.moreso@vallhebron.cat
Oriol Bestard,
oriol.bestard@vallhebron.cat

†These authors share senior authorship

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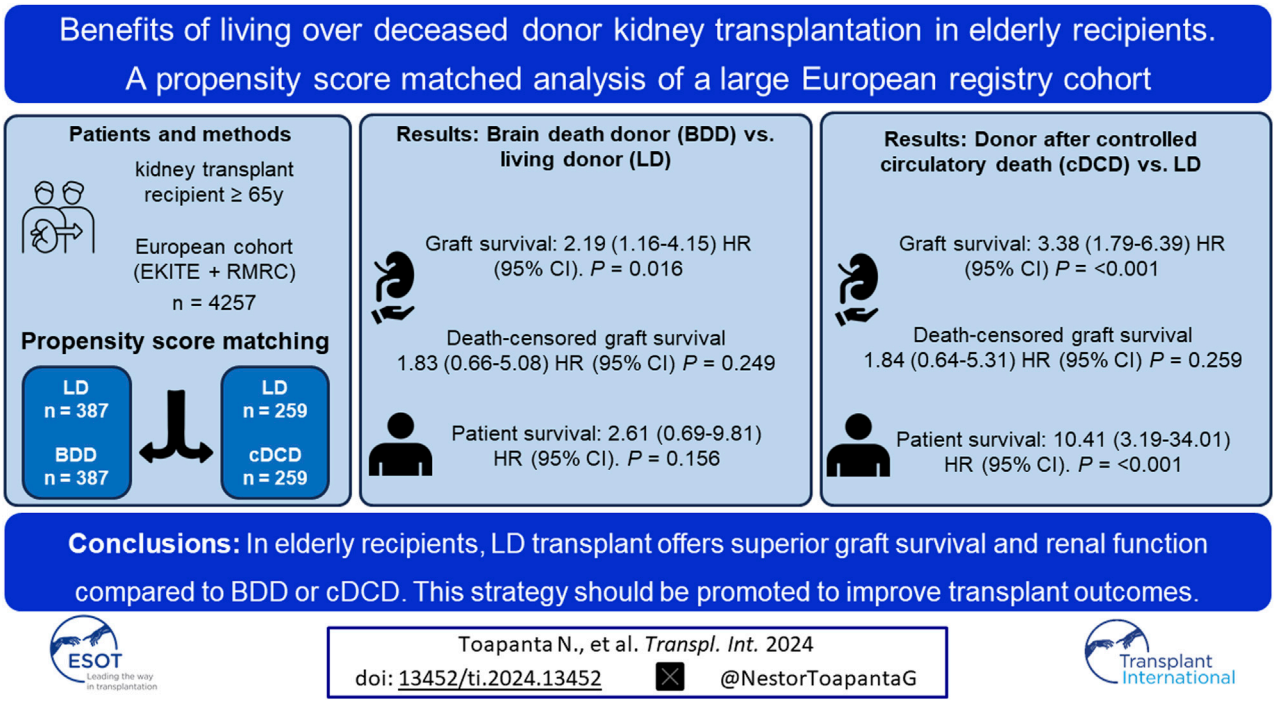
Although kidney transplantation from living donors (LD) offers better long-term results than from deceased donors (DD), elderly recipients are less likely to receive LD transplants than younger ones. We analyzed renal transplant outcomes from LD versus DD in elderly recipients with a propensity-matched score. This retrospective, observational study included the first single kidney transplants in recipients aged ≥65 years from two European registry cohorts (2013–2020, n = 4,257). Recipients of LD (n = 408), brain death donors (BDD, n = 3,072), and controlled cardiocirculatory death donors (cDCD, n = 777) were matched for donor and recipient age, sex, dialysis time and recipient diabetes. Major graft and patient outcomes were investigated. Unmatched analyses showed that LD recipients were more likely to be transplanted preemptively and had shorter dialysis times than any DD type. The propensity score matched Cox's regression analysis between LD and BDD (387-pairs) and LD and cDCD (259-pairs) revealing a higher hazard ratio for graft failure with BDD (2.19 [95% CI: 1.16–4.15], p = 0.016) and cDCD (3.38 [95% CI: 1.79–6.39], p < 0.001). One-year eGFR was higher in LD transplants than in BDD and cDCD recipients. In elderly recipients, LD transplantation offers superior graft survival and renal function compared to BDD or cDCD. This strategy should be further promoted to improve transplant outcomes.

Keywords: living donor, deceased donor, survival, elderly renal transplant, propensity score analysis



GRAPHICAL ABSTRACT |

INTRODUCTION

In recent decades, a growing number of elderly patients with end-stage kidney disease (ESKD) have needed to start renal replacement therapy [1–3]. Although kidney transplantation (KT) has been shown to offer better survival and quality of life than dialysis in elderly patients [4–8], some studies have questioned these benefits, especially for those receiving extended criteria donor grafts after circulatory death (DCD). In this sense, using data from the Dutch Organ Transplantation Registry, Peters-Sengers et al. reported that only 40% of elderly (≥65 years) recipients of elderly DCD transplants were alive with a functioning graft at 5 years compared with 53% of elderly recipients of elderly brain death donors (BDD) and 61% of elderly recipients from young donors. Notably, the authors also showed that this group of elderly recipients of elderly kidneys obtained from DCD had a 5-year mortality rate comparable to that of waitlisted elderly patients who remained on dialysis [9]. Similarly, our group recently described in a large European multicenter cohort, a significantly higher rate of graft loss among recipients of extended criteria controlled DCD (cDCD) (9.5 per 1,000 recipient-month [95% CI 6.8–12.7]) compared with recipients of extended criteria BDD (5.2 per 1,000 recipient-month [95% CI 4.2–6.3] or recipients of standard criteria donors (1.8 for standard BDD and 2.8 per 1,000 recipient-month for standard cDCD) [10]. Taken together, these results raise the question of whether highly extended kidneys should be assigned to similarly extended recipients, particularly if a DCD kidney transplant is employed.

Living donor (LD) kidney transplantation has been widely associated with superior graft and patient survival compared with deceased donor (DD) kidney transplantation in patients with ESKD [11]. However, information is scarce about the results of LD kidney transplantation in the elderly population. Along these lines, Berger et al. carried out a study of 219 LD kidney transplant recipients aged ≥70 and observed a greater graft loss as compared with LD aged 50–59 years (subhazard ratio 1.62), but not different from matched 50-to 59-year-old DD allografts without extended criteria. Importantly, mortality in LD aged ≥70 years was not higher than in matched healthy controls included in the NHANES III study [12]. Recently, Tegzess et al. conducted a retrospective single-center study of 348 elderly kidney transplants (median age 68 years [66–70]) performed between 2005 and 2017 and showed that recipients from an LD displayed a higher 5-year death-censored graft survival than recipients from the regular allocation (ETKAS) and the Euro-transplant Senior Program (ESP) (97.7% vs. 88.1% vs. 85.6; $p < 0.001$). Importantly, although the proportion of patients who received a preemptive kidney transplant was much higher in the LD cohort (60%) than in the other groups (11% and 13%), the authors did not observe any significant benefit in 5-year patient survival (71.7% vs. 67.4% vs. 61.9%, $p = 0.480$) [13].

To further characterize the benefits of LD compared with DD in the current era, we conducted a retrospective study in a large European cohort comprising 4,257 consecutive renal transplant

patients to analyze graft outcomes in elderly transplant recipients (≥65 years) who received a kidney organ from LD, BDD or cDCD between 2013 and 2021. Importantly, to overcome the unbalanced nature of the different groups for some relevant variables (preemptive transplants, time on dialysis and recipient comorbidities), we performed a propensity score analysis to accurately match the different study populations. To increase the statistical power of our analysis we analyzed data from two well-characterized European renal transplant Registries.

PATIENTS AND METHODS

Patients

For the present study we combined data on patients from two European transplant registries: 1) The Catalan Registry of Renal Patients (RMRC; approved by the Catalan Government; DOGC 402, 27 January 1984) which is a mandatory population-based registry of renal patients covering 7.5 million inhabitants that collects information from all patients with End Stage Renal Disease requiring Renal Replacement Therapy (www.trasplantaments.gencat.cat). This registry includes clinical data from all adult kidney transplant units in Catalonia: Hospital Universitari Vall d'Hebron, Hospital Clinic, Hospital Universitari Bellvitge, Fundació Puigvert, Hospital del Mar and Hospital Universitari Germans Trias i Pujol). 2) the EKITE cohort (approved by the CNIL, n°917155) [14] including data from seven European transplant centers from France (Nantes, Nancy, Lyon, Montpellier, Nice), Norway (Oslo) and Belgium (Leuven) since 2013 and merged into a single European cohort updated annually. All first kidney transplants from LD or DD, either BDD or cDCD aged 65 years or older, from January 2013 to December 2021, were considered for the present study. Recipients from uncontrolled donors after circulatory death were excluded. Patients were followed up until 31 December 2021. Baseline donor (age and type) and recipient variables (age, sex, time on dialysis, diabetes, cardiovascular disease) were recorded. Outcomes focused on graft survival, death-censored graft survival, patient survival and renal function.

Additionally, through the RMRC we gathered information on 95.4% (155/159) kidney donors from recipients over 65 years of age from 2013 to 2021, with follow-up until 31 December 2021.

The reported clinical and research activities adhere to the Declaration of Helsinki and are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Statistical Analysis

Variables were described as mean ± standard deviation, median and interquartile range, or frequencies according to their distribution. Qualitative variables were compared by the Chi-squared test, non-normally distributed quantitative variables by the Kruskal-Wallis test and normally distributed quantitative variables by the analysis of variance (ANOVA). Kaplan-Meier analysis was employed to calculate survival curves and the log-rank test was used for comparisons. Univariate and multivariable Cox's regression analysis was employed after verifying its proportionality to estimate risks.

Propensity score matching without replacement was employed to define a cohort of paired cases (recipients of LD vs. BDD and recipients of LD vs. cDCD) by age (donor and recipient), sex, time on renal replacement therapy before transplantation and diabetes mellitus. Cardiovascular disease was excluded from matching due to the presence of missing data (n = 72).

A two-tailed p-value <0.05 was considered significant and STATA17.0 was employed for statistical analysis.

RESULTS

Donor and Recipient Characteristics

This European study cohort included 4,257 consecutive, adult, single KT from LD (n = 408), BDD (n = 3,072) and cDCD (n = 777) (**Figure 1**). Baseline donor and recipient characteristics are displayed in **Table 1**. The mean donor and recipient age and dialysis vintage were lower in LD than in BDD and cDCD. Male recipients were more frequent in LD, while there were fewer LD patients with diabetes and cardiovascular disease. Time on dialysis was shorter in the case of LD and a higher percentage were transplanted pre-emptively (51.7%) as compared to BDD (10.8%) and cDCD (7.4%) (**Figure 2**). Regarding blood groups, A and O were the most common among the three groups. The time on dialysis was particularly long for patients with blood group O, while approximately 50% of DD transplants were on dialysis for more than 3 years before receiving a kidney transplant, only 20% of blood group A patients were on dialysis for more than 3 years before receiving a DD organ. Conversely, LD kidney transplants were much less likely to spend more than 3 years on dialysis across all blood groups (4.4% and 9.2% for blood groups A and O, respectively).

Survival Analysis Without Propensity Score

Univariate Kaplan-Meier analysis showed that 3-year graft survival including death with a functioning graft as well as both death-censored graft survival and patient survival were significantly higher in LD recipients than in BDD and cDCD recipients (**Figures 3A–C**). As shown in **Tables 2**, **3**, multivariable Cox's regression analyses adjusting for confounding variables such as donor and recipient age >70 years old, sex and relevant recipient comorbidities, confirmed these data for graft survival and death-censored graft survival. For patient survival censored after graft loss, univariate and multivariable analysis showed this similar trend (hazard ratios [95% confidence interval] of 3.03 [0.93–9.84], $p = 0.066$ and 11.34 [3.37–38.21], $p < 0.001$, for LD vs. BDD and LD vs. cDCD, respectively).

Propensity Score Matching

After propensity score matching, we obtained 387 pairs of recipients from LD and BDD and 259 pairs of recipients from LD and cDCD. Baseline donor and recipient characteristics are

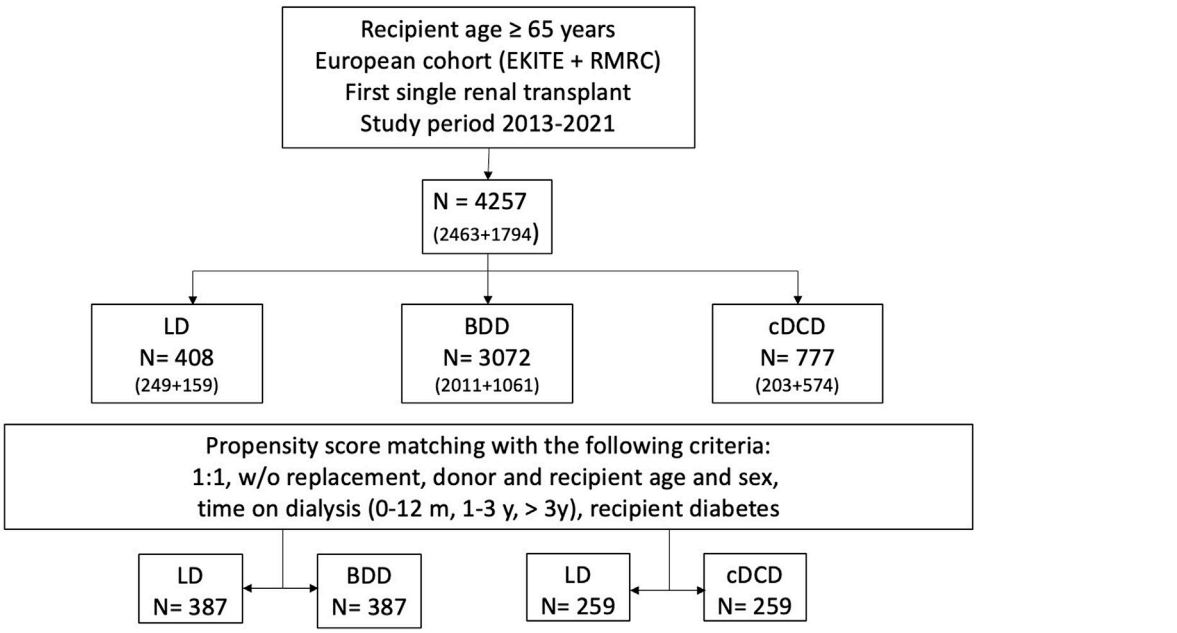


FIGURE 1 | Flow-chart of the included population.

TABLE 1 | Donor and recipient characteristics of renal transplants from the BDD, cDCD, and LD cohorts.

Variables	BDD (n = 3,072)	cDCD (n = 777)	LD (n = 408)	P
Age of donors, years	71.5 ± 9.8	67.2 ± 11.1	59.2 ± 11.2	<0.001
Age of recipient, years	71.4 ± 4.4	70.6 ± 4.4	69.4 ± 3.3	<0.001
Male sex, %	66.2	67.4	77.9	<0.001
Time on dialysis, Pre-emptive/0–12 mo./1–3 y/>3 y, %	10.8/12.5/39.3/37.2	7.4/14.5/45.3/32.6	51.7/20.3/21.5/6.3	<0.001
Blood group A/B/AB/0, %	45.2/10.3/4.7/39.7	44.7/8.1/2.9/44.1	50.1/9.6/2.7/37.4	0.016
Blood group A and time of dialysis 0–12 mo./1–3 y/>3y	32.8/45.2/21.9	31.7/49.4/18.8	78.2/17.3/4.4	<0.001
Blood group B and time of dialysis 0–12 mo./1–3 y/>3y	26.0/33.3/40.6	24.5/44.2/31.1	69.2/25.6/5.1	<0.001
Blood group AB and time of dialysis 0–12 mo./1–3 y/>3y	42.1/39.8/18.0	45.4/31.8/22.7	81.8/9.09/9.09	0.144
Blood group 0 and time of dialysis 0–12 mo./1–3 y/>3y	13.2/37.6/49.1	11.5/42.4/46.0	62.9/27.8/9.2	<0.001
Diabetes, %	42.9	44.2	41.4	0.635
Cardiovascular disease, %	57.8	59.7	44.3	<0.001

LD, Living donors; DBD, donors after brain death; cDCD, donors after controlled circulatory death.

displayed in **Tables 4**, **5**, respectively. As shown, the proportion of preemptive transplantations and the time on dialysis were now well matched between pairs from both cohorts (**Supplementary Figures S1A, B**).

Univariate Kaplan-Meier analysis showed that 3-year graft survival (including death with a functioning graft) and death-censored graft survival were significantly higher in LD recipients than in BDD and cDCD recipients (**Figures 4A–D**). However, patient survival censored for graft loss was not significantly different between LD and BDD recipients (**Figure 4E**) but was significantly lower in cDCD recipients than in LD recipients (**Figure 4F**). Adjusted multivariable Cox's regression analysis showed that graft survival was higher in LD recipients in both paired cohorts, whereas death-censored graft survival was not significantly different between groups (**Table 6**). Moreover, patient survival in the matched populations when censored for graft loss displayed a very high risk for cDCD vs. LD (hazard ratio: 10.41 [3.19–34.01], *p*-value <0.001) while this risk did not reach statistical significance for BDD (hazard ratio: 2.61 [0.69–9.81], *p*-value = 0.156).

Kidney Allograft Function

The estimated glomerular filtration rate (eGFR) from 1 to 3 years of follow-up was significantly higher in LD as compared to BDD and cDCD and was already higher at 12 months after transplantation (**Figure 5**).

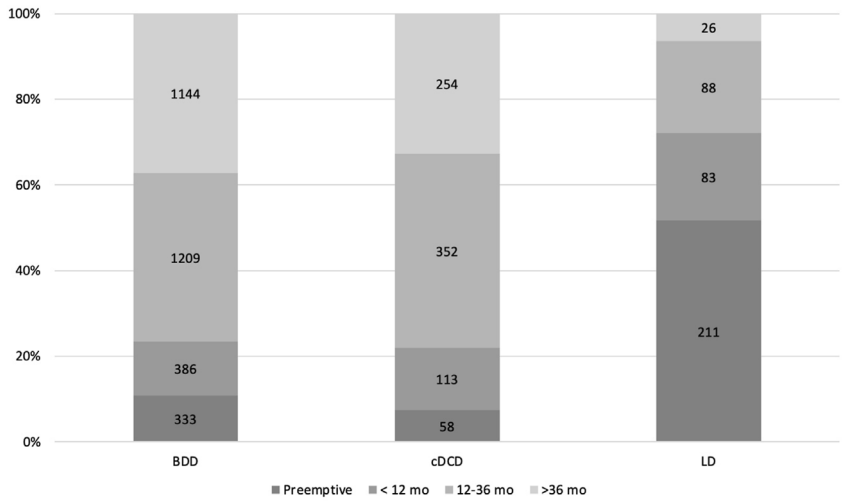


FIGURE 2 | Distribution of time on dialysis across the different donor sources. LD, living donor; DBD, donors after brain death; cDCD, donor after controlled circulatory death.

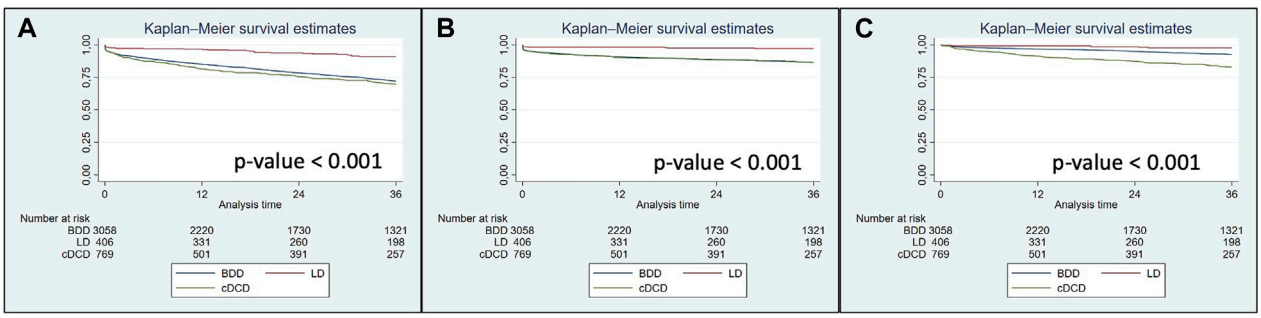


FIGURE 3 | Graft survival including graft failure and patient death with functioning graft **(A)**, death-censored graft survival **(B)** and patient survival censoring after graft loss **(C)** in kidney transplants performed during 2013–2021 in the European cohort. Log-rank *p*-value for all comparisons is displayed. LD, living donors; BDD, donors after brain death; cDCD, donor after controlled circulatory death.

TABLE 2 | Univariate and multivariate Cox's regression analysis comparing outcomes in living donor (LD) and donor after brain death (DBD) kidney transplantation.

	Univariate Cox's regression		Multivariate Cox's regression	
DBD vs. LD	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Graft survival	3.53 (2.43–5.11)	<0.001	2.64 (1.64–4.50)	<0.001
Death-censored graft survival	4.87 (2.60–9.13)	<0.001	2.59 (1.19–5.67)	0.017
Patient survival	3.33 (1.56–7.10)	0.002	3.03 (0.93–9.84)	0.066

Variables included in the multivariate analysis were donor age >70y, recipient age >70 y, recipient sex, recipient comorbidities (diabetes, cardiovascular disease) and time on dialysis.

TABLE 3 | Univariate and multivariate Cox's regression analysis comparing outcomes in living donor (LD) and donor after controlled circulatory death (cDCD) kidney transplantation.

	Univariate Cox's regression		Multivariate Cox's regression	
cDCD vs. LD	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Graft survival	3.97 (2.69–5.67)	<0.001	3.90 (2.15–7.06)	<0.001
Death-censored graft survival	4.90 (2.54–9.44)	<0.001	3.06 (1.27–7.39)	0.013
Patient survival	8.16 (3.78–17.60)	<0.001	11.35 (3.37–38.21)	<0.001

Variables included in the multivariate analysis were donor age >70 y, recipient age >70 y, recipient sex, recipient comorbidities (diabetes, cardiovascular disease) and time on dialysis.

TABLE 4 | Baseline donor and recipient characteristics with propensity score matching between LD and DBD.

Variables	BDD (n = 387)	LD (n = 387)	P
Age of donors, years	60.9 ± 13.6	60.3 ± 10.3	0.468
Age of recipients, years	69.6 ± 3.7	69.6 ± 3.3	0.740
Recipient sex (m/f), %	80.6/19.3	76.7/23.2	0.188
Time on dialysis, Pre-emptive/0–12 mo./1–3 y/>3 y, %	44.9/21.1/25.8/8.0	49.3/21.4/22.4/6.7	0.544
Diabetes, %	42.8	43.9	0.191
Cardiovascular disease, %	48.7	43.9	0.191

LD, Living donors; BDD, donors after brain death; DM, diabetes mellitus.

TABLE 5 | Baseline donor and recipient characteristics, with propensity score matching between LD and cDCD.

Variables	cDCD (n = 259)	LD (n = 259)	P
Age of donors, years	60.5 ± 12.9	61.6 ± 10.6	0.284
Age of recipients, years	69.4 ± 3.8	69.9 ± 3.4	0.122
Recipient sex (m/f), %	77.6/22.3	72.2/27.8	0.156
Time on dialysis, Pre-emptive/0–12 mo./1–3 y/>3 y, %	21.6/31.2/37.1/10.0	25.8/30.5/33.5/10.0	0.694
Diabetes, %	36.6	43.2	0.127
Cardiovascular disease, %	52.2	47.5	0.300

LD, Living donors; cDCD, donors after controlled circulatory death; DM, diabetes mellitus.

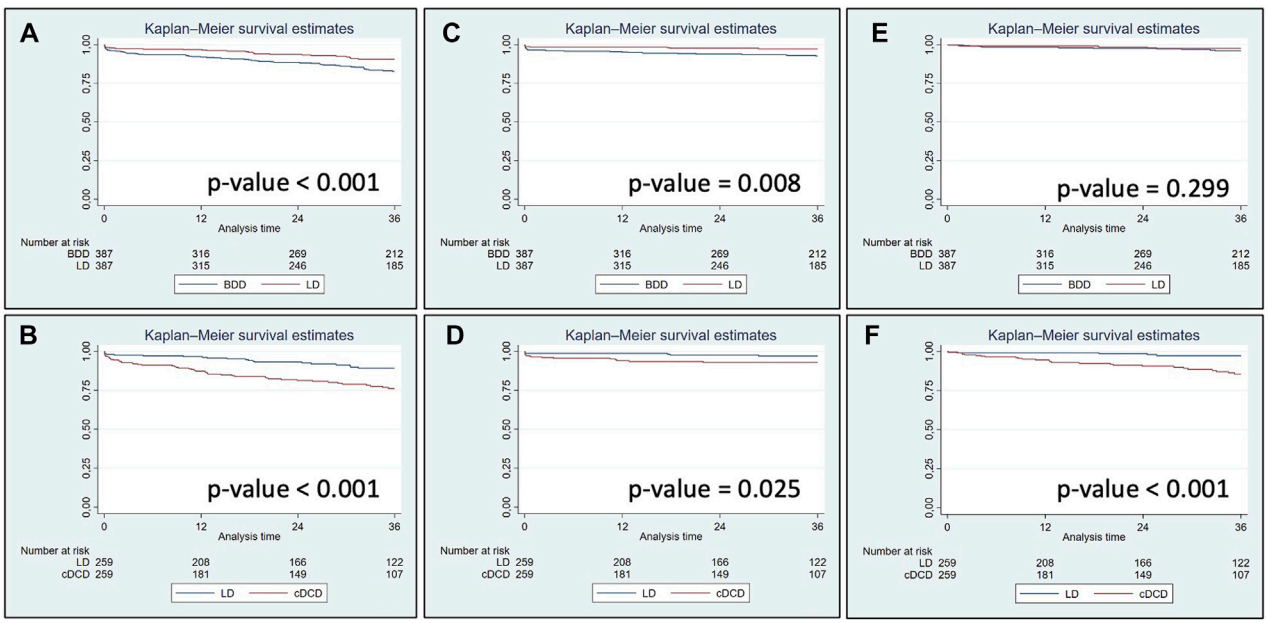


FIGURE 4 | Graft survival including patient death **(A, B)**, death-censored graft survival **(C, D)** and patient survival **(E, F)** in kidney transplants performed during 2013–2021 in the European cohort matched by the propensity score. Log-rank *p*-value for all comparisons is displayed. LD, living donors; BDD, donors after brain death; cDCD, donors after controlled circulatory death.

Kidney Donor Evolution

Data were available for 155 cases out of 159 living kidney donors employed to transplant elderly recipients from the RMRC. The mean age of the donors at the time of donation was 62.8 ± 8.9 years (range 36–78), female sex predominated (77.4%) and among the most relevant comorbidities were arterial hypertension (27.4%), dyslipidemia (30%), obesity (19.3%) and urolithiasis (3.8%). After nephrectomy, comorbidities remained stable (arterial hypertension in 15.8%, dyslipidemia in 29.1% and obesity in 7.9%) while a minority developed new-onset diabetes mellitus (1.3%). Notably, renal function remained stable after nephrectomy at 3 years (**Figure 6**).

TABLE 6 | Multivariable Cox's regression analysis in patients evaluated by the propensity score matching.

	BDD (n = 387)	LD (n = 387)	*p*-value	cDCD (n = 259)	LD (n = 259)	*p*-value
	HR (95% CI)			HR (95% CI)		
Graft survival	2.19 (1.16–4.15)		0.016	3.38 (1.79–6.39)		<0.001
Death-censored graft survival	1.83 (0.66–5.08)		0.249	1.84 (0.64–5.31)		0.259
Patient survival	2.61 (0.69–9.81)		0.156	10.41 (3.19–34.01)		<0.001

Variables included in the multivariate analysis were donor age >70 y, recipient age >70 y, recipient sex, recipient comorbidities (diabetes, cardiovascular disease) and time on dialysis. BDD, brain death donors; LD, living donors; cDCD, donors after controlled circulatory death.

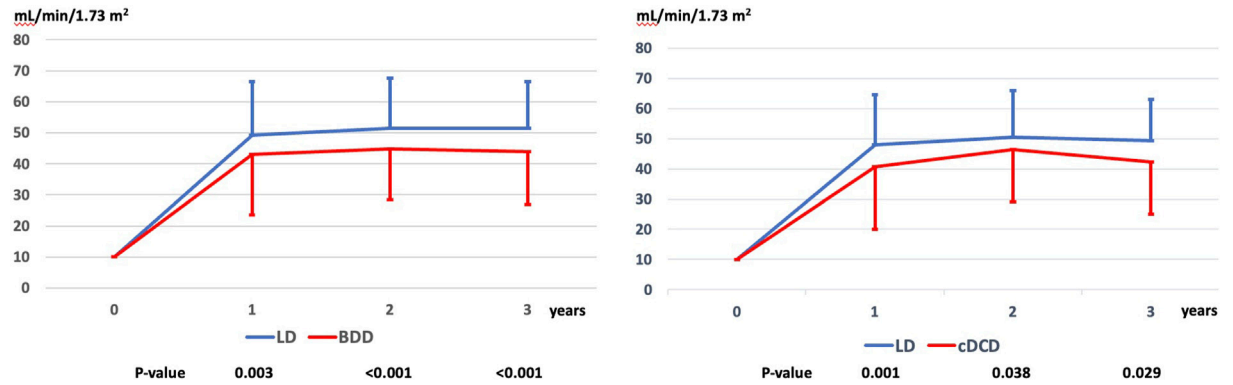


FIGURE 5 | Evolution of renal function (eGFR according to the CKD-EPI formula) up to 3 years in the matched cohorts. LD, living donor; BDD, donors after brain death; cDCD, donor after controlled circulatory death; eGFR, estimated Glomerular Filtration Rate by the CKD-EPI formula.

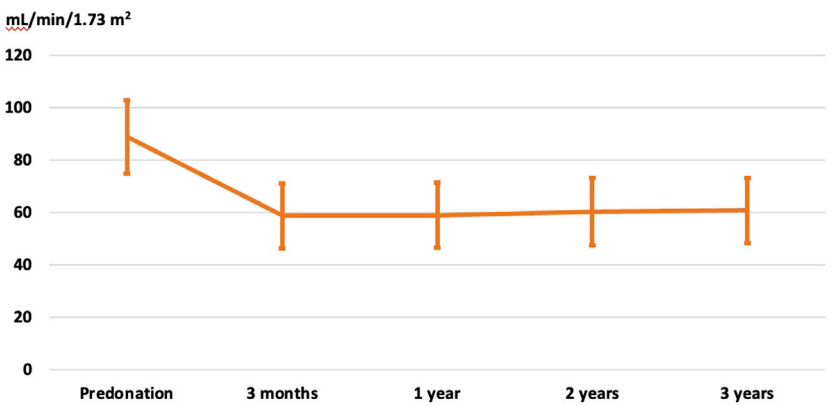


FIGURE 6 | Evolution of renal function in kidney donors after nephrectomy (eGFR according to the CKD-EPI formula).

DISCUSSION

We conducted a retrospective study of two large European cohorts of elderly renal transplant recipients to evaluate the benefits of receiving a graft from an LD versus a BDD or cDCD. Because these recipient populations were unbalanced for key clinical variables, we performed a propensity score analysis to match our populations. The results of our study confirm that LD offer advantages over DD (BDD or cDCD) in terms of graft survival including patient death and the need to return to dialysis. The propensity score analysis shows that the adjusted hazard ratio of graft failure in BDD recipients is more than twice that of LD, while it is more than three times that of cDCD. Because the rate of graft dysfunction after the first year is a low-frequency event in these matched cohorts, the adjusted model did not show significant differences in death-censored graft survival. Importantly, renal function was significantly higher in LD transplant recipients than in BDD or cDCD recipients, a key surrogate variable predicting long-term graft and patient outcomes [15]. More importantly, elderly LD transplant recipients are more likely to be transplanted preemptively and more quickly than both cDCD and DBD recipients.

The demographic profile of the ESKD population has changed over the last century, with older patients (≥65 years) representing the fastest-growing incident group starting maintenance dialysis therapy in developed countries [16, 17]. In parallel, elderly recipients have been progressively included in all kidney transplant programs in the United States and Europe [18]. In the present century, the number of elderly ESKD patients receiving a renal allograft has increased worldwide, changing in our geographical area from 12.3% of all renal transplants in 2000 to 38.2% in 2021 [19]. Therefore, there is an increasing interest in the outcome of transplantation in this cohort, as the proportion of older patients will gain significantly in terms of quality and quantity of life with successful kidney transplantation [5, 6, 20]. Although the outcomes of kidney transplantation from LD consistently exceed those from DD in terms of patient and graft survival [21], the opportunity for kidney transplantation from an LD is inconsistent across age categories. In the UK the likelihood of having an LD transplant rather than a DD transplant is almost 90% lower in those older than 65 years at the time of transplant, compared to young adults [22]. Similarly, in our country, the rate of LD kidney transplantation during the study period (2013–2021) was much lower in elderly recipients (8.8%) than in younger ones (24%).

In this study, one of the main differences between elderly KT receiving grafts from LD or DD is related to the time on dialysis. Importantly, more than 50% of LD received a pre-emptive KT while less than 10% of DD kidney transplants were performed before starting dialysis. The Descartes working group and the European Renal Best Practice (ERBP) Advisory Board recommend (grade 1D) that programs for pre-emptive kidney transplantation with LD kidneys should be encouraged [23]. However, they acknowledged a high risk of bias in their meta-analysis because patients selected for pre-emptive transplantation differed from those who were not. Patients receiving a pre-emptive transplant are more likely to receive a kidney from an LD and there were significant differences in comorbidities, socio-economic conditions, and education levels. A more recent meta-analysis including 76 studies comprising more than 120,000 patients confirmed the benefits of pre-emptive KT in terms of patient (adjusted HR: 0.78 [95% CI 0.66–0.92]) and death-censored graft survival (adjusted hazard ratio 0.81 [0.67–0.98]) [24]. However, as discussed well by the authors, the lead-time bias (e.g., the time difference in ESKD period in patients transplanted pre-emptively vs. those transplanted on dialysis) was not resolved by their meta-analysis. To overcome these limitations, we performed a propensity score matching to compare outcomes in kidney transplant recipients from LD donors vs. BDD or cDCD donors. The obtained cohorts (387 and 256 pairs, respectively) were well-matched for pre-emptive transplantation rates and dialysis duration, avoiding lead-time bias. Additionally, other key factors influencing patient and graft outcomes like donor and patient age, or patient comorbidities (diabetes) were also balanced in both cohorts. The propensity score-matched kidney transplant outcomes show that the adjusted hazard ratio for graft failure is more than twofold (hazard ratio 2.19 [95% CI 1.16–4.15]) for BDD recipients while it is more than threefold (hazard ratio 3.38 [95% CI 1.79–6.39]) for cDCD recipients. Notably, these differences were observed even though "very old" donors (>75 years) were not included in our propensity score analysis as this type of donor was much less represented in the LD cohort. In fact, the mean donor age in the matched cohorts was approximately 60 years, a figure very close to the mean donor age of deceased donors in our RMRC registry (58.6 years in 2021 and 60.8 years in 2020) [19]. Thus, our results confirm the benefit of LD kidney transplantation in the elderly population although we cannot estimate the potential benefit for elderly patients receiving highly extended DD kidneys. In this regard, data from the U.S. registry showed that recipients of older LD (≥65 years) have increased graft failure and long-term mortality compared to cases of younger LD; however, these recipients appear to do as well or better than recipients of standard or extended criteria deceased donors [25].

The number of KT with cDCD donors has exponentially increased in different countries in recent years, with a parallel increase in donor and recipient acceptance criteria. Although the outcomes of KT form cDCD have been reported to be comparable to those of BDD, studies in elderly recipients have yielded contradictory results [7, 9]. In the present study graft survival of kidney transplants from cDCD was lower than graft survival from BDD and patient death with a functioning graft is the major contributing factor to this finding (relative risk 10.6). Recently, data from the UK registry have shown that delayed graft function of more than 14 days in cDCD donors is associated with almost double the risk of patient death [26]. Although the presence of delayed graft function and its duration were not evaluated in our study, the high mortality risk in cDCD versus BDD recipients is consistent with a previous study conducted in patients from a large European patient cohort [10]. Management of cDCD donors for organ retrieval and organ preservation was also not recorded in our study. The benefits of normothermic regional perfusion over rapid recovery technique have been described in different studies [27–29] and the benefits of organ perfusion with different devices after retrieval over static cold storage have also been described, especially for kidney transplantation with long cold ischemia time [30].

An in-depth analysis of living donor outcomes is beyond the scope of the present study, but data from a subset of donors in this study confirm that renal function remains stable over the mid-term while major comorbidities (arterial hypertension, dyslipidemia, and obesity) are well controlled in this cohort of patients managed by transplant physicians.

Our study has some limitations because the data come from two large European transplant registries, and thus, detailed granularity on patient outcomes (e.g., cause of death) and graft outcomes (e.g., delayed graft function) was not available. However, the propensity score-matched analysis performed counterbalanced this constraint and allowed for accurate comparisons regarding the key hard outcomes investigated. Importantly, the mean donor age in the unmatched BDD and cDCD cohorts was close to 70 years, while after propensity score matching, the mean donor age dropped to 60 years, as "very old" donors were less frequently represented in the LD cohort.

However, these donors are more easily found in this elderly patient population and are an optimal source for transplantation. Additionally, our findings are subject to residual confounding due to the lack of data on cardiovascular disease and other unmeasured factors such as social support and socioeconomic status. These factors, along with frailty, smoking, treatment adherence, and lifestyle, may influence graft and patient survival. Furthermore, we did not adjust or match for transplant variables such as HLA mismatch, which may differ between the LD and DD populations. Another limitation is that these results may not be generalizable to other organ allocation systems. In certain regions, kidneys from older and higher-risk donors are prioritized for elderly recipients, which could lead to a greater disparity between LD and DD compared to systems that do not impose such allocation restrictions.

In conclusion, our study strongly supports that LD transplantation offers significant advantages for elderly transplant recipients in terms of elective surgery, timely transplantation, graft survival and mid-term graft function. Thus, transplant teams should offer this treatment to elderly kidney transplant candidates to avoid the age-based inequity in access to transplantation [31].

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by EKITE cohort (approved by the CNIL, n°917155. Catalan Registry of Renal Patients (RMRC; approved by the Catalan Government; DOGC 402, 27th January 1984). 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

NT: designed the study, interpreted the data, drafted the article; JC and EA: analyzed the data, interpreted the data; IR, AM, CF, MP-S, AV, JT, MG, MN, DK, and AA: revised the article critically; FM and OB: designed the study, interpreted the data, drafted the article and revised the article critically. All authors contributed to the article and approved the submitted version.

GROUP MEMBERS OF EKITE CONSORTIUM

Oslo: Karsten Midtvedt, Anna V Reisæter, Trond Jenssen, Kristian Heldal, AA. **Leuven:** Dirk Kuypers, MN, Borefore Jallah. **Lyon E. Hériot:** Lionel Badet, Maria Brunet, Fanny Buron, Rémi Cahen, Ricardo Codas, Sameh Daoud, Valérie Dubois, Coralie Fournie, François Gaillard, Arnaud Grégoire, Alice Koenig, Charlène Lévi, Emmanuel Morelon, Claire Pouteil-Noble, Maud Rabeyrin, Thomas Rimmelé, Olivier Thaunat. **Montpellier:** Nicolas Abdo, Sylvie Delmas, Moglie Le Quintrec, Vincent Pernin, Hélène Perrochia, Jean-Emmanuel Serre, Ilan Szwarc. **Nancy:** Alice Aarnink, Asma Alla, Pascal Eschwege, Luc Frimat, Sophie Girerd, Jacques Hubert, Raphaël Kormann, Marc Ladriere, François Lagrange, Emmanuelle Laurain, Pierre Lecoanet, Jean-Louis Lemelle; Anthony Mannuguerra, Charles Mazeaud, Michael Peres; **Nantes:** Gilles Blancho, Julien Branchereau, Diego Cantarovich, Agnès Chapelet, Jacques Dantal, Clément Deltombe, Lucile Figueres, Raphael Gaisne, Claire Garandeau, MG, Caroline Gourraud-Vercel, Clarisse Kerleau, Christophe Masset, Aurélie Meurette, Simon Ville, Christine Kandell, Anne Moreau, Karine Renaudin, Florent Delbos, Alexandre Walencik, Anne Devis. **Nice:** Laetitia Albano, Damien Ambrosetti, Nadia Ben Hassen, Mathilde Blois, Marion Cremoni, Matthieu Durand, Patricia Goldis, Clément Gosset, Fatimaezzahra Karimi, Antoine Sicard, Giorgo Toni. **Barcelona:** Irina Torres, Maria Meneghini, Delphine Kervella, Joana Sellares, Manel Perelló, José Zúñiga.

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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.2024.13452/full#supplementary-material

SUPPLEMENTARY FIGURE S1 | (A) Supplementary Figure S1 Distribution of time on dialysis after Propensity score matching in the living donor and brain death donor cohorts. **(B)** Distribution of time on dialysis after Propensity score matching in the living donor and controlled donor cohorts after circulatory death cohorts.

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ORIGINAL RESEARCH
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Impact of Blood Pressure on Allograft Function and Survival in Kidney Transplant Recipients

Hyo Jeong Kim[1‡], Kyung Won Kim[2‡], Young Su Joo[3], Junghwa Ryu[4], Hee-Yeon Jung[5], Kyung Hwan Jeong[6], Myung-Gyu Kim[7], Man Ki Ju[8], Seungyeup Han[9], Jong Soo Lee[10], Kyung Pyo Kang[11], Han Ro[12], Kyo Won Lee[13], Kyu Ha Huh[14], Myoung Soo Kim[14], Beom Seok Kim[15] and Jaeseok Yang[15†] for the KOTRY Study Group[‡§]*

[1]Division of Nephrology, Department of Internal Medicine, Gangnam Severance Hospital, Seoul, Republic of Korea, [2]Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea, [3]Department of Internal Medicine, College of Medicine, Yongin Severance Hospital, Yonsei University, Yongin, Republic of Korea, [4]Department of Internal Medicine, Seoul Hospital, Ewha Womans University, Seoul, Republic of Korea, [5]Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea, [6]Department of Internal Medicine, Kyung Hee University College of Medicine, Seoul, Republic of Korea, [7]Department of Internal Medicine, College of Medicine, Anam Hospital, Korea University, Seoul, Republic of Korea, [8]Department of Surgery, College of Medicine, Gangnam Severance Hospital, Yonsei University, Seoul, Republic of Korea, [9]Department of Internal Medicine, Dongsan Medical Center, Keimyung University, Daegu, Republic of Korea, [10]Department of Internal Medicine, Ulsan University Hospital, Ulsan, Republic of Korea, [11]Department of Internal Medicine, Research Institute of Clinical Medicine, Jeonbuk National University Medical School, Jeonju, Republic of Korea, [12]Department of Internal Medicine, Gil Hospital, Gachon University, Incheon, Republic of Korea, [13]Department of Surgery, Seoul Samsung Medical Center, Sungkyunkwan University, Seoul, Republic of Korea, [14]Department of Surgery, College of Medicine, Severance Hospital, Yonsei University, Seoul, Republic of Korea, [15]Department of Internal Medicine, College of Medicine, Severance Hospital, Yonsei University, Seoul, Republic of Korea

The optimal target blood pressure for kidney transplant (KT) patients remains unclear. We included 808 KT patients from the KNOW-KT as a discovery set, and 1,294 KT patients from the KOTRY as a validation set. The main exposures were baseline systolic blood pressure (SBP) at 1 year after KT and time-varying SBP. Patients were classified into five groups: SBP <110; 110–119; 120–129; 130–139; and ≥140 mmHg. SBP trajectories were classified into decreasing, stable, and increasing groups. Primary outcome was composite kidney outcome of ≥50% decrease in eGFR or death-censored graft loss. Compared with the 110–119 mmHg group, both the lowest (adjusted hazard ratio [aHR], 2.43) and the highest SBP (aHR, 2.25) were associated with a higher risk of composite kidney outcome. In time-varying model, also the lowest (aHR, 3.02) and the highest SBP (aHR, 3.60) were associated with a higher risk. In the trajectory model, an increasing SBP trajectory was associated with a higher risk than a stable SBP trajectory (aHR, 2.26). This associations were consistent in the validation set. In conclusion, SBP ≥140 mmHg and an increasing SBP trajectory were associated with a higher risk of allograft dysfunction and failure in KT patients.

Keywords: kidney transplantation, graft outcome, blood pressure, time-varying, trajectory

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***Correspondence**
Jaeseok Yang,
jcyjs@yuhs.ac

†ORCID:
Jaeseok Yang
orcid.org/0000-0002-5378-7797

§The full list of KOTRY study group was described in the Supplementary Material

‡These authors have contributed equally to this work

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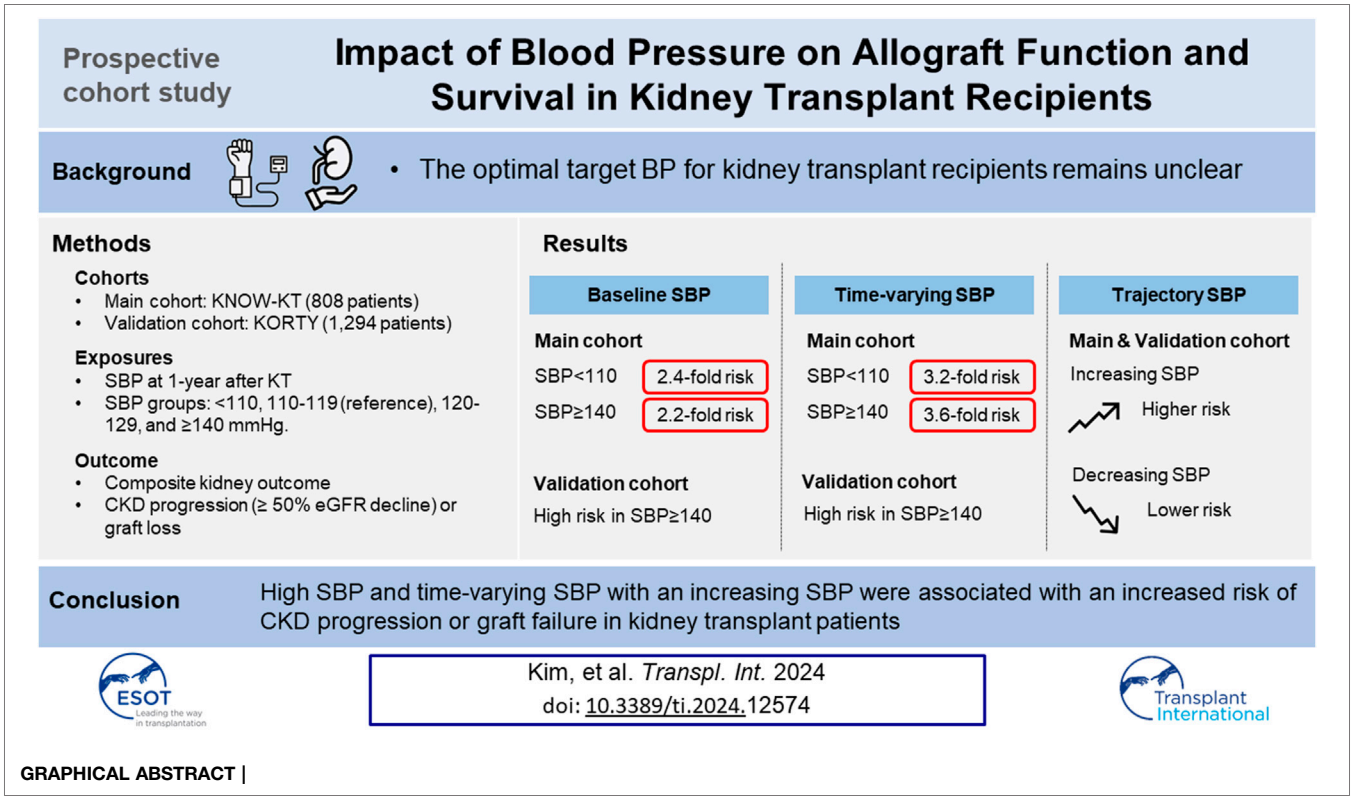

GRAPHICAL ABSTRACT |

INTRODUCTION

Post-transplant hypertension is one of the most common complications after kidney transplantation (KT). The prevalence of hypertension in kidney transplant recipients (KTRs) is reported to be approximately 50%–90% [1, 2]. Its risk factors include not only chronic kidney disease (CKD)-related risk factors, such as activation of the renin-angiotensin-aldosterone system (RAS), sympathetic nerve activity, and extracellular fluid volume expansion, but also KT-specific factors, such as calcineurin inhibitors (CNIs), corticosteroids, transplant renal artery stenosis, and angiotensin II type 1-receptor activating antibodies [3–14].

Hypertension is a well-recognized major risk factor for post-transplant cardiovascular diseases (CVD) such as congestive heart failure, ischemic heart disease, and stroke in KTRs [15–18]. Hypertension is also an independent risk factor for kidney function decline, and poor graft survival. In experimental studies, hypertension accelerates the progression of kidney failure by elevating glomerular capillary hydrostatic pressure and glomerular hyper-perfusion [19, 20]. Notably, grafted kidneys with vascular damage are likely to be susceptible to mechanical injury, which accelerates immune-mediated injury. Several clinical studies have shown the negative effect of hypertension on graft outcomes [2, 21, 22]. In an observational cohort study of living donor KTRs, the BP during the first year after KT was a significant risk factor for allograft failure, independent of kidney function [22].

Therefore, management of hypertension after KT is imperative to improve graft survival and patient survival. However, the optimal target BP for KTRs remains unclear. The SPRINT study recommended strict SBP control <120 mmHg for the reduction of cardiovascular events as well as mortality. A *post hoc* study of SPRINT also showed that intensive SBP control <120 mmHg decreased cardiovascular events in CKD patients [23, 24]. However, the ACCORD study did not find beneficial effects of strict BP control on cardiovascular events and mortality in diabetic CKD patients [25]. In the 2021 Kidney Disease Improving Global Outcomes (KDIGO) BP guidelines, the target BP for CKD patients was lowered to SBP <120 mmHg according to the SPRINT, whereas the target BP for KTRs was maintained at <130/80 mmHg [26]. No randomized controlled clinical trials (RCTs) have examined the effect of BP on CVD outcome, graft survival, or mortality in KTRs [18]. Therefore, we investigated the association between SBP and kidney outcomes in a large prospective cohort of KTRs.

PATIENTS AND METHODS

Study Design and Participants

The Korean Cohort Study for Outcome in Patients with Kidney Transplantation (KNOW-KT) is a multicenter, observational cohort study that investigated graft and patient outcomes along with risk factors in Korean KT patients [27]. A total of 1,080 participants were enrolled from eight Korean

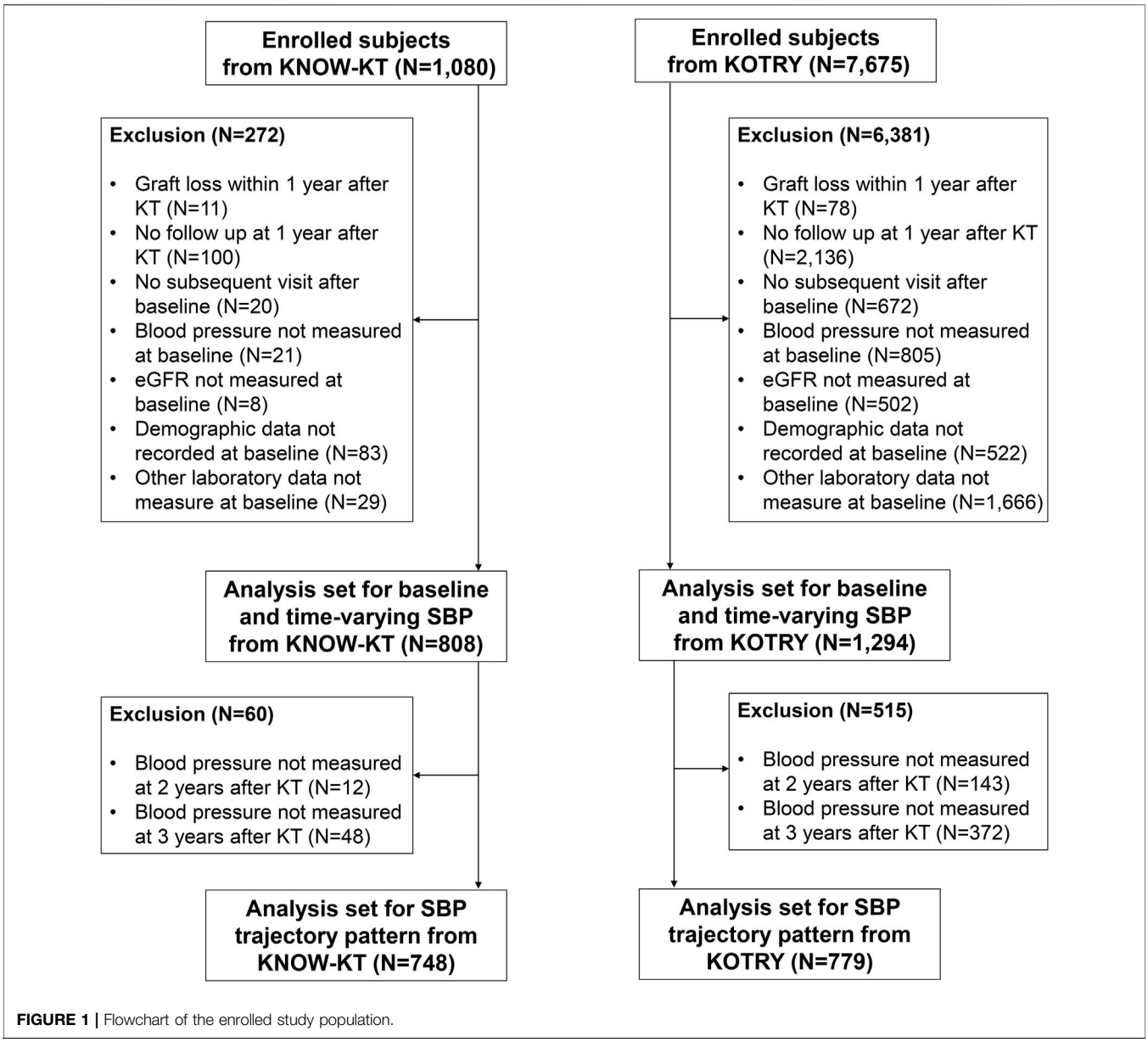

FIGURE 1 | Flowchart of the enrolled study population.

transplantation centers between July 2012 and August 2016 and followed up annually. We excluded 11 patients who suffered graft loss within 1 year of KT, 100 patients who had no follow-up at 1-year after KT (baseline), and 20 patients who underwent baseline examination only without subsequent visits thereafter**.** Moreover, patients with missing baseline SBP (n = 21), estimated glomerular filtration rate (eGFR) (n = 8), demographic (n = 83), and laboratory data (n = 29) were excluded. As a result, the final analysis included 808 patients (**Figure 1**). A total of 748 patients were enrolled in the trajectory analysis model, excluding an additional 60 patients without BP readings during the exposure period (**Figure 1**).

The Korean Organ Transplantation Registry (KOTRY), a nationwide cohort for organ transplantation in Korea, prospectively collected data on organ transplantation recipients and donors [28]. The KTRs between 2014 and 2020 in KOTRY were used as a validation cohort in this study. Among 7,675 eligible patients, we excluded 6,381 patients for the following reasons: graft loss within 1 year after KT (n = 78), no follow-up at 1-year after KT (n = 2,136), no subsequent visit after baseline visit (n = 672), and missing baseline SBP (n = 805), eGFR (n = 502), demographic data (n = 522), and laboratory data (n = 1,666). As a result, 1,294 patients were included in the final analysis (**Figure 1**).

The study was conducted in accordance with the principles of the Declaration of Helsinki and the Declaration of Istanbul, and the study protocol was approved by the Institutional Review Boards of the participating centers (4-2012-0223, 4-2014-0290). All participants provided informed consent.

Data Collection and Measurements

Socio-demographic characteristics including age, sex, and smoking history were collected during the pre-transplant screening period. General information about transplantation, including donor-recipient relationship, recipient information including comorbidities and medications, and donor information were collected at the time of KT. The resting office BP were conducted at each yearly visit. The eGFR was calculated using the Modification of Diet in Renal Disease equation [29].

Exposure and Outcome Ascertainment

The main exposures in this study were baseline and time-varying SBP. We defined the baseline of this study as 1 year after KT. In the time-varying analysis, we used the most recent SBP at each visit. Patients were categorized into five groups based on SBP: <110 mmHg (group 1), 110–119 mmHg (group 2, reference), 120–129 mmHg (group 3), 130–139 mmHg (group 4) and ≥140 mmHg (group 5). We performed additional analysis using the SBP trajectory determined by the differences in SBP between the baseline (1 year after KT) and after 2 years and between the baseline and after 3 years.

The primary outcome was the composite kidney outcome of CKD progression or graft loss. CKD progression was defined as a ≥50% decline in eGFR from baseline values. Graft loss was defined as the requirement for maintenance dialysis for more than 3 months or re-transplantation. Patients were censored at the date of the last visit, all events or death.

Statistical Analysis

Continuous variables are expressed as mean values with standard deviation for normally distributed data or medians with interquartile ranges (IQRs) for skewed data. The Kolmogorov–Smirnov test was performed to determine the normality of all continuous variables. Categorical variables are presented as frequencies with percentage. Comparisons between groups were performed using a one-way analysis of variance or Kruskal–Wallis test for continuous variables, as appropriate. The chi-squared test or Fisher's exact test was used for comparing categorical variables. Cox proportional hazards regression analysis evaluated the association between baseline SBP and study outcomes. In addition, we constructed marginal structural Cox models to reflect time-dependent changes in SBP and other covariates. In BP trajectory modeling, we used group-based trajectory modeling to categorize the trend of BP over time. The longitudinal BP was fitted as a mixture of multiple latent trajectories in a censored normal model with a polynomial function of time [30, 31]. Death events before the incidence of composite kidney outcome and loss to follow-up were treated by censoring at the date of death and the last examination, respectively. Significant variables related to CKD progression or graft loss in univariate analysis ($p < 0.10$) were included into all models for adjustment. Model 1 characterizes the crude hazard ratio (HR) without adjustment. Model 2 was adjusted for age, sex, body mass index (BMI), smoking status, diabetes mellitus (DM), CVD, eGFR, hemoglobin, albumin, low-density lipoprotein cholesterol (LDL-C), ABO compatibility, HLA compatibility, delayed graft function (DGF), acute rejection during the first year, donor type (living vs. deceased), donor age, donor BMI, donor hypertension, donor eGFR, and immunosuppressants (tacrolimus, cyclosporine, and steroids). Model 3 was further adjusted for BP-lowering medications (RAS blockers, beta-blockers, calcium channel blockers, alpha-blockers, and diuretics). In the trajectory model, baseline SBP was additionally adjusted. The results from multivariable hazard models are presented as HRs and 95% confidence intervals (CIs). All statistical analyses were performed with Stata 14 statistical software (StataCorp, College Station, TX), with a p-value <0.05 considered significant.

RESULTS

Baseline Characteristics

Table 1 shows baseline characteristics of 808 participants according to baseline SBP categories. The mean age of participants was 45.8 ± 11.4 years, and 62.7% were women. Almost all patients (96.0%) had hypertension, and the mean SBP and DBP were 124.3 ± 12.6 and 78.7 ± 10.7 mmHg, respectively. The mean baseline eGFR was 64.7 ± 18.0 mL/min/1.73 m^2. Numbers of patients with SBP <110, 110–119, 120–129, 130–140, and ≥140 mmHg were 93 (11.5%), 168 (20.8%), 292 (36.1%), 164 (20.3%), and 91 (11.3%), respectively. Patients with SBP ≥140 mmHg were older, more likely to be women, and had higher BMI. Moreover, those with highest SBP had more DM and treated with more RAS blockers, and beta-blockers than those with lower SBP groups.

Association of SBP With Adverse Kidney Outcomes

During a median follow-up period of 5.93 years, 85 (10.5%) participants reached the primary composite outcome and the overall incidence rate was 19.3 per 1,000 person-years (**Table 2**). The primary composite outcome of CKD progression or graft loss occurred in 15 (16.1%), 13 (7.7%), 29 (9.9%), 15 (9.1%), and 13 (14.3%) patients in groups 1 (SBP <110 mmHg), 2 (SBP 110–119 mmHg), 3 (SBP 120–129 mmHg), 4 (SBP 130–139 mmHg), and 5 (SBP ≥140 mmHg), respectively.

When the cumulative incidence of the primary composite outcomes was compared between the baseline SBP groups using the log-rank test, group 2 (SBP 110–119 mmHg) showed a lower incidence than group 1 (SBP <110 mmHg, $p = 0.041$) and a trend of lower incidence than group 5 (SBP ≥140 mmHg, $p = 0.085$) (**Figure 2A**). In Cox regression analysis, the risk of CKD progression or graft loss increased in both group 1 and 5 compared with that in group 2. After adjustment for potential confounding factors, the adjusted HRs for groups 1 and 5 were 2.43 (95% confidence interval [CI], 1.12–5.26) and 2.25 (1.00–5.02), respectively, compared with the reference group 2 (**Table 3**).

Next, we examined the association of time-varying SBP levels with the composite kidney outcome using a marginal structural Cox regression model. In the fully adjusted model, group 1 and 5 had a 3.02 (95% CI 1.11–8.22) and 3.60 (95% CI, 1.48–8.72) -fold higher risk of composite outcomes than the reference group 2 (**Table 3**).

TABLE 1 | Baseline characteristics of participants according to systolic blood pressure categories.

	SBP category (mmHg)						
	Total	**<110**	**110–119**	**120–129**	**130–139**	**≥140**	***p*-value**
Demographic data							
N (%)	808 (100)	93 (11.5)	168 (20.8)	292 (36.1)	164 (20.3)	91 (11.3)	
Age (years)	45.8 ± 11.4	46.5 ± 10.6	44.5 ± 11.4	44.9 ± 11.7	46.8 ± 11.2	48.3 ± 10.7	0.034
Female, n (%)	507 (62.7)	49 (52.7)	99 (58.9)	187 (64.0)	105 (64.0)	67 (73.6)	0.040
BMI (kg/m^2)	22.6 ± 3.2	21.7 ± 3.0	22.3 ± 2.9	22.8 ± 3.4	22.9 ± 3.3	23.5 ± 3.3	0.001
SBP (mmHg)	124.3 ± 12.6	103.2 ± 4.8	114.9 ± 2.9	124.1 ± 2.8	133.7 ± 2.8	146.7 ± 6.5	<0.001
DBP (mmHg)	78.7 ± 10.7	66.3 ± 7.1	74.5 ± 7.3	78.5 ± 8.8	84.0 ± 8.3	89.7 ± 11.6	<0.001
Diabetes mellitus, n (%)	207 (26.2)	34 (37.0)	28 (17.3)	69 (24.3)	38 (23.6)	38 (41.8)	<0.001
Hypertension, n (%)	759 (96.1)	86 (93.5)	155 (95.7)	271 (95.4)	158 (98.1)	89 (97.8)	0.330
Coronary artery disease, n (%)	47 (5.9)	4 (4.3)	13 (8.0)	15 (5.3)	6 (3.7)	9 (9.9)	0.210
Cerebrovascular disease, n (%)	28 (3.5)	7 (7.6)	3 (1.9)	13 (4.6)	3 (1.9)	2 (2.2)	0.075
Congestive heart failure, n (%)	13 (1.6)	1 (1.1)	4 (2.5)	5 (1.8)	1 (0.6)	2 (2.2)	0.720
Smoker, n (%)							0.730
Never	434 (53.7)	51 (54.8)	90 (53.6)	159 (54.5)	88 (53.7)	46 (50.5)	
Current	52 (6.4)	10 (10.8)	11 (6.5)	18 (6.2)	7 (4.3)	6 (6.6)	
Former	322 (39.9)	32 (34.4)	67 (39.9)	115 (39.4)	69 (42.1)	39 (42.9)	
Donor, n (%)							0.920
Living donor	682 (84.4)	80 (86.0)	145 (86.3)	244 (83.6)	137 (83.5)	76 (83.5)	
Deceased or DCD	126 (15.6)	13 (14.0)	23 (13.7)	48 (16.4)	27 (16.5)	15 (16.5)	
Donor age (years)	45.2 ± 11.7	43.8 ± 12.5	43.6 ± 11.3	45.6 ± 11.5	45.8 ± 12.0	47.7 ± 11.6	0.052
Donor BMI (kg/m^2)	23.8 ± 2.9	23.8 ± 2.7	23.6 ± 2.8	23.8 ± 3.1	23.7 ± 2.9	23.9 ± 2.8	0.920
Donor hypertension, n (%)	90 (37.3)	4 (21.1)	18 (35.3)	36 (37.5)	20 (41.7)	12 (44.4)	0.520
ABO-incompatibility, n (%)	147 (18.2)	21 (22.6)	29 (17.3)	55 (18.8)	21 (12.8)	21 (23.1)	0.200
Delayed graft function, n (%)	6 (0.7)	0 (0.0)	2 (1.2)	2 (0.7)	2 (1.2)	0 (0.0)	0.670
Laboratory parameters							
eGFR (ml/min/1.73 m^2)	64.7 ± 18.0	65.9 ± 17.9	66.5 ± 18.4	65.1 ± 18.4	62.4 ± 17.3	63.0 ± 16.6	0.220
Donor eGFR (ml/min/1.73 m^2)	99.2 ± 40.9	99.1 ± 27.3	101.9 ± 29.9	99.0 ± 53.4	96.8 ± 36.9	99.5 ± 29.7	0.870
Hemoglobin (g/dL)	13.5 ± 1.9	13.3 ± 1.8	13.5 ± 2.0	13.5 ± 1.9	13.6 ± 1.9	13.9 ± 1.8	0.380
Albumin (g/dL)	4.4 ± 0.3	4.4 ± 0.3	4.3 ± 0.4	4.4 ± 0.3	4.4 ± 0.3	4.4 ± 0.3	0.260
Fasting glucose (mg/dL)	109.9 ± 37.0	109.0 ± 31.3	104.9 ± 30.2	111.4 ± 37.1	109.8 ± 42.6	115.2 ± 42.5	0.270
T-Chol (mg/dL)	178.0 ± 36.6	173.1 ± 41.5	174.0 ± 36.3	178.5 ± 35.4	182.4 ± 36.0	181.0 ± 36.5	0.150
LDL-C (mg/dL)	96.7 ± 30.6	96.2 ± 32.8	91.9 ± 31.0	97.9 ± 30.0	97.8 ± 29.6	100.2 ± 30.6	0.200
HDL-C (mg/dL)	58.4 ± 17.4	57.9 ± 17.3	59.3 ± 18.1	58.1 ± 16.3	59.7 ± 19.0	55.7 ± 16.2	0.450
Triglyceride (mg/dL)	136.7 ± 96.0	115.5 ± 45.0	128.3 ± 85.7	142.3 ± 114.9	143.5 ± 101.6	143.7 ± 69.6	0.088
Drugs							
Tacrolimus, n (%)	755 (93.4)	88 (94.6)	155 (92.3)	275 (94.2)	154 (93.9)	83 (91.2)	0.800
Cyclosporine, n (%)	42 (5.2)	5 (5.4)	11 (6.5)	12 (4.1)	8 (4.9)	6 (6.6)	0.790
Steroid, n (%)	744 (92.1)	86 (92.5)	157 (93.5)	263 (90.1)	148 (90.2)	90 (98.9)	0.071
RAS blockers, n (%)	120 (14.9)	6 (6.5)	17 (10.1)	50 (17.1)	27 (16.5)	20 (22.0)	0.010
Diuretics, n (%)	50 (6.2)	5 (5.4)	10 (6.0)	19 (6.5)	8 (4.9)	8 (8.8)	0.790
Beta-blockers, n (%)	274 (33.9)	22 (23.7)	54 (32.1)	94 (32.2)	58 (35.4)	46 (50.5)	0.003
Calcium channel blockers, n (%)	379 (46.9)	21 (22.6)	76 (45.2)	139 (47.6)	92 (56.1)	51 (56.0)	<0.001
Alpha blockers, n (%)	15 (1.9)	2 (2.2)	2 (1.2)	5 (1.7)	4 (2.4)	2 (2.2)	0.930

Data are expressed as mean ± standard deviation, median [interquartile range], or proportion n (%).

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; DCD, donation after circulatory death; eGFR, estimated glomerular filtration rate; T-Chol, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; RAS blockers, renin-angiotensin system blockers.

Association of SBP Trends With Adverse Kidney Outcomes

We further analyzed the association between SBP trends and adverse kidney outcomes. Incidence rates of composite kidney outcomes in the decreasing, stable, and increasing SBP trajectory groups were 11.2, 15.8, and 32.8 per 1,000 person-years, respectively (**Table 4**). The stable SBP group showed better outcomes than the increasing SBP group by log-rank test ($p = 0.002$, **Figure 2B**). In a fully adjusted Cox model, the HR for the increasing SBP trajectory group was 2.26 (95% CI, 1.34–3.81) compared with the stable SBP trajectory group (**Table 5**). The decreasing SBP trajectory group showed better outcomes than the stable SBP trajectory group (HR, 0.63; 95% CI 0.26–1.51, **Table 5**); however, the difference was not statistically significant.

Association of SBP or SBP Trends With Adverse Kidney Outcomes in the Validation Cohort

Supplementary Table S1 shows the baseline characteristics of 1,294 participants according to baseline SBP categories. The mean age of participants was 47.8 ± 11.4 years, and 44.1% were women. The prevalence of hypertension was 75.2%, and the mean SBP and DBP were 125.4 ± 14.0 and 77.0 ± 11.0 mmHg,

TABLE 2 | The CKD progression[a], graft loss, and composite outcome[b] rates according to baseline SBP.

Outcomes	SBP categories (mmHg)					
	Overall	<110	110–119	120–129	130–139	≥140
No. of participants, n (%)	808	93 (11.5)	168 (20.8)	292 (36.1)	164 (20.3)	91 (11.3)
CKD progression						
No. of person-years	4386.9	497.1	906.0	1591.6	905.0	487.2
Incidence of outcome, n (%)	76 (9.4)	13 (14.0)	9 (5.4)	26 (8.9)	15 (9.1)	13 (14.3)
Incidence rate per 1,000 person-year	17.3	26.2	9.9	16.3	16.6	26.7
Graft loss						
No. of person-years	5744.1	644.7	1188.2	2084.0	1191.1	636.1
Incidence of outcome, n (%)	36 (4.5)	8 (8.6)	6 (3.6)	10 (3.4)	7 (4.3)	5 (5.5)
Incidence rate per 1,000 person-year	6.3	12.4	5.0	4.8	5.9	7.9
Kidney composite outcome						
No. of person-years	4400.3	495.8	910.4	1602.1	904.9	487.1
Incidence of outcome, n (%)	85 (10.5)	15 (16.1)	13 (7.7)	29 (9.9)	15 (9.1)	13 (14.3)
Incidence rate per 1,000 person-year	19.3	30.3	14.3	18.1	16.6	26.7

Abbreviations: CKD, chronic kidney disease; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate.

[a]*CKD progression was defined as a decline of ≥50% in eGFR.*

[b]*Composite outcome was defined as CKD progression or graft loss.*

respectively. The mean baseline eGFR was 64.5 ± 18.3 mL/min/1.73 m^2. The numbers of patients with SBP <110, 110–119, 120–129, 130–139, and ≥140 mmHg were 156 (12.1%), 241 (18.6%), 402 (31.1%), 308 (23.8%), and 17 (14.5%), respectively.

During a median follow-up period of 2.29 years, the overall incidence of the primary composite outcome was 17.2 per 1,000 person-years (**Supplementary Table S2**). The primary composite outcome occurred in 7 (4.5%), 6 (2.5%), 18 (4.5%), 13 (4.2%), and 14 (7.5%) patients in groups 1 (SBP <110 mmHg), 2 (SBP 110–119 mmHg), and 3 (SBP 120–129 mmHg), 4 (SBP 130–139 mmHg), and 5 (SBP ≥140 mmHg), respectively.

Although the risk of composite kidney outcome was high in group 5 (SBP ≥140 mmHg) than in group 2 (SBP 110–119 mmHg) of this validation cohort (HR, 3.85; 95% CI 1.42–10.43) in parallel with the discovery cohort, there was no statistically significant increase in risk in group 1 (SBP <110 mmHg) (**Supplementary Table S3**).

When the association of time-varying SBP levels with the composite kidney outcome was analyzed in the validation cohort, the group with group 5 had a 4.16-fold higher risk of composite kidney outcome than the reference group with group 2 similar to the discovery cohort (**Supplementary Table S3**).

When the cumulative incidence of the primary composite outcomes was compared between the SBP trajectory groups using multivariable Cox regression analysis, the trend was similar in the validation cohort as in the discovery cohort that the increasing SBP trajectory was associated with a higher risk of adverse kidney outcome compared with the stable SBP trajectory (HR, 2.75; 95% CI 1.10–6.84, **Supplementary Table S4**).

DISCUSSION

In this study, we examined the association of baseline and time-varying SBP after kidney transplantation with composite kidney outcomes reflecting allograft function. Furthermore, we identified three patterns of SBP trends using trajectory modeling and evaluated the association between SBP trends and adverse kidney outcomes in KTRs. We found that baseline SBP at 1 year after transplantation higher than 140 mmHg was associated with a higher risk of adverse kidney outcomes of CKD progression or graft failure. Additionally, the risk of adverse kidney outcomes was 3.60-fold higher in patients with time-varying SBP ≥140 mmHg than in those with well-controlled SBP of 110–119 mmHg. In the BP trajectory model, the increasing BP trajectory was associated with a higher risk of composite kidney outcomes than those with a stable BP trajectory. Our findings suggest that chronically elevated BP after transplantation is associated with a declining kidney function in KTRs.

Hypertension is a well-established, major cause of cardiovascular events and a non-immunological factor of graft loss for KTRs [16, 32–35]. However, no prospective RCTs have studied the association of optimal BP targets with clinically significant outcomes, including CVD, graft survival, and mortality. The latest 2021 KDIGO and 2017 ACC/AHA guidelines recommended a target of BP less than 130/80 mmHg in KTRs [26, 36]. Current guidelines are mainly based on retrospective studies and registry data. The *post hoc* analysis of the FAVORIT trial showed that higher SBP is independently associated with an increased risk of CVD and all-cause mortality in KTRs [18]. The Collaborative Transplant Study registry examined the impact of post-transplant BP on long-term kidney graft outcomes in 29,751 deceased donor KTR [32]. This study concluded that increased BP is associated with functional graft loss. A US single-center study studied the relationship between blood pressure adjusted for renal function and allograft survival in 277 deceased donor KTR [21]. They showed that elevated SBP, DBP, and mean arterial BP at 1-year post-transplantation were significantly associated with allograft survival independent of baseline renal allograft function. Several prior studies for deceased donor KTRs, have examined the association of BP and allograft survival [21, 32, 37]. For living donor KTRs, a US single center study with 392 KTRs reported that BP during the first year after transplantation is a significant factor of allograft failure independent of renal function [22].

Our discovery cohort analysis suggested a U-shaped association of SBP at 1 year after KT with an increased risk of adverse kidney graft outcomes in Korean KTRs. The denervation status of kidney allografts and CNI may impair myogenic

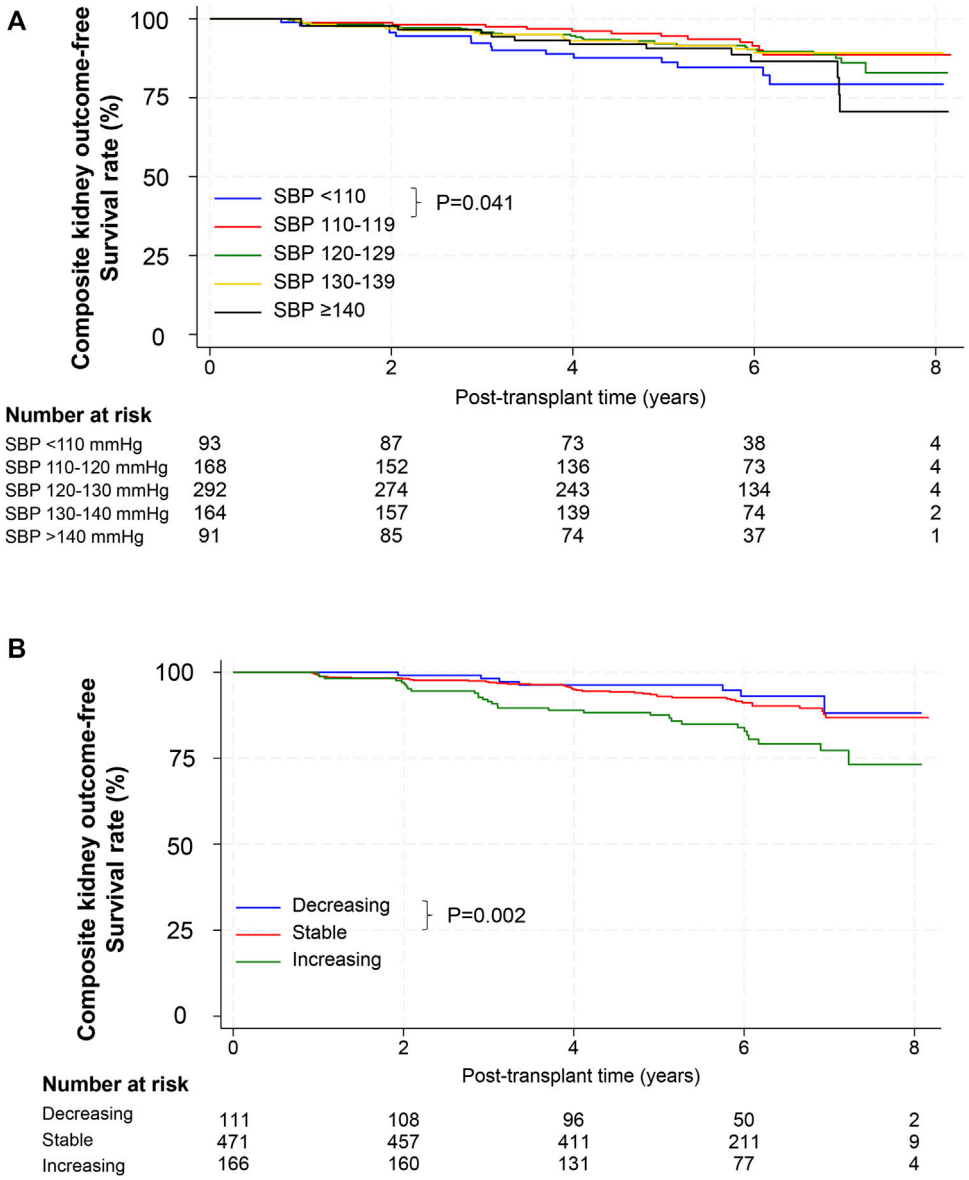

FIGURE 2 | Composite outcomes according to SBP. **(A)** Kaplan–Meier survival curves for composite outcomes after kidney transplantation according to baseline SBP. *p*-value, comparison for the 110–119 mmHg group by the log-rank test. **(B)** Kaplan–Meier survival curves for composite outcomes after kidney transplantation according to SBP trajectory. *p*-value, comparison for the stable group by the log-rank test. Abbreviations: SBP, systolic blood pressure.

autoregulation, leading to a higher risk for acute kidney injury and more rapid loss of kidney function with low BP [38]. In parallel, a retrospective study also suggests controlling SBP within the range of 121–130 mmHg and implies that overly strict control of SBP below 120 mmHg might impair kidney allograft function [39]. However, our validation cohort analysis failed to confirm a significantly higher risk of low SBP, although it confirmed a higher risk of high SBP. Similarly, a conflicting result have been reported in previous studies. A *post hoc* analysis of the FAVORIT trial reported that low SBP <110 mmHg was not associated with a higher risk for eGFR decline or allograft failure in KTRs with no evidence of a "U" shaped relationship [38]. Although high SBP is universally acknowledged as a risk factor [2, 18, 22, 32, 40], the optimal range of SBP to maximize graft and patient survival remains a topic of ongoing research.

In time-varying analysis and trajectory models, we showed that chronically high SBP and persistently increasing SBP have adverse effects on allograft function. Despite ongoing debate regarding the optimal SBP target, our findings underscore the critical importance of not only achieving optimal BP levels but also implementing regular monitoring and management of BP in KTRs. These results emphasize the necessity for healthcare providers to closely track and adjust treatment plans in response to fluctuations in blood pressure.

This study had several strengths, although many findings are consistent with those of prior seminal studies. First, while previous studies mainly studied the association between baseline BP at spot

TABLE 3 | The hazard ratios for the composite outcome of CKD progression or graft failure according to baseline SBP or time-varying SBP.

Baseline SBP	Model 1		Model 2		Model 3	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
<110	2.13 (1.01–4.48)	0.046	2.31 (1.07–4.98)	0.032	2.43 (1.12–5.26)	0.024
110–119	1.00		1.00		1.00	
120–129	1.26 (0.65–2.42)	0.492	1.21 (0.62–2.35)	0.579	1.22 (0.63–2.39)	0.552
130–139	1.18 (0.56–2.47)	0.670	1.26 (0.59–2.70)	0.547	1.26 (0.59–2.70)	0.550
≥140	1.91 (0.88–4.12)	0.099	2.21 (0.99–4.94)	0.053	2.25 (1.00–5.02)	0.049
Time-varying SBP	**Model 1**		**Model 2**		**Model 3**	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
<110	2.14 (0.85–5.40)	0.107	2.99 (1.10–8.09)	0.031	3.02 (1.11–8.22)	0.030
110–119	1.00		1.00		1.00	
120–129	1.95 (0.91–4.16)	0.085	2.30 (0.99–5.37)	0.054	2.29 (0.98–5.35)	0.055
130–139	1.68 (0.75–3.74)	0.204	2.08 (0.85–5.12)	0.109	2.06 (0.84–5.07)	0.116
≥140	3.20 (1.48–6.89	0.003	3.67 (1.52–8.82)	0.004	3.60 (1.48–8.72)	0.005

Model 1: Unadjusted. Model 2: Adjusted for age, sex, BMI, smoking status, DM, CVD, ABO compatibility, HLA compatibility, DGF, acute rejection during the first year, type of kidney donor (living or deceased donor), donor age, donor eGFR, donor BMI, donor hypertension, laboratory parameters (eGFR, hemoglobin, albumin, and LDL-C), and immunosuppressant use (tacrolimus, cyclosporine, and steroid). Model 3: Model 2 + BP-lowering drugs (RAS inhibitors, beta-blockers, calcium channel blockers, alpha-blockers, and diuretics).
Abbreviations: CKD, chronic kidney disease; SBP, systolic blood pressure; HR, hazard ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; CVD, cardiovascular disease; HLA, human leukocyte antigen; DGF, delayed graft function; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; RAS, inhibitors, renin-angiotensin system inhibitors.

TABLE 4 | Outcome event rates according to SBP trajectory pattern.

Outcomes	SBP trajectory pattern			
	Overall	Decreasing	Stable	Increasing
No. of participants n (%)	748 (100.0)	111 (14.8)	471 (63.0)	166 (22.2)
≥50% decline in eGFR[a]				
No. of person-years	4187.2	625.5	2653.2	908.5
Incidence of outcome, n (%)	72 (9.6)	7 (6.3)	37 (7.9)	28 (16.9)
Incidence rate per 1,000 person-year	17.2	11.2	13.9	30.8
Graft loss				
No. of person-years	4688.2	691.9	2972.7	1023.6
Incidence of outcome, n (%)	35 (4.7)	0 (0.0)	20 (4.2)	15 (9.0)
Incidence rate per 1,000 person-year	7.3	0	6.4	14.7
Kidney composite outcome[b]				
No. of person-years	4196.0	625.5	2656.5	914.0
Incidence of outcome, n (%)	79 (10.5)	7 (6.3)	42 (8.9)	30 (18.1)
Incidence rate per 1,000 person-year	18.8	11.2	15.8	32.8

Abbreviations: CKD, chronic kidney disease; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate.
[a]CKD progression was defined as a decline of ≥50% in eGFR.
[b]Composite outcome was defined as CKD progression or graft loss.

TABLE 5 | The hazard ratios for the composite outcome of CKD progression or graft failure according to SBP Trajectory Patterns.

SBP trajectory	Model 1		Model 2		Model 3	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Decreasing	0.72 (0.32–1.60)	0.417	0.62 (0.26–1.49)	0.287	0.63 (0.26–1.51)	0.302
Stable	1.0		1.0		1.00	
Increasing	2.06 (1.29–3.30)	0.002	2.33 (1.38–3.92)	0.002	2.26 (1.34–3.81)	0.002

Model 1: Unadjusted. Model 2: Adjusted for baseline SBP, age, sex, BMI, smoking status, DM, CVD, ABO compatibility, HLA compatibility, DGF, acute rejection during the first year, type of kidney donor (living or deceased donor), donor age, donor eGFR, donor BMI, donor hypertension, laboratory parameters (eGFR, hemoglobin, albumin, and LDL-C), and immunosuppressant use (tacrolimus, cyclosporine, and steroid). Model 3: Model 2 + BP-lowering drugs (RAS blockers, beta-blockers, calcium channel blockers, alpha-blockers, and diuretics).
Abbreviations: CKD, chronic kidney disease; SBP, systolic blood pressure; HR, hazard ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; CVD, cardiovascular disease; HLA, human leukocyte antigen; DGF, delayed graft function; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; RAS inhibitors, renin-angiotensin system inhibitors.

time and graft failure, our study investigated the association between time-varying SBP and graft outcomes. Since a time-varying analysis was performed, it was possible to reflect BP fluctuation over time, and the effect of long-term BP after transplantation on graft outcomes could be evaluated. Moreover, this study examined the temporal association of various BP trends with the risk of graft outcomes by trajectory modeling. Second, this was an intermediate-sized, multicenter transplant study with complete follow-up data collected prospectively over several years. Furthermore, we implemented the same analysis using a validated cohort of large, nationwide population to support our main findings. Third, we included recipients who received kidney grafts from living and deceased donors to reflect real-world situations and adjusted covariates related to KT-specific factors, such as donor characteristics, DGF, and compatibility of donors and recipients to minimize the influence of transplant-related factors that could affect kidney graft function. Fourth, as the first Asian data, this study can contribute to generalization of the previous results derived from the Western countries.

This study had several limitations. First, owing to the observational design of this study, our results cannot prove causality between SBP and adverse kidney outcomes, and all potential confounding factors could not be completely controlled. However, this study consisted of a large and homogeneous population, and multiple potential confounding factors were included in the adjustment model. Second, the SBP used as the baseline was based on a single measurement. To overcome this limitation, we employed time-varying and trajectory statistical method, further supporting our primary study results. Third, there was a discrepancy between the study results using the discovery and validation cohort. In the discovery cohort, although not statistically significant, the risk of adverse kidney outcomes tended to increase in the group with time-varying SBP less than 110 mmHg, whereas it seemed to decrease in the validation cohort. There were several differences between the two cohorts. Comparing the baseline characteristics of participants in the two cohorts, deceased donor KT occupied a larger proportion in the validation cohort than in the discovery cohort. The medication use could not be adjusted in the regression model since there was no information on medications, including immunosuppressants and BP-lowering medications, in the validation cohort. In addition, the validation cohort had a shorter median follow-up period than the discovery cohort. Further, large-scale, randomized, controlled trials with longer follow-up periods are needed to confirm the present results for the optimal BP target and the impact of BP on kidney allograft outcomes in KTRs.

In conclusion, high SBP (≥140 mmHg) at 1 year after KT was associated with an increased risk of CKD progression or graft failure in KTRs. A higher time-varying SBP (≥140 mmHg) and an increasing trend of SBP were also associated with an increased risk of adverse kidney allograft outcomes.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by the Institutional Review Boards of Severance Hospital, Yonsei University (4-2012-0223, 4-2014-0290). 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

Research idea and study design: JY; data acquisition: HJK, KWK, JR, H-YJ, KHJ, M-GK, MJ, SH, JL, KPK, HR, KL, KH, and MKJ; data analysis/interpretation: HJK, KWK, YSJ, BSK, and JY; statistical analysis: HJK, KWK, and YSJ; supervision or mentorship: BSK and JY. 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.2024.12574/full#supplementary-material

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ORIGINAL RESEARCH
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Management of Arteriovenous Fistula After Successful Kidney Transplantation in Long-Term Follow-Up

Jana Janeckova[1,2], Petr Bachleda[1,2], Petr Utikal[1,2] and Jirir Orsag[2,3]*

[1]2nd Department of Surgery, University Hospital Olomouc, Olomouc, Czechia, [2]Faculty of Medicine, Palacký University in Olomouc, Olomouc, Czechia, [3]3rd Department of Internal Medicine, University Hospital Olomouc, Olomouc, Czechia

Arteriovenous fistula (AVF) is the best method of vascular access for hemodialysis. This approach can lead to several complications, such as hyperkinetic heart failure due to a hyperfunctional AVF or dilatation of the feeding artery. These are late complications, especially in patients after a successful kidney transplantation. An observational study was performed focusing on patients more than 12 months after kidney transplantation. The AVF was evaluated by ultrasound and, if the outflow exceeded 1.5 L/min, an echocardiogram was performed. Surgical management was indicated if the cardiac index was higher than 3.9 L/min/m^2 or upon finding a brachial artery aneurysm. A total of 208 post- kidney transplantation patients were examined over a 3-year period, of which 46 subjects (22.11%) had hyperfunctional AVF and 34 cases (16.34%) of feeding artery dilatation were determined. In total, 40 AVF flow reduction and 6 AVF ligation procedures were performed. The median AVF flow before and after the reduction was 2955 mL/min and 1060 mL/min, respectively. Primary patency after flow reduction was 88.3% at 12 months. Late AVF complications in patients following kidney transplantation are quite common. It is necessary to create a screening program to monitor AVFs in these patients.

Keywords: AVF flow reduction, AVF ligation, kideny transplantation, screening, hyperfunctional AVF

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***Correspondence**
Jana Janeckova,
jana.janeckova@fnol.cz

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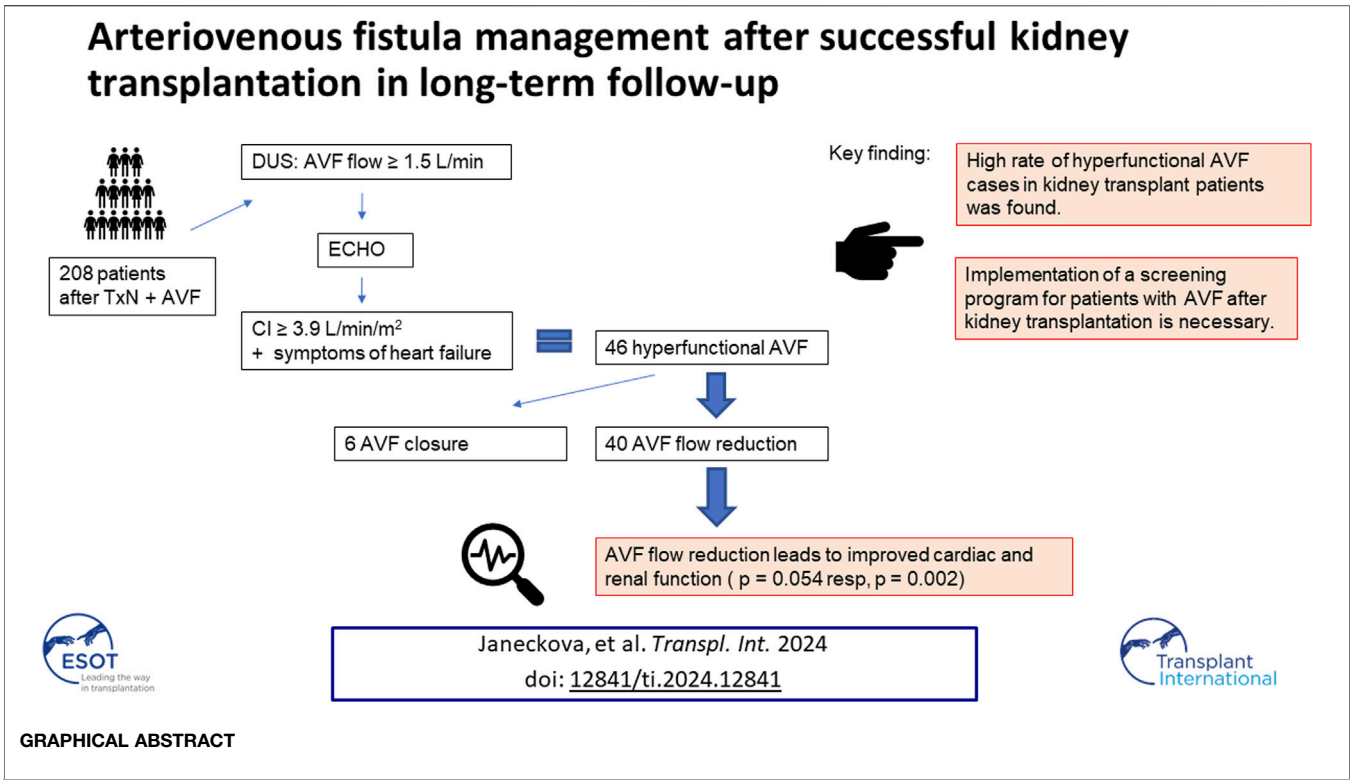
INTRODUCTION

Kidney transplantation is superior to other forms of renal replacement therapy in end-stage kidney disease (ESKD) patients in terms of overall survival and improvement in quality of life [1]. The superior results are achieved by kidney transplantation in the preemptive stage. Despite the slowly increasing number of living donors, most ESKD patients undergo hemodialysis or peritoneal dialysis while waiting for a suitable donor. Arteriovenous fistula (AVF) is the first-line method of connecting a patient to a hemodialysis machine. It is associated with the lowest complication rate when compared to other vascular accesses [2]. Nevertheless, even this vascular access can lead to several complications. Late complications include hyperkinetic cardiac failure due to hyperfunctional AVF or dilatation of the feeding artery, which puts the patient at risk of distal embolism. These late complications also threaten patients after a successful transplantation. Cardiovascular disease is a leading cause of mortality in kidney transplant patients.

After the creation of an AVF, a so-called systemic shunt is formed in the body and the sympathetic nervous system is activated. Several alterations, e.g., cardiac output increase, are immediate, while others develop over time [3]. Left ventricular hypertrophy (LVH), associated with concentric or



GRAPHICAL ABSTRACT

eccentric remodeling, and dilatation of the left atrium with or without systolic dysfunction develops [4]. The prevalence of LVH in kidney transplant patients remains high, despite the clear benefit of transplantation [5]. Both volume and pressure overload are implicated in the development of LVH. Left ventricular volume overload leads to increased cardiac output (CO). Other factors relevant to LV volume overload are anemia, cyclic hyperhydration and AVF flow. Persistent patent AVF contributes to increased LVH [6]. There is also dilatation of both the feeding artery and the draining vein.

The decision for further management of a functional AVF after successful transplantation remains difficult [7, 8]. In addition to cosmetic aspects, the patient is most at risk for a hyperfunctional AVF, steal syndrome, bleeding and infection. The decision on whether to maintain or ligate the AVF is influenced by the patient's age, AVF flow, ejection fraction and cardiac output.

There is no clear-cut definition of high-flow AVF. The Vascular Access Society defines high AVF flow as 1–1.5 L/min or 20% of cardiac output. Other authors use a threshold of 2 L/min as high-flow AVF [9, 10].

Retaining the AVF gives the patient a chance to maintain vascular access for hemodialysis after kidney transplant failure. Published literature clearly shows that 20%–50% of AVFs will disappear within the first year after transplantation [11, 12]. The long-term AVF patency rate is no more than 55% [13]. However, the remaining 45% of patent AVFs may be hyperfunctional and threaten the patient due to their "cardiotoxicity." Deterioration of the transplanted kidney function has been reported after AVF closure [14]. On the other hand, the effect of AVF ligation or flow reduction on LVH has also been reported [9, 15]. Therefore, these procedures are considered justified.

There is no widely accepted screening program for AVF after transplantation. In 2018 we started an observational study with a focus on AVF after kidney transplantation. Due to the high incidence of ultrasound-defined high-flow AVFs, we expanded the study protocol to include an echocardiographic examination when the established threshold AVF flow rate or signs of cardiac insufficiency were exceeded. The observational study became an interventional study focusing on late complications of AVF in patients after kidney transplantation.

MATERIALS AND METHODS

The study included patients who were at least 12 months post kidney transplantation, had an AVF prior to the transplant procedure, and had at least 3 successful cannulations for hemodialysis. The baseline inclusion criteria did not specify whether the AVF was functional.

Patients underwent a doppler ultrasound (DUS) examination at the consultation center for vascular access. The brachial artery diameter and its AVF flow were measured. An echocardiographic examination was added when AVF flow was greater than 1.5 L/min. A CO value of 6 L/min, a cardiac index (CI) of 3.9 L/min/m^2 and symptoms of heart failure were defined as the threshold for the diagnosis of hyperfunctional AVF. Demographic data, renal function, type of immunosuppressive therapy, time since

transplantation, time since AVF creation and AVF type were also recorded. Brachial artery aneurysm was defined as a diameter greater than 1 cm and/or the presence of mural thrombi. A simple dilatation of the feeding artery greater than 1 cm in diameter was evaluated as a supply artery dilatation. The diameter of the brachial artery, type of immunosuppression and eventual detection of feeding artery dilatation and aneurysms were part of a previously published paper [16].

When a high AVF flow rate of more than 1.5 L/min was observed, and suprathreshold CO/CI values and symptoms of heart failure were detected, surgery was indicated, namely AVF flow reduction or AVF ligation. Patient preference, history of previous vascular access for dialysis and its complications, function of the transplanted kidney, and time since transplantation influenced the selected surgical procedure. AVF ligation was indicated in cases with very high CO and problematic local findings, in which case the new AVF reconstruction had to be performed using a long expanded polytetrafluoroethylene (ePTFE) prosthesis. For example, a brachiobasilic AVF without transposition of the outflow vein was performed in the past, resulting in a very short cannulation segment.

Flow Reduction Technique

The patients were operated on by two experienced vascular surgeons. The procedure was performed under a regional anesthetic block with antibiotic coverage. After AVF anastomosis, a draining vein with a minimum length of 5 cm was dissected. In the case of a draining vein aneurysm, the entire aneurysm was dissected to the required length. The original anastomosis was resected after heparin administration (2,500–5000 IU) and staple positioning. The excess draining vein wall with aneurysm was resected using Hegar's dilator and sutured in the sense of aneurysmorraphy. An ePTFE prosthesis with a diameter of 6 mm and a length of approximately 2 cm was then externally attached to the draining vein at the anastomosis (**Figure 1**). Depending on the local conditions, a new anastomosis was sutured to the artery more distally or the original anastomosis was reduced to a length of 4 mm. If the described technique could not be performed due to the wall thickness of the draining vein or other local findings, the draining vein was resected and a short ePTFE prosthesis was interposed.

Beginning in July 2023, we started measuring the supply artery flow intraoperatively using transit time flow measurement (TTFM) probes before and after flow reduction. After completion of the procedure, drainage is performed, the surgical wound is sutured in layers and a padded bandage is applied. The patient is administered 3 doses of broad-spectrum antibiotics, and after extraction of the drain on the 1st postoperative day the patient is discharged on postoperative days 2 or 3. The first DUS control takes place 4 weeks after the procedure, the next one 5 months after the procedure, followed by further DUS evaluations at 6-month intervals. A follow-up echocardiographic examination is performed 6 weeks after the surgery. Renal function after flow reduction was assessed the first next scheduled post-transplant follow-up visit.

Ligation of the AVF

The procedure was performed under local anesthesia with antibiotic coverage. After anastomosis dissection, the draining vein at the anastomosis was transected and the original anastomosis was sutured. A DUS control was performed 6 weeks after the procedure. Further ultrasound examinations were performed at 6-month intervals to evaluate the size of the brachial artery.

Statistics

IBM SPSS Statistics version 22 statistical software was used to analyze the data. A significance level of 0.05 was implemented and a hazard curve was evaluated with a 95% confidence interval. The patency of the reconstructions was evaluated using the Kaplan-Meier curve. Subject data in the monitored groups were anonymized. Spearman's correlation analysis was used to statistically evaluate the change in CI and CO before and after flow reduction. The Wilcoxon paired test was used to compare paired data.

RESULTS

A total of 208 kidney transplant patients were examined by DUS from 2018 to 2023. Of the total patient group, 106 functional AVFs (51%) were detected at the initial examination. 46 hyperfunctional AVF cases (43.4% functional AVFs, 22.11% overall) and 34 feeding artery dilatation cases (32.1% functional AVFs, 16.34% overall) were detected, of which 9 were brachial artery aneurysms.

An AVF flow reduction procedure was performed in 40 patients in the study and 6 patients had their AVF closed. Patients indicated for AVF closure had a mean CO of 7.3 L/min, a CI of 4.3 L/min/m^2 and NYHA III. Five of the six patients who had their AVF closed had a brachiobasilic AVF.

The characteristics of the patients indicated for the flow reduction procedure are provided in **Table 1**.

Aneurysmorrhaphy with external ePTFE prosthesis support was performed in 30 patients (75%). A short ePTFE interposition was inserted after anastomosis resection in 10 patients (25%).

The average AVF flow before flow reduction was 2982 mL/min, with a median of 2918 mL/min, and a range of 1531–5490 mL/min. The average flow 6 weeks after flow reduction was 1126 mL/min, with a median of 1098 mL/min, and a range of 377–1859 mL/min. The primary patency 6 months after the procedure was 95.0% (88.2%–100% with 95%CI), 88.9% at 12 months (78.5%–99.2% with 95%CI), 64.4% at 36 months (42.2%–86.6% with 95% CI); the Kaplan-Meier curve is shown in **Figure 2**.

Relief of dyspnea and improved performance were reported by 36 patients (90%) at the first outpatient check-up 4 weeks after surgery. A reduction in NYHA classification was found and was statistically significant (<0.0001) after flow reduction.

One patient underwent percutaneous balloon angioplasty of the AVF-reduced anastomosis 36 months after the procedure with good results. One patient underwent flow reduction 11 months after a kidney transplant for high-flow AVF with

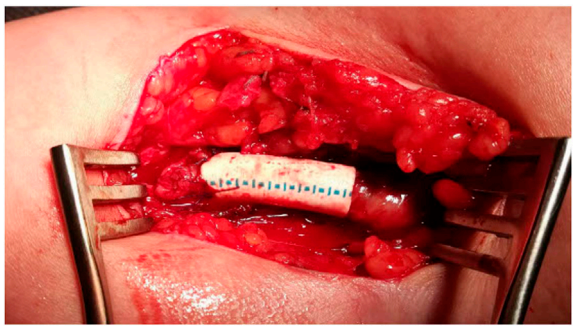


FIGURE 1 | Flow reduction technique: aneurysmorrhaphy with ePTFE prosthesis.

dyspnea, NYHA III and CO more than 10 L/min. In total, 10 patients completed the follow-up visit 48 months after the procedure. AVF obliteration occurred in two patients. A further 5 patients returned to regular hemodialysis treatment via AVF after flow reduction.

Table 2 lists the parameters considered as possible risk factors for primary patency reduction. None of the monitored parameters is a significant predictor of primary patency duration. No significant difference in primary patency duration was found between the individual types of reduction (external support vs. ePTFE interposition). **Table 3** shows the development of cardiac function and renal function before and after flow reduction. An improvement in renal function (serum creatinine and glomerular filtration rate) was observed after flow reduction. A significant decrease in the serum creatinine level and an increase in glomerular filtration rate were demonstrated, $p = 0.0002$ resp. <0.0001.

Perioperative flow directly measured with the TTFM probe was 375 mL/min on average (range of 278–409 mL/min), corresponding to a two-fold increase based on indirect ultrasound flow measurement at the brachial artery at 6 weeks.

Infection of the ePTFE cuff developed in 4 patients; there were no cases of early infection of the ePTFE replacement. Almost identical infections occurred in all patients 12-13 months after the flow reduction procedures. All patients had a history of trauma to the affected limb, followed by a brief vascular graft infection complication.

Statistical analysis revealed a positive correlation between the minimum flow and brachial artery size ($r = 0.509$). Flow reduction was positively correlated with the change in CI (difference before-after), with a correlation coefficient of $r = 0.490$. The p-value was slightly above the significance level ($p = 0.054$).

AVF closure was indicated in 6 patients in the monitored group (2.9%). These patients had a dilated AVF feeding artery and very good function of the transplanted kidney. Brachial artery diameter decreased after AVF closure by a median of 4 mm (range 2–8 mm).

Nine cases of brachial artery aneurysm were managed surgically during the monitored period, with a primary reconstruction patency in 87.5% of cases after 12 months. One patient developed an infection of the ePTFE prosthesis, followed by an infection of the basilic vein acquired from the other limb. After the removal of the vascular grafts, the limb was free of ischemia with a patent deep brachial artery.

Based on the findings of the study, a methodology for monitoring vascular access has been proposed. During hospitalization after a successful transplant, patients are advised about the need for a follow-up visit at the consultation center for vascular access for an ultrasound examination of the AVF 12 months after the index procedure. This examination is recommended even in the event of vascular access closure within the 1 year. The next follow-up ultrasound examination depends on the outcomes of the first brachial artery size and AVF flow evaluation. If AVF flow is greater than 1.5 L/min, an echocardiographic examination is added. AVF retention, reduction or removal is then considered depending on the cardiac index, brachial artery size and AVF flow. The management process is shown in **Figure 3**. In addition to the established protocol, patients with clinical problems in the AVF area, dyspnea or hypertension resistant to conservative therapy with a functional AVF are referred for evaluation to the consultation center for vascular access.

DISCUSSION

Despite the clear benefits of a functional AVF, there are several long-term risks associated with it. This is especially true for patients after a successful kidney transplantation. The decision for further AVF management must be individualized, taking into account the history of vascular access for dialysis, the performance of the transplanted kidney and cardiac symptoms. In the past, the only options were preserving or closing the AVF. With a median graft function of 10.8 years and an average kidney recipient age of 42 years, one-third of transplant patients require dialysis again within 5 years [12]. A retained AVF facilitates this return. Therefore, some authors warn against the ligation of asymptomatic AVFs after transplant [17]. Furthermore, cases of functional deterioration of the transplanted kidney after AVF closure have been published [18], which is why many centers choose to retain AVFs. The cardiotoxicity of a hyperfunctional AVF must be considered in these patients [19]. There is a large study about the hemodialysis access profile in failed kidney transplant patients from the Catalan Renal Registry. It shows, that the main type of vascular access when returning to hemodialysis for failed patients is AVF. In this study, the patients with AVF at the time of kidney transplant showed greater kidney transplant survival compared to those using a catheter. This study is observational, without any information on AVF flow or cardiac function [20]. However, it shows the importance of AVF preservation after a kidney transplant.

Preservation of a functional AVF by aneurysmorrhaphy with external ePTFE support has proven to be an effective and functional option. The borderline statistical significance of the reduction in the decrease in the cardiac index is limited by the small number of patients. We also use this method successfully

TABLE 1 | Characteristics of patients and vascular access.

		Count	Percentage
sex	Female patients	24	52.2
	Male patients	12	47.8
age	60.2 (36–86)		
time since AVF creation/years	6.0 (1–20; median 4.0)		
time since Tx/years	6.5 (0–25; median 6.8)		
vascular access for dialysis	radiocephalic AVF	13	28.2
	brachiocephalic AVF	22	47.8
	brachiobasilic AVF	11	23.9
cause of ESKD	glomerular disease	9	19.6
	polycystic kidney disease	8	17.4
	interstitial disease	16	34.8
	diabetic nephropathy	8	17.4
	others	5	10.9
immunosuppressive therapy	cyclosporin	4	
	corticosteroids	39	
	mycophenolate mofetil	36	
	tacrolimus	28	
	basiliximab	13	
	everolimus	3	
other comorbidities	peripheral vascular disease	4	8.7
	coronary artery disease	6	13
	diabetes mellitus (not as a primary kidney disease)	7	15.2

TX, transplant procedure.

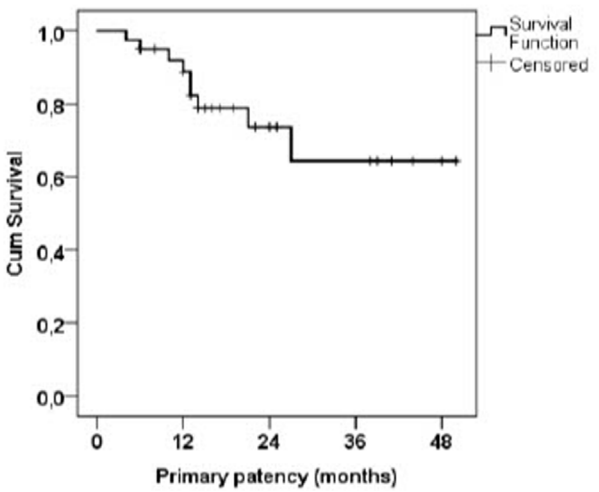


FIGURE 2 | Kaplan-Meier curve of AVF primary patency after flow reduction.

TABLE 2 | Possible risk factors affecting primary patency.

	p-value	RR	95.0% CI for RR	
			Lower	Upper
Age	0.259	0.968	0.914	1.024
time since AVF creation (in years)	0.707	0.969	0.821	1.143
reduction I	0.809	1.219	0.245	6.056
time since Tx/year	0.654	1.020	0.935	1.112
vascular access (1 = reference)	0.639			
vascular access 2 vs. ref.	0.731	0.768	0.171	3.445
vascular access 3 vs. ref.	0.541	1.750	0.290	10.554
Flow before correction	0.970	1.000	0.999	1.001
Sex m	0.503	1.573	0.417	5.929

AVF, arteriovenous fistula.
Vascular access: 1, Radiocephalic AVF; 2, Brachiocephalic AVF; 3, Brachiobasilic AVF; m, male; I, ePTFE, interposition.

TABLE 3 | Results of AVF flow reduction in 40 patients.

	Before surgery	After	p-value
CO (L/min)	6.51 (5.4–10)	5.72 (3.9–6.61)	0.078
CI (m^2/L/min)	4.24 (3.9–5,3)	2.99 (2.4–4.5)	0.054
NYHA gr.III (n)	36	4	<0.0001
serum creatinine (umol/L)	163 (83–201)	149 (76–188)	0.0002
GF mL/s/1,73m^2	0.47 (0.42–1.29)	0.76 (0.44–1.38)	<0.0001

with non-transplanted patients. The procedure is relatively simple, on a small scale, and can be performed in regional anesthesia. The most substantial effect reported by patients is the rapid relief of dyspnea, followed by improved cardiac function. Furthermore, we noted an improvement in renal function, with the previously published decrease in GF not observed. There was also a decrease observed in the diameter of the brachial artery. This decrease is rather individual. However, we consider it essential that there is no further increase in the size of the arteria brachialis and, with an average flow rate of approximately 1060 mL/min, the risk of developing a brachial artery aneurysm is 3.04 times lower than if the surgery had not been performed [16]. The flow reduction technique and the consequences of a hyperfunctional AVF have also been published by other authors. Our technique with external support is similar to the technique described by Baláž, but we

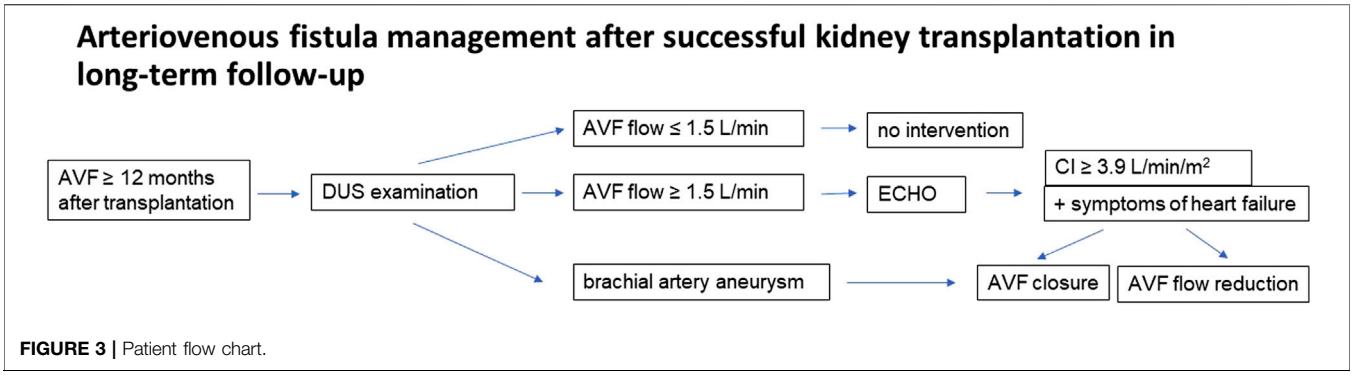


FIGURE 3 | Patient flow chart.

see no reason to consider the use of the prosthesis in the entire extent of the draining vein due to the increase in the size of the surgical wound and the risk of infection [21]. In 2020 the same author described different results of aneurysmorrhaphy in a review. The primary patency of these reconstructions is about 85%, depending on the technique (stapler or no stapler), decreasing to 74% after 12 months [22]. Our results are comparable and, above all, we have a long-term follow-up. The aneurysmorrhaphy technique with external support was used in only 39% of patients with a hyperfunctional AVF. The surgery was intended for aneurysm management and the other patients only had a dilated draining vein [23]. The report did not provide further information about cardiological follow-up, echocardiography control or results after surgery. The same authors recommend AVF ligation in kidney transplant patients with AVF aneurysms and cardiac overload in agreement with the patient and nephrologist [24].

There is no definite AVF flow level that would be completely safe for the patient. A high-flow AVF is defined as an AVF with a flow rate greater than 2 L/min or an AVF flow greater than 30% of cardiac output [25]. Some authors also base the diagnosis of high-flow AVF on signs of heart failure. Other authors define it as a flow rate greater than 1.5–2 L/min regardless of the presence of heart failure [26]. AVF flow may increase over months and years due to feeding artery and anastomosis remodeling. The AVF should always be considered a systematic shunt leading to a decrease in peripheral vascular resistance, a decrease in systemic arterial pressure and an increase in cardiac output. It increases the metabolic demands of the myocardium and leads to the activation of the sympathetic system [9]. Pulmonary hypertension may also develop, leading to a two-fold increase in mortality [27]. Up to 39% of patients with structural heart changes due to a hyperfunctional AVF may be asymptomatic [9]. The clinical effect of AVF depends on the balance between cardiac reserve and AVF function. High-flow AVF can lead to hyperkinetic heart failure and even cardiac arrest. The relationship between AVF flow and cardiac output is nonlinear. Flows above 2 L/min are associated with a significant increase in cardiac output, with all its consequences [3]. In collaboration with our department, Valeriánová described the effect of AVF flow reduction on the myocardium. It is not clear whether cardiac output is related to brachial artery size [10]. However, we confirmed a size reduction of the arteria brachialis after a flow rate decrease or AVF closure. This effect is beneficial in patients with a thin-walled dilated brachial artery, without the risk of distal embolism, but leads to hyperkinetic cardiac overload. Gkotsis published a minimally invasive AVF flow reduction procedure in transplant patients. The technique is similar, but our follow-up is much longer and also monitors the effect of the surgery on the size of the artery [28]. A reduction in flow is clearly associated with an improvement in patient quality of life. Maintaining a functional AVF is of particular benefit in patients with a history of repeated surgeries, where autologous AVF options are limited.

One of the limitations of our study is the long-term risk of immunosuppressive therapy use in the case of ePTFE prosthesis implantation to reduce flow as a possible source of infection. Although the number of infectious complications in our study was low, this risk cannot be neglected. An extracellular matrix instead of ePTFE material may be considered. This material has been used in two kidney transplant patients to reduce AVF flow. The technique of the reduction is unknown; thrombosis occurred in both patients due to stenosis in the venous anastomosis [29]. An extracellular matrix is associated with a relatively high rate of stenosis complications. Therefore, the risk-benefit ratio of not using an artificial material may not be favorable due to the financial burden and the risk of technical failure. Among our 40 patients, only one underwent percutaneous angioplasty due to the stenosis of the anastomosis 36 months after the procedure.

Our data underline the importance of long-term AVF monitoring after kidney transplantation. With a well-adjusted regimen of ultrasound examinations every 12 months, this is not a time-consuming or economically demanding procedure. Close cooperation between the nephrologist and the vascular surgeon is necessary during this monitoring. Similar to the determination of immunosuppressive therapy and the creation of vascular access for hemodialysis, the decision for further AVF management after kidney transplantation must be individualized and based on interdisciplinary collaboration. The possible late complications of AVF, which may be forgotten with prolonged time after kidney transplantation, should always be kept in mind.

Our study had other limitations. The effect of flow reduction on renal allograft survival at our institution could not be considered. The improvement in renal function was not further investigated and may have been influenced by better patient cooperation. The group of patients with high flow

AVF is very variable in age, time from kidney transplant and different types of immunosuppressive therapy.

CONCLUSION

Our observational-interventional study demonstrated a high rate of hyperfunctional AVF cases in kidney transplant patients. High AVF flow was associated with an increased cardiac index and heart failure symptoms. Patients indicated for a flow reduction procedure benefited substantially, as evidenced by echocardiographic and renal outcomes. Long-term follow-up confirmed this procedure as a safe approach with good results. It is necessary to consider late AVF complications and to implement a screening program for patients after kidney transplantation. The screening program by ultrasound should be started 12 months after a successful kidney transplant. Echocardiography is crucial in high flow AVF. The decision for AVF flow reduction or AVF ligation should be individualized. AVF preservation is preferred. AVF ligation should be done in cases of very high cardiac index with NYHA III or more and problematic local findings for cannulation for hemodialysis.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by the Ethics Commitee ot tfe Faculty of Medicine of Palacky University in Olomouc. 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

JJ, PB, PU, and JO contributed to the conception and design of the study. 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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Incidence, Nature and Natural History of Additional Histological Findings in Preimplantation and Implantation Kidney Transplant Biopsies

A. L. Paterson[1], V. Broecker[2], M. Gray[3], A. Chalisey[4], G. J. Pettigrew[5]* and D. M. Summers[3]*

[1]Department of Histopathology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, [2]Department of Clinical Pathology, Sahlgrenska University Hospital, Gothenburg, Sweden, [3]Department of Transplant Surgery, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, [4]Department of Medicine, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, [5]Department of Surgery, University of Cambridge, Cambridge, United Kingdom

The quality assurance provided by preimplantation biopsy quantification of chronic damage may allow greater use of kidneys from expanded criteria donors, and thereby expand the deceased donor pool. Preimplantation biopsy may, however, identify additional acute or chronic pathologies not considered in the scoring of chronic damage, and these may influence the decision to implant or discard the kidney. This single-centre retrospective cohort study of a contemporary UK donor population systematically characterised the nature of additional findings in 1,046 preimplantation and implantation biopsies over an eight-year period. A diverse range of findings were identified in 111/1,046 (11%) organs; most frequently diabetic glomerulopathy, focal segmental glomerulosclerosis, (micro)thrombi, neutrophil casts, and immunoglobulin/complement staining. Seventy (63%) of these were transplanted, with subsequent biopsy in 41 (58%) cases confirming that 80% of the initial acute changes had spontaneously resolved, while there was no progression of diabetic glomerulopathy, and the lesions of focal segmental glomerulosclerosis were not identified. Over 75% of assessable grafts with additional histological findings at the time of transplant showed adequate function at one-year following transplant. In conclusion, most histological abnormalities that may be identified in addition to chronic scarring in preimplantation kidney biopsies would not preclude transplantation nor predict poor graft function.

Keywords: kidney transplantation, preimplantation biopsy, histopathology, donor utilisation, implantation biopsy

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***Correspondence**
A. L. Paterson,
alp37@cam.ac.uk
G. J. Pettigrew,
gjp25@cam.ac.uk

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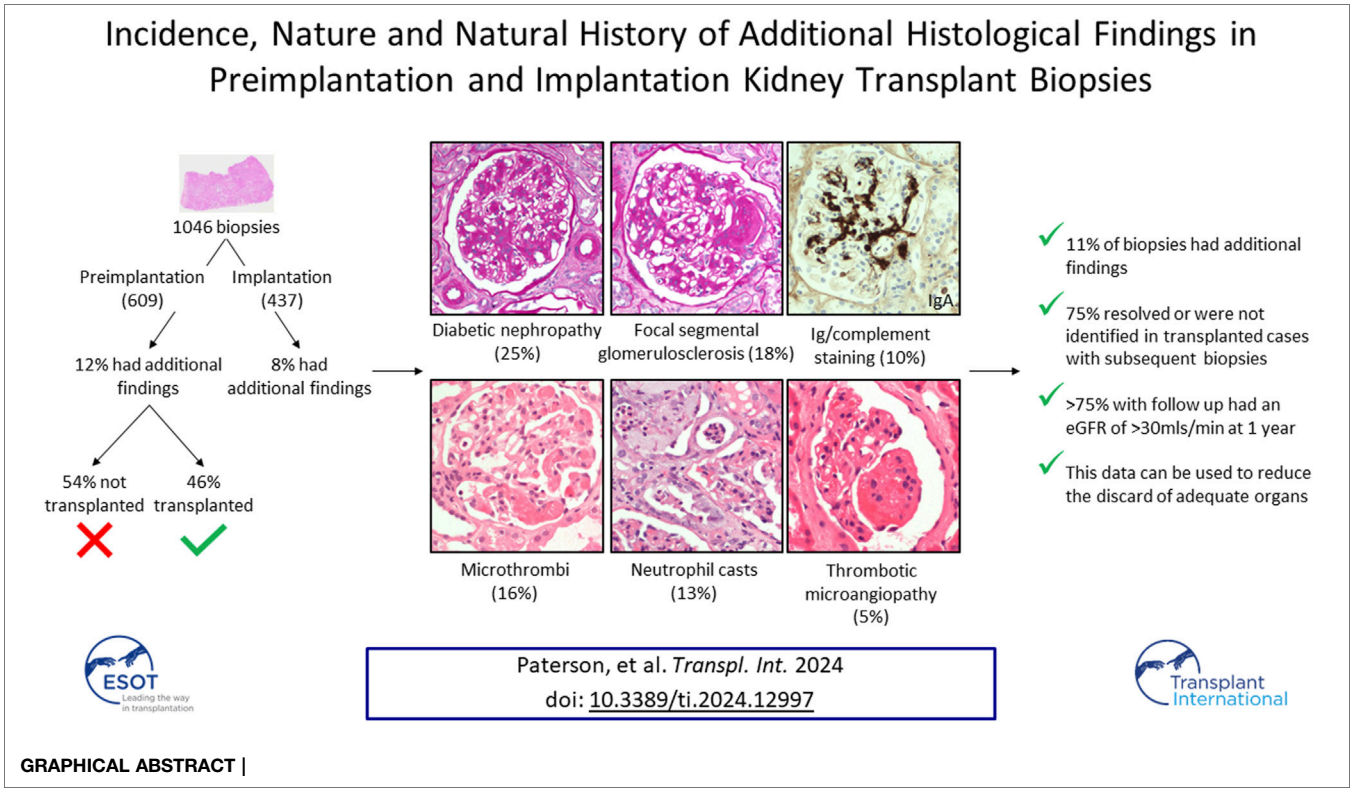
Abbreviations: DCD, donation after circulatory death; NHSBT, National Health Service Blood and Transplant; eGFR, estimated glomerular filtration rate; uACR, urine albumin-creatinine ratio; FSGS, focal segmental glomerulosclerosis; TMA, thrombotic microangiopathy.



GRAPHICAL ABSTRACT |

INTRODUCTION

Kidney transplantation is the most cost-effective treatment for end-stage kidney disease and can improve both survival and quality of life for most patients when compared to dialysis [1]. In 2021-2022 just over 2000 kidney-only deceased donor transplants were undertaken in the United Kingdom (UK) [2]. Despite this, in March 2023 there remained over 5,500 adult patients active on the kidney transplant waiting list demonstrating the significant mismatch between the number of organs being transplanted and those required [2]. Multiple strategies are being explored and adopted to increase both organ donation and utilisation in the UK, including changes to the law regarding consent for deceased donation, increasing donation after circulatory death (DCD), and considering single or dual kidney transplants from donors of older age and/or donors with co-morbidities that previously would have led to them being considered unsuitable [3–7].

There is a substantially increased risk of graft loss following transplantation of kidneys from older donors and/or those with significant comorbidities. Along with consideration of donor and recipient characteristics and macroscopic evaluation of the donor kidney, histological assessment of the donor kidney may be undertaken following retrieval to inform the decision regarding organ quality [8, 9]. Preimplantation biopsy assessment is routinely available to the Transplant team at our centre and uses a scoring system based on the Remuzzi score [9]. The Pre-Implantation Trial of Histopathology In renal transplant Allografts (PITHIA trial) was undertaken at the other twenty-one kidney transplant centres in the UK in 2019–2022, with the aim of determining whether access to preimplantation kidney biopsies at a national level would increase the number and quality of organs being implanted [10]. The results are awaited. In cases where a preimplantation biopsy is not taken, a biopsy taken at the time of kidney reperfusion and assessed in a similar manner can provide a useful baseline assessment of organ quality and has been shown to correlate with allograft survival even after adjusting for donor characteristics [11, 12].

The Remuzzi score assesses four parameters associated with chronic damage: global glomerulosclerosis; tubular atrophy; interstitial fibrosis; and arteriosclerosis. Additional histological abnormalities that are not considered for this score may, however, also be revealed. These may impact on the decision to transplant the organ and on peri-transplant management of the recipient. The available literature describing additional histological findings in either preimplantation kidney biopsies or those taken at organ implantation, almost exclusively focuses on the significance of either glomerular microthrombi or incidental IgA deposits. Glomerular fibrin thrombi have been described in 3%–10% of preimplantation and/or implantation kidney biopsies [13–15], particularly in donors with a history of central nervous system injury secondary to trauma [13, 14, 16, 17]. In most cases the fibrin thrombi were focal, rapidly resolved and were not associated with adverse long-term outcomes [13–16]. IgA deposits have been reported in 9%–29% of peri-transplant kidney biopsies, with a higher prevalence in donors of Hispanic or Asian origin [18–20]. The majority were of a low

intensity and without associated hypercellularity, consistent with latent IgA deposition, and cleared on follow up biopsies [18–20].

Importantly, the nature of additional histological findings will be influenced by the characteristics of the donor pool and therefore differ between countries and over time as organ utilisation practice evolves. The majority of the literature is based on cohorts from the United States, whereas kidney donors in the UK are: significantly older (with 11% being ≥70 years old); more frequently DCD donors; less likely to have died from trauma; and a higher proportion are Caucasian [21].

This study aimed to facilitate future informed decision-making regarding organ use and recipient management by systematically reviewing the frequency and spectrum of additional histological findings in transplant biopsies taken prior to, or at the time of, transplantation from a contemporary UK donor population. The natural history of these changes was explored in biopsies taken after transplantation during standard practice follow up to determine whether the observed abnormalities persisted, progressed or resolved.

PATIENTS AND METHODS

This was a retrospective single-centre cohort study. The local electronic record was searched to identify all kidney transplant biopsies taken either prior to transplantation (preimplantation), or following reperfusion (implantation), from 1st November 2014 until 31st December 2022. Preimplantation biopsies were taken at the discretion of the on-call consultant transplant surgeon and consultant nephrologist based on the donor's history and macroscopic appearances of the organ. Circumstances where a preimplantation biopsy would be considered included advanced donor age, a donor history of long-standing hypertension and/or being on multiple antihypertensive medications for hypertension control, a donor history or finding of cardiovascular disease such as left ventricular hypertrophy which may suggest co-existing renovascular disease, a donor history of diabetes mellitus, an abnormal donor creatinine without a baseline preceding the current illness, atherosclerosis in the arterial patch, and/or macroscopic features suggestive of cortical scarring. Implantation biopsies were taken at the discretion of the consultant surgeon following reperfusion, particularly in older donors. All the biopsies were reported by subspecialist renal pathologists at the study centre. The study was registered and approved as a service evaluation at our institution (clinical project ID5034); ethical approval was not required in accordance with the local legislation and institutional requirements.

Preimplantation biopsies, typically 4 mm punch biopsies, were formalin-fixed, underwent rapid processing, and were then paraffin-embedded. A ten-slide serial was cut with two profiles per slide. Slides 1, 5, and 10 were stained with haematoxylin and eosin. Slides 2, 6, and 9 were stained with periodic acid Schiff (PAS). The biopsies were assessed using the Remuzzi score [9] and other pertinent findings noted. The findings were then discussed between the reporting pathologist and on-call transplant surgeon. Implantation biopsies were formalin-fixed, paraffin-embedded and cut as per preimplantation biopsies, however they had a longer processing time and were reported within normal working hours as the biopsy result would not influence immediate decisions regarding transplantation.

The histopathology reports for all preimplantation and implantation biopsies were reviewed to identify those with findings in addition to those captured as part of the Remuzzi score, other than acute tubular injury. For preimplantation biopsies, the donor organ donation and transplantation number was cross-checked with the NHS Blood and Transplant (NHSBT) register to determine which kidneys were subsequently transplanted. Further biopsies taken following transplant were identified from the local electronic record and the reports reviewed to determine whether the changes identified at preimplantation or implantation had persisted. These were indication biopsies, rather than protocol biopsies, that were taken to investigate delayed graft function or an unexplained rise in serum creatinine. Demographic and clinical follow up data for the transplanted cases was accessed from a combination of the local electronic records and the NHSBT register depending on the location of follow up after transplantation. Twelve month estimated glomerular filtration rate (eGFR) was used as the clinical outcome measure. Urine albumin-creatinine ratio (uACR) was used to assess the degree of proteinuria following transplantation; <30 mg/mmol was considered to be mild, 30–70 mg/mmol moderate; and >70 mg/mmol severe. The final timepoint of data collection was in December 2023, 13 months after the last transplant.

RESULTS

A total of 1,046 biopsies were assessed during the study time-period, comprising 609 preimplantation biopsies from 404 donors, and 437 implantation biopsies. Significant histological findings in addition to global glomerulosclerosis, tubular atrophy, interstitial fibrosis and/or vascular sclerosis were identified in 76 (12%) preimplantation biopsies from 50 donors, and 35 (8%) implantation biopsies from 34 donors [total 111 additional pathologies in 1,046 (11%) biopsies]. Donor demographic data is shown in **Supplementary Table S1**. The nature of the additional abnormalities was diverse (see **Table 1**), but with diabetic glomerulopathy (25%), focal segmental glomerulosclerosis (FSGS; 18%), and deposition of thrombi/microthrombi (16%), reported most frequently (**Table 1**). The diabetic changes varied in severity, with approximately half showing predominantly pre-nodular glomerulopathy, and the remainder, nodular glomerulopathy.

Forty-one (54%) kidneys with significant additional findings in the preimplantation biopsy were not subsequently transplanted (**Tables 1**, **2**), with the most frequent findings being diabetic glomerulopathy (37%), FSGS (32%) and/or neutrophil casts suggestive of ascending infection (17%). Sixteen (39%) of these biopsies had a Remuzzi score of 4 or less, and therefore the kidney could have been considered for

TABLE 1 | Nature of the additional histological findings identified in preimplantation biopsies where the organ was or was not subsequently used; and in implantation biopsies. *Three cases had two co-existing additional findings; ^one case had two co-existing additional findings; +one case had three co-existing additional findings and one case two co-existing additional findings.

Finding	Preimplantation not transplanted (n = 41*)	Preimplantation transplanted (n = 35^)	Implantation (n = 35+)	All biopsies with additional findings (n = 111)
Glomerular Changes				
Diabetic glomerulopathy – all	15/41 (37%)	11/35 (31%)	2/35 (6%)	28/111 (25%)
Prenodular	8/41 (20%)	5/35 (14%)	2/35 (6%)	15/111 (14%)
Nodular	7/41 (17%)	6/35 (17%)	-	13/111 (12%)
Focal segmental glomerulosclerosis	13/41 (32%)	4/35 (11%)	3/35 (9%)	20/111 (18%)
Thrombi/microthrombi – all	---	6/35 (17%)	12/35 (34%)	18/111 (16%)
Focal	---	4/35 (11%)	8/35 (23%)	12/111 (11%)
Diffuse	---	2/35 (6%)	4/35 (11%)	6/111 (5%)
Complement/immunoglobulin staining	---	4/35 (11%)	7/35 (20%)	11/111 (10%)
Glomerulonephritis	2/41 (5%)	---	2/35 (6%)	4/111 (4%)
Hyperfiltration features	2/41 (5%)	2/35 (6%)	---	4/111 (4%)
Vascular Changes				
Thrombotic microangiopathy	2/41 (5%)	2/35 (6%)	1/35 (3%)	5/111 (5%)
Infarction	2/41 (5%)	---	1/35 (3%)	3/111 (3%)
Focal arteriolar necrosis	1/41 (2%)			1/111 (1%)
Cholesterol emboli	---	1/35 (3%)	1/35 (3%)	2/111 (2%)
Arteriolar hyalinosis	---	---	1/35 (3%)	1/111 (1%)
Tubulointerstitial Changes				
Neutrophil casts	7/41 (17%)	2/35 (6%)	5/35 (14%)	14/111 (13%)
Obstructive features	---	2/35 (6%)	---	2/111 (2%)
Myoglobin casts	---	2/35 (6%)	---	2/111 (2%)
Interstitial foam cells	---	---	1/35 (3%)	1/111 (1%)
Interstitial calcium deposits	---	---	1/35 (3%)	1/111 (1%)
Tubulointerstitial inflammation	---	---	1/35 (3%)	1/111 (1%)

TABLE 2 | Additional findings in preimplantation biopsies which were not subsequently used shown by Remuzzi score group. ^one case had both neutrophil casts and FSGS, *two cases had both nodular diabetes and FSGS.

	Remuzzi score 0–4 (n = 16^)	Remuzzi score 5-6 (n = 15)	Remuzzi score 7–12 (n = 7*)	Insufficient for Remuzzi scoring (n = 3)
Glomerular Changes				
Diabetic glomerulopathy - all	8/16 (50%)	3/15 (20%)	4/7 (57%)	---
Prenodular	4/16 (25%)	2/15 (13%)	2/7 (29%)	---
Nodular	4/16 (25%)	1/15 (7%)	2/7 (29%)	---
Focal segmental glomerulosclerosis	2/16 (13%)	8/15 (53%)	3/7 (43%)	---
Glomerulonephritis	2/16 (13%)	---	---	---
Hyperfiltration features	---	2/15 (13%)	---	---
Vascular Changes				
Thrombotic microangiopathy	---	---	1/7 (14%)	1/3 (33%)
Infarction	2/16 (13%)			
Focal arteriolar necrosis	---	1/15 (7%)	---	---
Tubulointerstitial Changes				
Neutrophil casts	3/16 (19%)	1/15 (7%)	1/7 (14%)	2/3 (67%)

single transplantation, with the additional findings likely a factor in the organ discard. Similarly, a further fifteen (37%) had a Remuzzi score of 5 or 6, and could have been considered for dual transplant if both kidneys had been locally available [10], with the additional histopathological findings potentially contributing to the decision not to implant. Seven (17%) had a Remuzzi score of 7 or more and would therefore not have been considered suitable for transplantation regardless of the additional histological findings. In the remaining three cases the biopsy sample was insufficient for Remuzzi scoring.

Additional preimplantation or implantation histological findings were identified in 70 kidneys which were transplanted into 67 recipients during the study time-period. Recipient demographic data is shown in **Supplementary Table S2**. The most prevalent abnormalities were: the presence of (micro) thrombi (26%); diabetic glomerulosclerosis (19%); complement

TABLE 3 | Proportion of transplanted kidneys with additional histological abnormalities in preimplantation or implantation biopsies which had further biopsies following transplant. The number where the peri-transplant change had resolved or was not identified in the latest biopsy following transplant is shown.

Finding	Proportion with follow up biopsies	Preimplantation/implantation change resolved or not identified
Glomerular Changes		
Diabetic glomerulopathy – all	6/13 (46%)	3/6 (50%)
Prenodular	4/7 (57%)	3/4 (75%)
Nodular	2/6 (33%)	0/2 (0%)
Focal segmental glomerulosclerosis	5/7 (71%)	5/5 (100%)
Thrombi/microthrombi – all	12/18 (67%)	9/12 (75%)
Focal	9/12 (75%)	8/9 (89%)
Diffuse	3/6 (50%)	1/3 (33%)
Complement/immunoglobulin staining	5/11 (45%)	4/5 (80%)
Glomerulonephritis	2/2 (100%)	1/2 (50%)
Hyperfiltration features	2/2 (100%)	1/2 (50%)
Vascular Changes		
Thrombotic microangiopathy	2/3 (67%)	2/2 (100%)
Infarction	0/1 (0%)	---
Cholesterol emboli	1/2 (50%)	1/1 (100%)
Arteriolar hyalinosis	0/1 (0%)	---
Tubulointerstitial Changes		
Neutrophil casts	3/7 (43%)	3/3 (100%)
Obstructive features	1/2 (50%)	0/1 (0%)
Myoglobin casts	1/2 (50%)	1/1 (100%)
Interstitial foam cells	0/1 (0%)	---
Interstitial calcium deposits	0/1 (0%)	---
Tubulointerstitial inflammation	0/1 (0%)	---

and/or immunoglobulin deposition (16%); FSGS (10%); and neutrophils casts 10%. Data regarding follow up biopsies were available for 59/67 (88%) of these recipients. The remaining organs were transplanted at other UK centres. The number of biopsies following transplant ranged from 1–5 biopsies per recipient (median 2 biopsies), with 37/59 (63%) having at least one subsequent biopsy during follow up. Of these, 24% were taken in the first 10 days after transplant, 69% within the first 6 months and 81% within the first year. The findings from this cohort are summarised in **Table 3**.

In those with a follow up biopsy, in 8 of 9 (89%) with focal microvascular thrombi, this had resolved. In the remaining case where a small arterial thrombus was present in the implantation biopsy, a subsequent biopsy on day 29 revealed an organised infarct. Despite this, the kidney transplant continues to provide good function at 5 years following transplant, with a stable eGFR of 45 mL/min. Two patients with more widespread microvascular thrombi at implantation, who had received a kidney from the same DCD donor, had a diffuse severe ischaemic injury comprising areas of infarction on subsequent biopsies taken on days 7, 8, and 36. Both had a subsequent transplant 6 months later due to on-going poor graft function. In the remaining patient with widespread microvascular thrombi at baseline and a follow up biopsy, the changes had resolved by day 7.

In 4 of 5 (80%) patients with complement/immunoglobulin deposition present on preimplantation or implantation biopsy, these deposits had resolved on follow-up biopsy. In one patient IgA deposition was still identified on biopsy at day 124 after transplant. Eight patients with complement/immunoglobulin deposition on the preimplantation or implantation biopsy had follow-up at our centre, none had a uACR more than 10 mg/mmol on samples taken within the first 3 months following transplantation, median uACR 5 mg/mmol (range 1–10 mg/mmol).

In three patients with neutrophil casts identified on preimplantation/implantation biopsy, these were no longer evident on subsequent biopsy taken on days 5, 6, and 140 after transplant. One patient without a follow up biopsy had a positive urine culture for *Proteus* species within the first 30 days following transplant; they had received a dual transplant and preimplantation biopsies from both kidneys had shown the presence of focal neutrophil casts. This patient was successfully treated with antibiotics and had an eGFR of 35 mL/min 1 year following transplant. Small numbers of preimplantation or implantation biopsies revealed features of urinary obstruction, glomerulonephritis without positive staining for complement/immunoglobulin, or glomerular hypertrophy, with persisting changes observed in one case each on repeat biopsy on day 7, day 82, and day 1919 following transplant, respectively (**Table 3**).

Seven preimplantation/implantation biopsies revealed FSGS; the number of lesions were small with only one (4/7, 57%) or two lesions (3/7, 43%) of segmental sclerosis per case, with a median of 23 glomeruli, range 8–59, on the assessed level per case. Further lesions of FSGS were not present in the 10 biopsies performed on 5 of these kidneys after transplantation, consistent with the FSGS lesions only involving a small proportion of glomeruli. This is supported by all five cases with follow up at our centre having a uACR less than 30 mg/mmol following transplantation consistent with at most mild proteinuria.

Follow up biopsies were available in 6 of 13 patients who had diabetic glomerulopathy identified in the preimplantation/

TABLE 4 | Proportion of recipients receiving grafts with additional histological findings at baseline who had a 3-month and/or 12-month estimated glomerular filtration rate (eGFR) greater that 30 mL/min. [+]Three patients received a dual transplant and are shown once. The data is shown per additional finding at the time of transplant, one graft had two co-existing abnormalities and one graft had three co-existing abnormalities. *one and ^two had unknown function at 12 months; [#]one patient died 7 months following transplant from an unrelated cause–all these patients have been removed from the respective columns including one with dual pathology.

	Proportion of recipients with eGFR at 3 months >30 mL/min	Proportion of recipients with eGFR at 12 months >30 mL/min
Glomerular Changes		
Diabetic glomerulopathy – all	10/11 (91%)^	9/12 (75%)*
Prenodular	6/6 (100%)*	6/7 (86%)
Nodular	4/5 (80%)*	3/5 (60%)*
Focal segmental glomerulosclerosis	3/6 (50%)*	3/5 (60%)^
Thrombi/microthrombi - all	15/18 (83%)	16/18 (89%)
Focal	11/12 (92%)	12/12 (100%)
Diffuse	4/6 (66%)	4/6 (67%)
Complement/Immunoglobulin staining[+]	8/9 (89%)*	7/9 (78%)*
Glomerulonephritis	1/2 (50%)	2/2 (100%)
Hyperfiltration features	0/2 (0%)	0/2 (0%)
Vascular Changes		
Thrombotic microangiopathy	1/3 (33%)	0/3 (0%)
Infarction	1/1 (100%)	1/1 (100%)
Cholesterol emboli	2/2 (100%)	1/2 (50%)
Arteriolar hyalinosis	1/1 (100%)	1/1 (100%)
Tubulointerstitial Changes		
Neutrophil casts[+]	5/6 (83%)	5/5 (100%)[#]
Obstructive features[+]	1/1 (100%)	1/1 (100%)
Myoglobin casts	2/2 (100%)	2/2 (100%)
Interstitial foam cells	1/1 (100%)	1/1 (100%)
Interstitial calcium deposits	1/1 (100%)	1/1 (100%)
Tubulointerstitial inflammation	1/1 (100%)	1/1 (100%)

implantation biopsy (**Table 3**). In three patients, the diabetic glomerular changes were not reported on their latest biopsies (performed on days 6, 218 and 1,428 after transplantation), suggesting that diabetic features had either resolved or were not prominent. In the remaining three, the diabetic changes were still present in the most recent follow up biopsy (on days 328, 427, and 447) and although numbers are small, the features that persisted were typically the more advanced nodular forms of glomerulopathy (**Table 3**). Arteriolar hyalinosis, another feature of diabetes-related kidney disease was noted in one patient at day 6 following transplant.

One year graft eGFR was available for 63/67 (94%) patients who had received a graft with additional histological findings on preimplantation/implantation biopsy. One patient died with a functioning graft 7 months after transplant following cardiac surgery, whilst data was not available for three patients who had received their transplant at other UK centres. These four cases have been removed from subsequent analyses. At 1 year, 48/63 (76%) of patients had an eGFR >30 mL/min consistent with adequate graft function, **Table 4**. All assessable patients with neutrophil casts, focal microthrombi or hypercellular glomeruli at the time of transplantation had adequate graft function at 1 year. Four (66%) of those with diffuse glomerular microthrombi had adequate function at 1 year; the remaining two patients as detailed above received a kidney from the same DCD donor with subsequent poor function, despite preimplantation Remuzzi scores of 0 and 1 (**Supplementary Table S3**).

The majority [9/12 (75%)] of kidneys transplanted with features of diabetic glomerulopathy at baseline biopsy achieved an eGFR >30 mL/min at 1 year, with a higher proportion of those with early, prenodular features doing so than those with more established nodular features, albeit numbers are small in each group (**Table 4**). The Remuzzi score did not add value when predicting which organs with nodular diabetic glomerulosclerosis would have adequate subsequent function (**Supplementary Table S3**). None of the six patient with prenodular diabetic glomerulopathy that were transplanted at our centre had more than mild proteinuria on a uACR taken within the first 3 months, median 10 mg/mmol (range 5–29 mg/mmol). Four of the six patients with nodular diabetic glomerulopathy had uACR measurements available following transplantation. In two patients these showed moderate proteinuria at 3 months, further measurements were available for one of these patients which showed a reduction in proteinuria to 14 mg/mmol at 10 months following transplant. Two patients had severe proteinuria 3 months following transplantation, 71 mg/mmol and 118 mg/mmol, which had increased to 120 mg/mmol and 584 mg/mmol respectively 12 months following transplantation although in the latter case the increase is likely partly attributable to the development of chronic active antibody mediated rejection which also resulted in a fall in eGFR from 62 mL/min at 3 months to 22 mL/min at 12 months.

With regards to FSGS on baseline biopsy, 3/5 (60%) kidney grafts had an eGFR >30 mL/min at 1 year. The two organs with poor function both had a Remuzzi score of 4, which was higher than the grafts which had an adequate subsequent function (**Supplementary Table S1**), suggesting that the combination of a higher Remuzzi score and FSGS may be a marker of potential

poor function however the study is not powered for further statistical analysis.

None of the three kidneys with features of thrombotic microangiopathy (TMA) at the time of transplant had adequate function at 1 year; although in two cases the TMA had resolved on biopsies taken on day 9 and 16 following transplant. In the first case, features of TMA were identified in the preimplantation biopsy in one glomerulus and postulated to be related to peri-transplant ischaemia. Subsequent biopsies for delayed graft function showed severe acute tubular injury with parenchymal necrosis. The persistent poor function was considered most likely to reflect donor vascular disease and interstitial fibrosis. The implantation biopsy for the second patient that showed TMA also received a Remuzzi score of 5, indicating moderately severe chronic injury, which may explain the persistent suboptimal function. The third kidney achieved excellent early graft function however was removed at 2 months due to haemorrhage from nephrostomy placement, which had been indicated because of the development of ureteric stenosis.

Both kidneys with glomerular hypertrophy at baseline had poor function from the time of transplant and an eGFR <30 mL/min at 1 year following transplant, although with 12-month uACRs of 6 mg/mmol and 7 mg/mmol consistent with minimal proteinuria. They were from the same donor who had a history of severe left ventricular dysfunction, congestive cardiac failure and hypertension however had an eGFR >60 mL/min 8 days prior to organ donation and 37 mL/min at the time of donation. Preimplantation biopsies showed diffuse glomerular enlargement with mild vascular disease although without global glomerulosclerosis and with only focal tubular atrophy and interstitial fibrosis affecting less than 5% of the cortical area, both Remuzzi score 3, which would predict adequate function following transplantation. The poor graft function therefore could not have been anticipated and is likely specific to the circumstances of this donor.

DISCUSSION

This retrospective study of a large UK donor population has demonstrated that, in addition to the features considered for Remuzzi evaluation, preimplantation biopsy reveals histological abnormalities in up to 12% of biopsies. A broad range of abnormalities were identified; some anticipated, such as diabetic glomerulosclerosis; and others unanticipated, such as glomerular microthrombi or intratubular neutrophil casts. Forty-one organs with additional histological findings on preimplantation biopsies were not transplanted, of which 16 (39%) and 15 (37%) would have otherwise been considered for single or dual organ transplantation respectively based on the Remuzzi score. This suggests that the additional findings may have contributed to discard/decline of up to an extra 5% of kidneys that were biopsied. On follow up of transplanted organs with these findings, the majority of acute changes resolved after transplantation, and even chronic features were not always identified in subsequent biopsies, presumably because they were focal and non-progressive within the timeframe of the study. Furthermore, in the majority the 12-month eGFR achieved was >30 mL/min. This suggests that these histological features may have led to the unnecessary discard of some otherwise transplantable organs.

The most commonly observed additional feature identified on preimplantation/implantation biopsy was diabetic glomerulosclerosis, present in 2.7% of biopsies. The prevalence of diabetes mellitus in deceased donors in the UK is approximately 7%, increasing to 9% in those ≥60 years old [6, 21]. There is, however, limited literature on the prevalence, natural history and function of grafts with diabetic glomerulosclerosis at baseline. Truong et al [22] reported that baseline biopsy revealed diabetic glomerulopathy in only 19% of donors with a history of diabetes, and that all were at an early stage, with only a minority progressing following transplantation; with similar findings in a subsequent study of thirty-four recipients [23]. Similarly, in the time course of our study, no increase in disease stage was identified. This also provides reassurance that the preimplantation/implantation biopsy did not underestimate the stage of disease. All but one graft with prenodular diabetic glomerulosclerosis at the time of transplant achieved adequate function 12 months later, although this was only true for 60% of donors with nodular diabetic glomerulosclerosis. This data would suggest that adequate function, at least in the short term, would be anticipated when utilising organs with prenodular diabetic glomerulosclerosis and these are therefore suitable for use; however caution is required if nodular diabetic glomerulosclerosis is identified.

Focal and diffuse microvascular thrombi were identified in 1.1% and 0.5% of all biopsies respectively. Microthrombi were more prevalent in implantation than preimplantation biopsies, as observed previously, which may partly reflect reperfusion injury [13, 15]. In keeping with previous studies [13, 14, 16], most follow up biopsies revealed no sequelae, apart from two patients whose clinical course likely reflects peri-transplant events, including a prolonged warm ischaemia time, specific to their shared donor. This highlights the importance of integrating biopsy results with the broader clinical context. The study data, when combined with that in the literature, supports the use of kidneys for transplantation where the preimplantation biopsy has shown focal microvascular thrombi; however if diffuse thrombi are present a more detailed consideration in combination with other case-specific factors such as warm and cold ischaemic time and Remuzzi score would be appropriate as occasional cases have poor outcomes post transplantation.

Intratubular neutrophil casts were identified in 1.3% of biopsies. Their presence, particularly when accompanied by neutrophilic tubulitis and surrounding inflammation, or in biopsies from older and/or diabetic patients, may suggest an ascending urinary tract infection [24, 25]. However the feature is not specific, occurring in other causes of acute tubular injury and interstitial inflammation [26], and it is not possible to judge the overall extent of inflammation. Hence when neutrophil casts are isolated and focal, their significance is uncertain. All transplanted organs with this finding had adequate function at 12 months, apart from one recipient who died from an unrelated cause with a functioning graft. One recipient had a potentially donor-derived

urinary tract infection which was successfully treated. These observations suggest that focal neutrophil casts on a preimplantation biopsy should not automatically result in organ discard. However if used, transport medium cultures, urine cultures and/or prophylactic antibiotics should be considered.

Immunoglobulin and/or complement deposition, most frequently IgA, was identified in 1.1% of biopsies, with minimal hypercellularity and resolution in most cases with a follow-up biopsy. Latent IgA deposits have long been recognised at the time of transplantation, particularly in Asian and Hispanic donors, with the majority resolving rapidly and spontaneously without negatively impacting on long term function [18, 19]. Knowledge of these deposits is most relevant when interpreting biopsies following transplantation but would not influence immediate decisions regarding transplantation, because immunohistochemistry analysis is not possible while maintaining acceptably short cold ischaemic times. Given the good outcomes of these transplanted organs both in this study and the literature, minor features on a preimplantation biopsy such as slight mesangial expansion and/or hypercellularity which may suggest IgA nephropathy in the donor, should not preclude organ use. There is insufficient data to draw conclusions regarding the use of organs with endocapillary hypercellularity.

The remaining additional findings were diverse and, apart from FSGS, were each restricted to an occasional donor. The clinical relevance of some, such as features of obstruction, glomerulomegaly or interstitial foam cells is unclear, particularly if isolated findings. Similarly with other features, such as cholesterol thromboemboli, it is difficult to know from the single biopsy if these are focal or represent a more widespread embolic shower that may lead to subsequent scarring. Where follow up biopsies were available, few changes persisted or progressed. Therefore a discussion between the Histopathologist and Transplant team regarding the nature and extent of additional findings, their likely significance, and any potential sequelae in addition to the Remuzzi score is suggested.

Despite our study covering over 8 years and a thousand biopsies, due to the diversity of the histological findings, each subcohort contains a small number of transplanted organs which limits conclusions regarding graft outcome. However over 75% of transplanted organs had a 12-month eGFR of >30 mL/min consistent with adequate graft function [27]. Exploration of the natural history of the histological changes is further impacted by only a subset having further biopsies and the majority occurring within the first year following transplant. This is most relevant for grafts with chronic changes since progression or even regression of structural changes is likely to occur over long timeframes. Our study cohort included both preimplantation and implantation biopsies in order to maximise the size of these subgroups and data available following transplant. Whilst the incidence of the different additional histological findings does vary between the two groups, in part due to their different demographics, the natural history of the additional pathological findings following transplantation would be expected to be similar.

In summary, a diverse range of histological findings may be encountered in preimplantation/implantation biopsies from a UK donor population. Most acute changes are anticipated to spontaneously resolve without sequelae, whilst most chronic changes appear to be focal, at an early stage and/or non-progressive. This study suggests that many of these organs are suitable for transplantation and would be anticipated to have adequate function at 1 year. In the context of an organ shortage this would further expand the donor pool.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because it comprises medical information related to study patients. Requests to access the datasets should be directed to alp37@cam.ac.uk.

ETHICS STATEMENT

The study was registered and approved as a service evaluation at our institution (clinical project 117 ID5034); ethical approval was not required in accordance with the local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

AP: study concept and design, data collection and interpretation, writing of the manuscript; VB: study concept and review of the manuscript; MG: data collection and review of the manuscript; AC: study design and review of the manuscript; GP: data interpretation and writing of the manuscript; DS: study design, data collection and interpretation, writing of 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.2024.12997/full#supplementary-material

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Accessibility of Percutaneous Biopsy in Retrocolic-Placed Pancreatic Grafts With a Duodeno-Duodenostomy

*Clara Bassaganyas[1,2], Anna Darnell[1], Alexandre Soler-Perromat[1], Gerard Rafart[1], Pedro Ventura-Aguiar[3], Miriam Cuatrecasas[4], Joana Ferrer-Fàbrega[5], Carmen Ayuso[1,2,6] and Ángeles García-Criado[1,2]**

[1]Radiology Department, Centre Diagnòstic per la Imatge (CDI), Hospital Clinic de Barcelona, Barcelona, Spain, [2]Universitat de Barcelona, Barcelona, Spain, [3]Nephrology and Kidney Transplant Department, Institut Clínic de Nefrologia i Urologia (ICNU), Hospital Clinic de Barcelona, Barcelona, Spain, [4]Pathology Department, Centre de Diagnòstic Biomèdic (CDB), Hospital Clinic de Barcelona, Barcelona, Spain, [5]Hepatobiliopancreatic Surgery and Liver & Pancreas Transplant Department, Institut Clínic de Malalties Digestives i Metabòliques (ICMDM), Hospital Clinic de Barcelona, Barcelona, Spain, [6]Agust Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain

Duodeno-duodenostomy (DD) has been proposed as a more physiological alternative to conventional duodeno-jejunostomy (DJ) for pancreas transplantation. Accessibility of percutaneous biopsies in these grafts has not yet been assessed. We conducted a retrospective study including all pancreatic percutaneous graft biopsies requested between November 2009 and July 2021. Whenever possible, biopsies were performed under ultrasound (US) guidance or computed tomography (CT) guidance when the US approach failed. Patients were classified into two groups according to surgical technique (DJ and DD). Accessibility, success for histological diagnosis and complications were compared. Biopsy was performed in 93/136 (68.4%) patients in the DJ group and 116/132 (87.9%) of the DD group (p = 0.0001). The graft was not accessible for biopsy mainly due to intestinal loop interposition (n = 29 DJ, n = 10 DD). Adequate sample for histological diagnosis was obtained in 86/93 (92.5%) of the DJ group and 102/116 (87.9%) of the DD group (p = 0.2777). One minor complication was noted in the DD group. The retrocolic position of the DD pancreatic graft does not limit access to percutaneous biopsy. This is a safe technique with a high histological diagnostic success rate.

Keywords: pancreas transplantation, biopsy, ultrasound-guided biopsy, percutaneous, duodeno-duodenostomy

***Correspondence**
Ángeles García-Criado,
magarcia@clinic.cat

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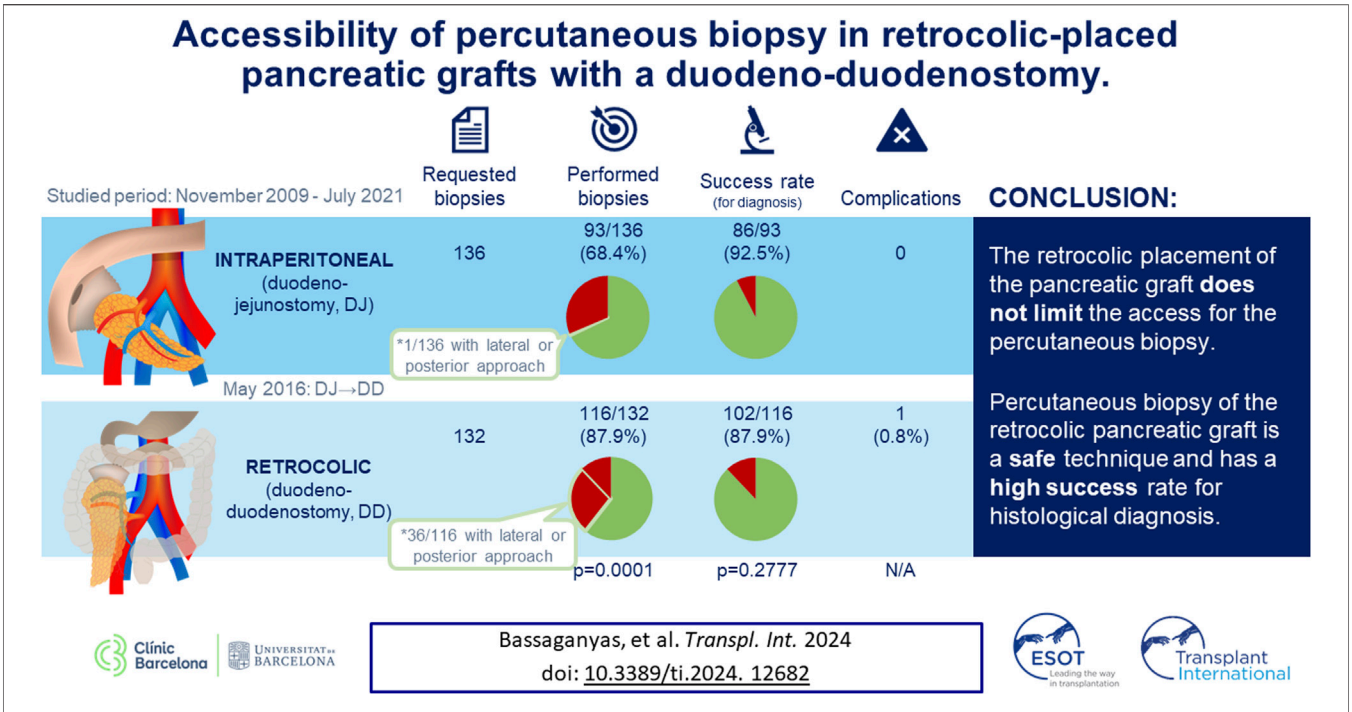
INTRODUCTION

During the last decades, several surgical and therapeutic advances in pancreas transplantation have improved both patient and graft survival [1, 2]. However, graft rejection is one of the main causes of graft failure (25% of the grafts) [3] and remains a diagnostic challenge. Clinical manifestations and laboratory markers are non-specific [4, 5]. Although imaging studies are key to rule out many other

Abbreviations: CT, computed tomography; DD, duodeno-duodenostomy; DJ, duodeno-jejunostomy; US, ultrasound.



GRAPHICAL ABSTRACT

causes of graft dysfunction (graft pancreatitis, vascular events, relapse of type 2 diabetes mellitus . . .) [6–8], they do not provide specific findings for diagnosing graft rejection. Pancreatic graft biopsy is therefore the gold standard for diagnosing graft rejection. Histological evaluation provides additional information, distinguishing cellular from antibody-mediated rejection, grading its severity and excluding other causes of dysfunction.

There are different techniques for obtaining pancreatic graft samples. Laparoscopic access offers a good success rate for histological diagnosis (around 95%) [9] but it is more expensive, less available, and has been reported to have a 2.5% conversion to laparotomy [9, 10]. The endoscopic approach is less invasive but it is a complex technique only performed in some centers [11–13], with low accessibility rates [13] and a low success rate for histopathological diagnosis (50%) [11, 12]. Besides, it mainly uses sampling of the graft duodenal mucosa (instead of sampling the pancreatic graft), whose utility in diagnosing graft rejection is still under debate [14–16]. Percutaneous access is the most widely used technique because it has been demonstrated to be safe and effective for the classical intraperitoneal positioning of the graft, whether guided by ultrasound (US) [17, 18] or computed tomography (CT) [19]. In addition, it is a simple and cheap technique that does not require sedation or an operating room, thereby contributing to decreased costs and occurrence of comorbidities.

Classically, pancreatic exocrine secretions were derived to the jejunum through a duodeno-jejunostomy (DJ), placing the graft in an intraperitoneal position (**Figure 1A**). Recently, an alternative technique has emerged, in which the graft is placed retrocolically through a duodeno-duodenostomy (DD, **Figure 1B**), to mimic the physiology of the exocrine secretion in the native pancreas. In addition, it can improve the feasibility to reach the anastomotic sites [20, 21] and access to endoscopic procedures [22]. Despite the potential physiological and surgical benefits of this technique, some authors have pointed out that the retrocolic position of the pancreatic graft could limit the accessibility of percutaneous biopsy [20, 21]. Although accessibility for percutaneous graft biopsy after this surgical technique is an interesting topic, the recommendations of the first World Consensus Conference on pancreas transplantation published in 2021 [23], point out that percutaneous biopsy accessibility to retroperitoneally placed grafts still remains to be proven.

DJ intraperitoneal graft has been demonstrated to be accessible to percutaneous biopsy. To date, there are no reports on the accessibility to percutaneous biopsy on DD retrocolic grafts.

The aim of this study was to evaluate graft accessibility, the success rate for histological diagnosis and the safety of percutaneous biopsy of pancreatic grafts placed using the DD technique for enteric drainage. Furthermore, we compared these results with those obtained previously in intraperitoneal DJ grafts.

MATERIALS AND METHODS

Study Population

The study was approved by the Institutional Ethics Committee for Clinical Research of our hospital (Reg. HCB/2020/0369).

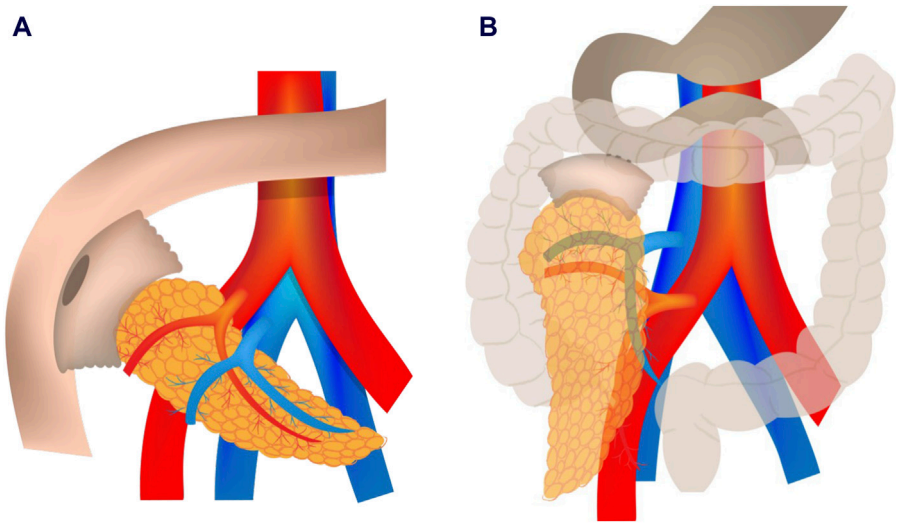


FIGURE 1 | Enteric anastomosis in pancreas transplantation: classic duodeno-jejunostomy **(A)** with intraperitoneal placement and novel duodeno-duodenostomy **(B)** with retrocolic placement.

Informed consent was waived due to the retrospective nature of the study.

We conducted a retrospective study including all pancreatic grafts referred for percutaneous biopsy in our center, from the beginning of the implementation of this technique in November 2009 until July 2021. Biopsies were requested for 1) graft dysfunction (increase in serum amylase and/or lipase tripling normal value, hyperglycemia, or presence of *de novo* donor-specific antibodies) and 2) follow up of a previously treated rejection episode (4 weeks after the treatment). Furthermore, since November 2016, surveillance biopsies were requested in all patients at 3 weeks and 12 months after transplantation.

The intraperitoneal DJ with head-up graft was the stablished surgical technique employed in all pancreatic transplantations until May 2016. From this date, it was replaced by the DD, performed side-to-side by means of a hand-sewn, double layered anastomosis, returning the colon to its original position, thus completely covering the pancreas. In both cases, the venous anastomosis was performed end-to-side between donor portal vein and recipient vena cava or right iliac vein. The arterial anastomosis was constructed end-to-side between the graft superior mesenteric artery or the common iliac graft artery (depending on the backtable reconstruction as described before) [24].

Biopsy Technique

Informed consent was obtained from all patients. All patients were required to undergo coagulation blood tests with a prothrombin time value >50% and a platelet count >50.000/mm.

All biopsies were performed by three senior radiologists with more than 10 years of experience in US- and CT-guided percutaneous biopsies. An Acuson S3000 Helx (Siemens®) was used with convex multifrequency (1–4.5 MHz) or linear multifrequency (4–9 MHz) transducers, depending on the depth of the graft.

Before the biopsy, a complete US B-mode study of the graft and Doppler assessment of vascular patency were conducted. Contrast-enhanced US was performed to confirm vascular permeability in cases with weak Doppler signals. After excluding vascular complications or other findings justifying graft dysfunction, the biopsy was performed.

Free-hand US guidance was the technique of choice. The percutaneous approach point was chosen based on the site with the greatest pancreatic parenchyma thickness without interposed intestinal loops, always avoiding large pancreatic vessels and the pancreatic duct if visible. The anterior approach was preferred when the patient was in a supine position, if possible. When the interposition of intestinal loops prevented the anterior approach, compression with the transducer was intended to gain access; when this maneuver did not work, a lateral approach with the patient in a decubitus lateral position or a posterior approach with the patient in the prone position was intended. If suboptimal visibility persisted after these maneuvers, a CT was performed to determine the best entry point for a posterior US-guided biopsy. If this approach was not possible, an entirely CT-guided biopsy was attempted.

The biopsy was performed after the instillation of local anesthesia (2% mepivacaine), using an automatic 18-gauge needle with a 13 mm sample length. A second sample was obtained if the first attempt yielded a sample <10 mm, with no more than three attempts.

After the procedure, firm pressure was applied at the approach point for 10 min. Patients remained admitted to the hospital 24 h after biopsy to monitor their vital signs, hematocrit, amylase and lipase levels every 4–6 h. In the absence of complications, patients were discharged within 24 h after biopsy.

TABLE 1 | Main characteristics of the two groups of patients.

	Total	DJ	DD	*p*-value
Requested biopsies (n, %)	268	136 (50.7%)	132 (49.3%)	N/A
Sex (% male)	58.6%	63.24%	53.8%	0.1165
Recipient age (median [IQR], years)	43 [37–51]	44 [38–52]	41 [36–50]	0.0046
Donor's age (median [IQR], years)	37 [22–44]	33 [21–42]	37 [24–45]	0.0505
Post-transplant time (median [IQR], years)	10 [1–22]	20 [4–81]	3 [1–12]	<0.0001
Transplant type				
Simultaneous pancreas-kidney	210	99	111	N/A
Pancreas after kidney	53	35	18	
Pancreas transplant alone	1	1	0	
Pancreas retransplant	4	1	3	
Biopsy indication:				
Graft dysfunction	145 (54.1%)	119 (87.5%)	26 (19.7%)	<0.0001
Follow up (after rejection)	47 (17.5%)	15 (11%)	32 (24.2%)	
Surveillance (3 weeks and 12 months)	76 (28.4%)	2 (1.5%)	74 (56.1%)	

DJ, duodeno-jejunostomy; DD, duodeno-duondenostomy; N/A, not applicable.

Fresh graft biopsy samples were immediately sent to the pathology department for tissue processing. After formalin fixation, tissue processing and paraffin embedding of the graft biopsy, hematoxylin and eosin stains were performed for pathological analysis, and histochemical staining with Masson's trichrome was performed for the fibrous component. Immunohistochemical staining with the antibodies CD3, CD68, insulin, glucagon, C4d, Cytomegalovirus and *in situ* hybridization for Epstein Barr virus were also performed.

All biopsy samples were examined by a single senior pathologist (MC). They were considered adequate for evaluation when sufficient to establish a diagnosis according to the Banff criteria (2011 revision) [25].

Data Collection and Analysis

Requested biopsies were classified into two groups according to the type of surgical technique (retrocolic-DD vs. intraperitoneal-DJ). Demographic patient data, donor's age, post-transplantation days (graft's age), surgical technique and indication for biopsy were recorded in both groups. Data related to the biopsy procedure were also recorded for both groups: accessibility to the graft (yes/no), cause of non-accessibility, number of obtained samples, patient position when performing the biopsy, imaging guiding technique, sample adequacy for histopathological evaluation (success rate) and post-procedural complications.

The accessibility rate was calculated in both groups according to the number of performed biopsies among the total number of requested biopsies. To avoid the influence of the operator learning curve, a second analysis of the accessibility rate was performed excluding biopsies performed during the first year after the introduction of the biopsy technique (November 2009–December 2010).

As is well known, some grafts experience atrophy of the gland over time [7, 26, 27]. Thus, an analysis of the accessibility rate related to graft age was performed. To do this, all procedures were classified into five groups according to the time after transplantation: 0–3 months, 3–12 months, 1–5 years, 5–10 years and >10 years, performing a descriptive analysis of accessibility rates in each group. To avoid the influence of graft age on accessibility rate, a second subanalysis was performed that included only pancreatic grafts younger than 5 years.

Statistical Analysis

Quantitative variables are expressed as median and interquartile range**.** Categorical variables are presented as absolute frequencies and percentages. A chi-squared test was used to compare categorical variables and the T Student test was used to compare quantitative variables. The significance level was set at 5% (two-sided).

RESULTS

We received a total of 268 biopsy requests in 145 patients (83 in the DJ group, 60 in the DD group and two patients with a first DJ graft and a retransplantation with a DD graft). Patient characteristics are summarized in **Table 1** and data related to the biopsies are summarized in **Table 2**.

Accessibility of the Pancreatic Graft

As shown in **Figure 2** and **Table 2**, the graft was accessible to biopsy in 209 out of the 268 requested biopsies (78%): 93/136 (68.4%) in DJ and 116/132 (87.9%) in DD ($p = 0.0001$). When analyzing accessibility over time (**Figure 3**), a lower accessibility rate was detected in the first year after implementing the biopsy procedure (43.8%). The posterior subanalysis excluding the first year (to avoid the effect of the learning curve), showed accessibility of 86/120 (71.6%) in the DJ group and 116/132 (87.9%) in the DD group, maintaining the statistical differences ($p = 0.0022$).

As shown in **Table 3** and **Figure 4**, the highest accessibility rate was obtained when biopsy was performed during the first year after transplantation (82.4%). Subsequently, accessibility progressively decreased to 72.7% in 5–10-year-old grafts, with a significant posterior drop in grafts older than 10 years (46.7%). The additional subanalysis of accessibility including only grafts younger than 5 years (to avoid graft age bias), also showed statistical differences between the groups (70/99 in DJ and 116/132 in DD).

US was used to guide almost all biopsies (201/209, 96.1%), six of them with the additional support of CT. The eight remaining

TABLE 2 | Details of the biopsy procedures.

	Total	DJ	DD	*p*-value
Requested biopsies, n	268	136	132	N/A
Performed biopsies (accessibility), n (%)	209 (78%)	93 (68.4%)	116 (87.9%)	0.0001
Guidance technique in performed biopsies (n)				
US	195 (93.3%)	91 (97.8%)	104 (89.7%)	N/A
CT	8 (3.8%)	1 (1.1%)	7 (6%)	
US+CT	6 (2.9%)	1 (1.1%)	5 (4.3%)	
Patient position, n (%):				
Supine position	172 (82.3%)	92 (98.9%)	80 (69%)	N/A
Lateral position	13 (6.2%)	0	13 (11.2%)	
Prone position	24 (11.5%)	1 (1.1%)	23 (19.8%)	
Graft not accessible, n (%)	59 (22%)	43 (31.6%)	16 (12.1%)	0.0001
Intestinal loops interposition	39	29	10	
Graft atrophy	11	9	2	
Graft hypervascularization	5	3	2	
Liquid interposition	4	2	2	
Needle passes (n)				
1	166	54	112	
2	40	36	4	
3	3	3	0	
Mean	1.22	1.45	1.03	<0.0001
Success rate for histological diagnosis, n (%)[a]	188 (89.9%)	86 (92.5%)	102 (87.9%)	0.2777
Complication rate, n (%)[a]	1 (0.5%)	0 (0%)	1 (0.8%)	N/A

DJ, duodeno-jejunostomy; DD, duodeno-duodenostomy; US, ultrasonography; CT, computed tomography; N/A, not applicable.
[a]*Success rate and complication rate are calculated over the number of performed biopsies (not the requested biopsies).*

biopsies were performed only under CT guidance due to a lack of US visibility.

The interposition of intestinal loops prevented biopsy in 76 cases (30/136 in DJ and 46/132 in DD) when the graft was assessed in the supine position. However, in 1/30 patients in the DJ group and 36/46 patients in the DD group, the graft could be accessed via a lateral or posterior approach biopsy with the patient in a lateral or prone position (**Table 2**). Finally, the rate of non-accessible grafts due to intestinal loop interposition was 29/136 (21.3%) in the DJ group and 10/132 (7.6%) in the DD group (p = 0.0001). Graft atrophy, graft hypervascularization and liquid interposition were less frequent causes of failed biopsy attempt (**Table 2**).

The average number of needle passes required to obtain a good sample was low (1.22), which was significantly higher in the DJ group than in the DD group as shown in **Table 2**.

Success Rate for Histopathological Diagnosis

When calculated over the number of performed biopsies, in 87.9% of the DD cases, the obtained pancreatic sample was adequate to establish a histopathological diagnosis (63.2% of the requested biopsies), without statistically significant differences with the 92.5% of success rate in the DJ group (77.3% of the requested biopsies).

Complication Rate

Only one minor complication was recorded in the DD group: an immediately mild self-limited intraabdominal hemorrhage detected by US, which did not require surgical intervention or blood transfusion (1 needle pass biopsy).

DISCUSSION

This study demonstrates that retrocolic pancreatic grafts placed using the DD technique are accessible to percutaneous biopsy with an accessibility rate higher than 85%. The success rate for histological diagnosis was 87.9%, which is similar to that reported for percutaneous biopsies in grafts placed with the classical surgical techniques [17, 18, 27–29]. Therefore, accessibility for a subsequent biopsy should not be a limitation to implementing the novel DD technique.

Until 2016, the intestinal drainage in our center was performed with DJ, performed side-to-side to the jejunum, 70–80 cm from the ligament of Treitz, with good results: the incidence of intestinal complications of this DJ technique from 2000 to 2016 (337 pancreas transplants) published for our group was 6.8% [30]. From this date, the DD technique was adopted successfully and with a good level of acceptance by all members of the pancreatic transplant group, with a low rate of complications (initial data published in 2017), with no intestinal complications recorded in the first 10 pancreatic DD grafts [20]. The rationale of using retrocolic graft placement over the intraperitoneal position is the easy access and dissection of the vascular anastomosis site, and easy reconstruction of venous and arterial anastomosis. To be more specific describing the surgical postoperative complications, we published in 2022, the first retrospective single-center study

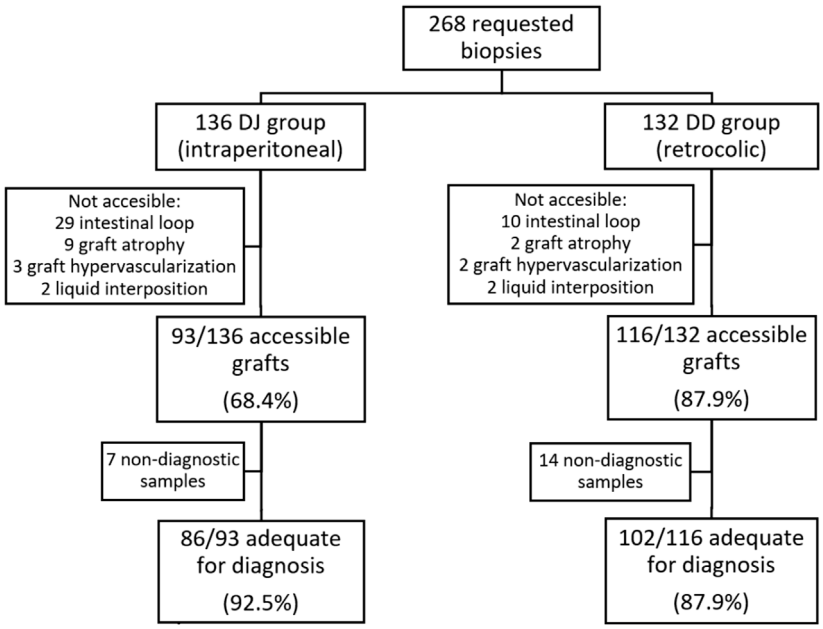


FIGURE 2 | Flow-chart showing requested biopsies according to DJ and DD groups, accessibility rate and success rate for histopathological diagnosis in both groups. DJ, duodeno-jejunostomy; DD, duodeno-duodenostomy.

comparing the effects of the four most commonly used preservation solutions in PTx, i.e., UW, CS, HTK, and IGL-1, on early pancreatic graft function as well as long-term patient and graft survival. A total of 43 out of 380 cases were performed using the duodenoduodenostomy, but this fact does not affect immediate reperfusion injury rates, as vascular anastomoses were performed with the same technique throughout the time period in question. When analyzing the surgical complications according Clavien-Dindo grade no statistical differences were found between the DJ and DD groups [31]. Recently, a descriptive review of 407 pancreas transplants performed at our center (1999–2019) by analyzing the type of arterial reconstruction technique and long-term survival were published. The DD was used in 57 patients with three of them presenting with acute arterial thrombosis [24]. Due to these good results, the DD technique is the one used in our center. Initially, it was feared that this technique would limit the percutaneous biopsy accessibility, but the results of the present study demonstrate that grafts placed with the DD technique are accessible for percutaneous biopsy. In fact, in our study, accessibility was even better in the retrocolic-DD group than in the intraperitoneal-DJ group. One of the factors favoring this higher accessibility is the more cranial and posterior position of the DD graft (**Figure 1B**). This position offers the possibility of performing a lateral or a posterior approach, avoiding the interposition of intestinal loops, which is the main cause of not accessing the graft, both in our study and in previously reported studies, including other surgical techniques [17, 27, 28]. The lower position of DJ grafts limits the posterior and lateral approaches because the iliac bone surrounds the posterior aspect of the graft (**Figure 1A**). Up to 36/132 patients (27.3%) in the DD group benefited from the lateral or posterior approach (in prone or lateral patient position), thereby increasing graft accessibility from 60.6% to 87.9% in this group.

US has proven to be an excellent technique to guide percutaneous biopsy for DJ grafts [17, 18, 27, 28, 32], and it has some advantages over CT [19], as it is a faster procedure without radiation exposure. Our results demonstrated that US is also an excellent tool for guiding biopsies of retrocolic-DD graft. In our series, 89.7% of the performed biopsies in the DD group were guided by US (**Table 2**). This differs from the native pancreas, which is also retroperitoneal but is located in the midline position and is not accessible using the posterior approach.

In addition, percutaneous biopsy is a safe technique. Only one minor complication was recorded in the DD group, with a total complication rate of 0.5%, lower than that reported in the literature (2%–3.6%) [17, 18, 27, 28, 32]. One factor that could contribute is the low number of passes performed related to other studies [19, 27, 32]. Aideyan et al. [19], point out that CT-guided biopsy is associated with a higher risk of severe hemorrhage. This could be explained by the static imaging provided by CT, which could lead to the possibility of traversing both sides of the graft with the needle [19]. US-guided biopsy allows continuous control over the needle trajectory, which might favor a lower complication rate. The experience level of the operator could also play a role in reducing complication rates, as all our biopsies were performed by senior radiologists with vast experience in percutaneous biopsies. Another contributing factor could be the needle gauge. In our study, an 18G automatic needle was used in all patients, but no clear relationship between needle gauge and bleeding in pancreatic biopsies has been demonstrated. Lee et al. [32] compared the performances between 18G and 20G needles,

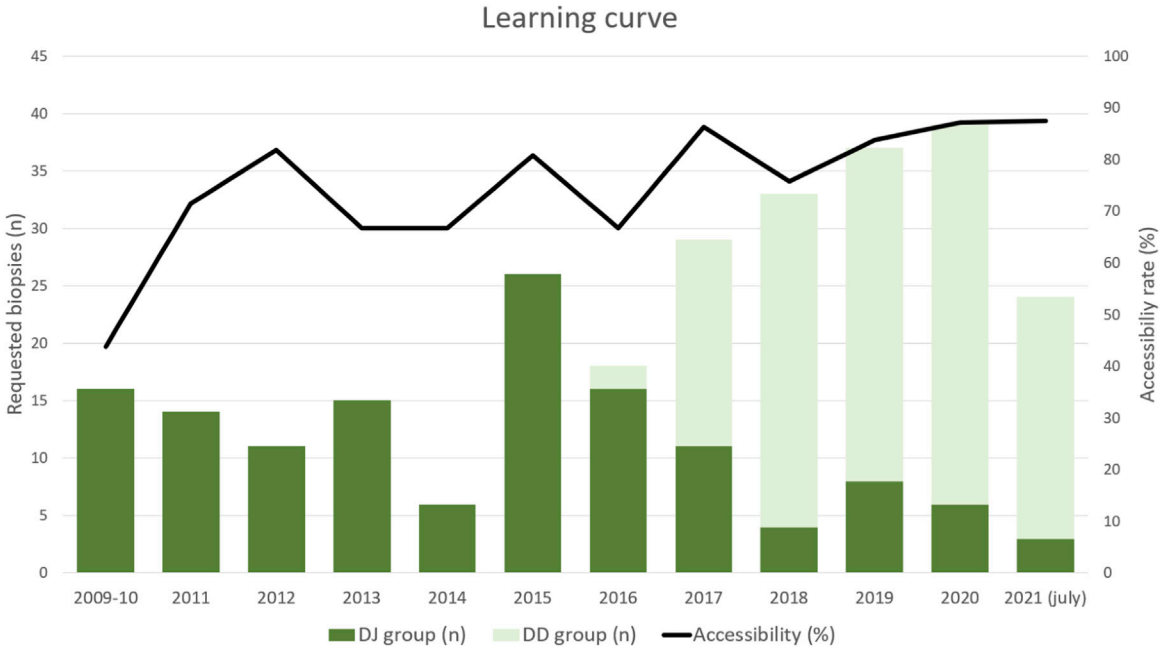


FIGURE 3 | Learning curve: histogram showing the annual number of requested biopsies along the study and the total annual accessibility rate over time. DJ, duodeno-jejunostomy; DD, duodeno-duodenostomy.

TABLE 3 | Accessibility rate related to graft age and causes of not performing the biopsy in each group.

	0–3 months	3–12 months	1–5 years	5–10 years	>10 years
Requested biopsies, n (DJ:DD)	94 (26:68)	71 (29:42)	66 (44:22)	22 (22:0)	15 (15:0)
Accessibility rate (%)	83%	81.7%	75.8%	72.7%	46.7%
Graft not accessible, n (DJ:DD):					
Intestinal loops interposition	11 (5:6)	8 (5:3)	12 (11:1)	1 (1:0)	7 (7:0)
Graft atrophy	0	1 (0:1)	4 (3:1)	5 (5:0)	1 (1:0)
Graft hypervascularization	3 (1:2)	2 (2:0)	0	0	0
Liquid interposition	2 (1:1)	2 (1:1)	0	0	0

DJ, duodeno-jejunostomy; DD, duodeno-duodenostomy.

reporting only a minor complication (bleeding) in the 20G group. The safety of this technique, as shown in our study, could favor the recommendation of a standardized surveillance biopsy program to detect subclinical rejection for an early treatment.

This study has some limitations. First, the DD technique was implemented in May 2016, thus all biopsies performed in the first part of the inclusion period (November 2009–May 2016) belonged to the DJ group. This means that the learning curve limitations affect only DJ patients. However, their impact on the results was reduced by excluding the biopsies performed during the first year (n = 16), which still showed significant differences in accessibility rates between groups.

Second, some grafts experience atrophy of the gland over time [7, 26, 27], potentially due to multiple episodes of undiagnosed acute rejection that may lead to chronic rejection [8, 33–36], limiting access to percutaneous biopsy. This fact is also supported by our study in which atrophy was a relevant cause for not accessing grafts older than 5 years (**Table 3**). Due to the implementation of the DD technique in May 2016, the DD group included patients with grafts younger than 5 years (the study ended in July 2021). Although this fact could have contributed to a decrease in the accessibility of the DJ grafts, statistically significant differences remained between groups when analyzing the accessibility rates only for young grafts (<5 years).

Third, the retrospective and monocentric nature of the study, may also be considered a limitation. But, in the scenario of pancreas transplantation with a wide variety of surgical techniques used throughout the world and the fact that it is a minority type of solid organ transplantation, it makes it difficult to carry out a multicenter study. This fact becomes more important if we take into account that the application of pancreatic biopsy in the different centers is in its infancy, both due to the worry of complications and the obvious learning curve that is needed in the context of a minority transplant. To our knowledge, this is the largest series analyzed using two different positions of the pancreatic graft, including a significant number of biopsies

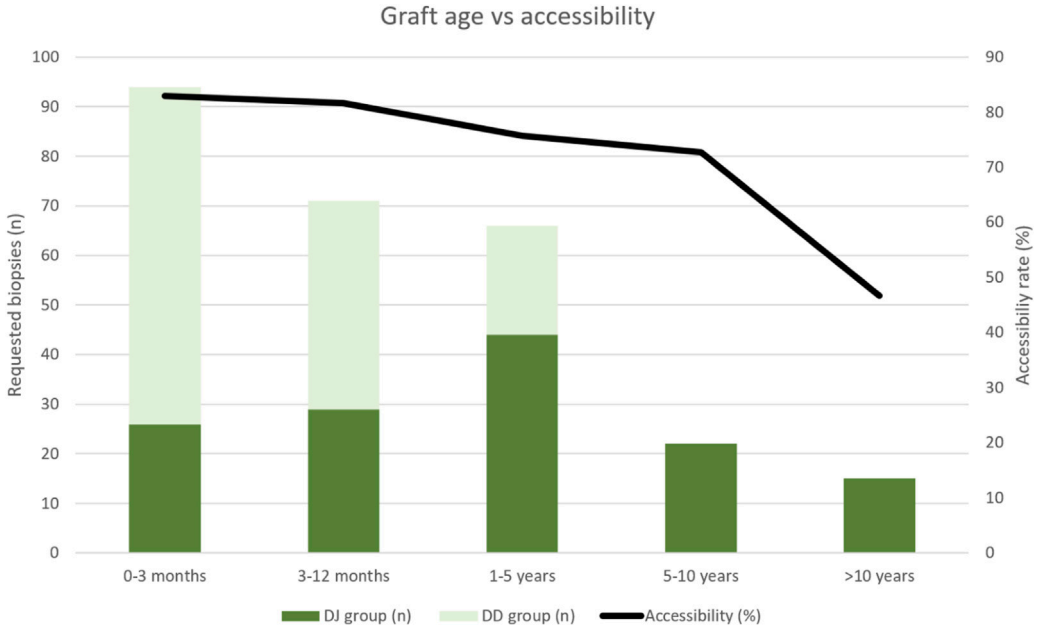


FIGURE 4 | Histogram showing percutaneous biopsy accessibility rate related with the age of the graft in both groups of patients. Graft age accounts for the period of time after transplantation (in months). DJ, duodeno-jejunostomy; DD, duodeno-duodenostomy.

performed, not only in clinically indicated cases but also in those performed per protocol; without losing sight of the fact that analysis has also been carried out from an intention to treat point of view. In the absence of a reliable and proven method for the diagnosis of rejection, beyond surrogate blood analytical data, the results of the present study are of vital importance for the scientific community since it offers the possibility of making a very precise histopathological diagnosis to treat subclinical rejection with impact on long-term graft survival.

In conclusion, our results demonstrate that US-guided percutaneous biopsy of retrocolic pancreatic grafts placed by DD is a safe and effective method for the histologic diagnosis of rejection, with an accessibility rate even better than that obtained for intraperitoneal pancreatic grafts. We firmly believe that this is the first step to eliminate fears of associated morbidity to the detriment of the benefits provided, and move towards the worldwide implementation of pancreas graft percutaneous biopsy in real life to improve the outcomes of such a challenging type of transplant.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by Comitè d'Ètica de la Investigació amb medicaments (CEIm), Hospital Clínic de Barcelona (Spain). 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 due to the retrospective character of the study.

AUTHOR CONTRIBUTIONS

CB, AG-C, and CA participated in the conceptualization, design and analysis of the data. CB collected the data and wrote the first draft of the manuscript. CB, AG-C, CA, PV-A, MC, and JF-F participated in editing the manuscript. AD, AS-P, and GR participated in reviewing 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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ORIGINAL RESEARCH
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Antibiotic Prophylaxis in Patients Undergoing Lung Transplant: Single-Center Cohort Study

Renato Pascale[1,2]†, Beatrice Tazza[2], Armando Amicucci[1], Elena Salvaterra[3], Giampiero Dolci[4], Filippo Antonacci[5], Massimo Baiocchi[6], Saverio Pastore[6], Simone Ambretti[1,7], Maddalena Peghin[8], Pierluigi Viale[1,2] and Maddalena Giannella[1,2]*

[1]Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy, [2]Infectious Diseases Unit, Scientific Institute for Research, Hospitalization and Healthcare Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [3]Division of Interventional Pulmonology Unit, Scientific Institute for Research, Hospitalization and Healthcare Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [4]Thoracic Surgery, Azienda Ospedaliero Universitaria di Ferrara, Ferrara, Italy, [5]Thoracic Surgery, Scientific Institute for Research, Hospitalization and Healthcare Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [6]Anaesthesiology and Intensive Care, Scientific Institute for Research, Hospitalization and Healthcare Azienda Ospedaliero-Universitaria Di Bologna, Bologna, Italy, [7]Microbiology Unit, Scientific Institute for Research, Hospitalization and Healthcare Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [8]Infectious and Tropical Diseases Unit, Department of Medicine and Surgery, University of Insubria-ASST-Sette Laghi, Varese, Italy

Perioperative antibiotic prophylaxis (PAP) in lung transplant recipients (LuTRs) has high heterogeneity between centers. Our aim was to investigate retrospectively the approach to PAP in our center over a 20-year period (2002–2023), and its impact on early post-operative infections (EPOIs) after lung transplantation (LuT). Primary endpoint was diagnosis of EPOI, defined as any bacterial infection including donor-derived events diagnosed within 30 days from LuT. Main exposure variables were type of PAP (combination vs. monotherapy) and PAP duration. We enrolled 111 LuTRs. PAP consisted of single-agent or combination regimens in 26 (25.2%) and 85 (74.8%) LuTR. Median PAP duration was 10 days (IQR 6–13) days. Piperacillin/tazobactam was the most common agent used either as monotherapy (n = 21, 80.7%) or as combination with levofloxacin (n = 79, 92.9%). EPOIs were diagnosed in 30 (27%) patients. At multivariable analysis no advantages were found for combination regimens compared to single-agent PAP in preventing EPOI (OR: 1.57, 95% CI: 0.488–5.068, p: 0.448). The impact of PAP duration on EPOIs development was investigated including duration of PAP ≤6 days as main exposure variables, without finding a significantly impact (OR:2.165, 95% CI: 0.596–7.863, p: 0.240). Our results suggest no advantages for combination regimens PAP in preventing EPOI in LuTR.

Keywords: lung transplant, antibiotic prophylaxis, bacterial infection, donor derived infections, idiopatic pulmonary fibrosis

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***Correspondence**
Renato Pascale,
renato.pascale2@unibo.it

†ORCID:
Renato Pascale
orcid.org/0000-0003-2687-4235

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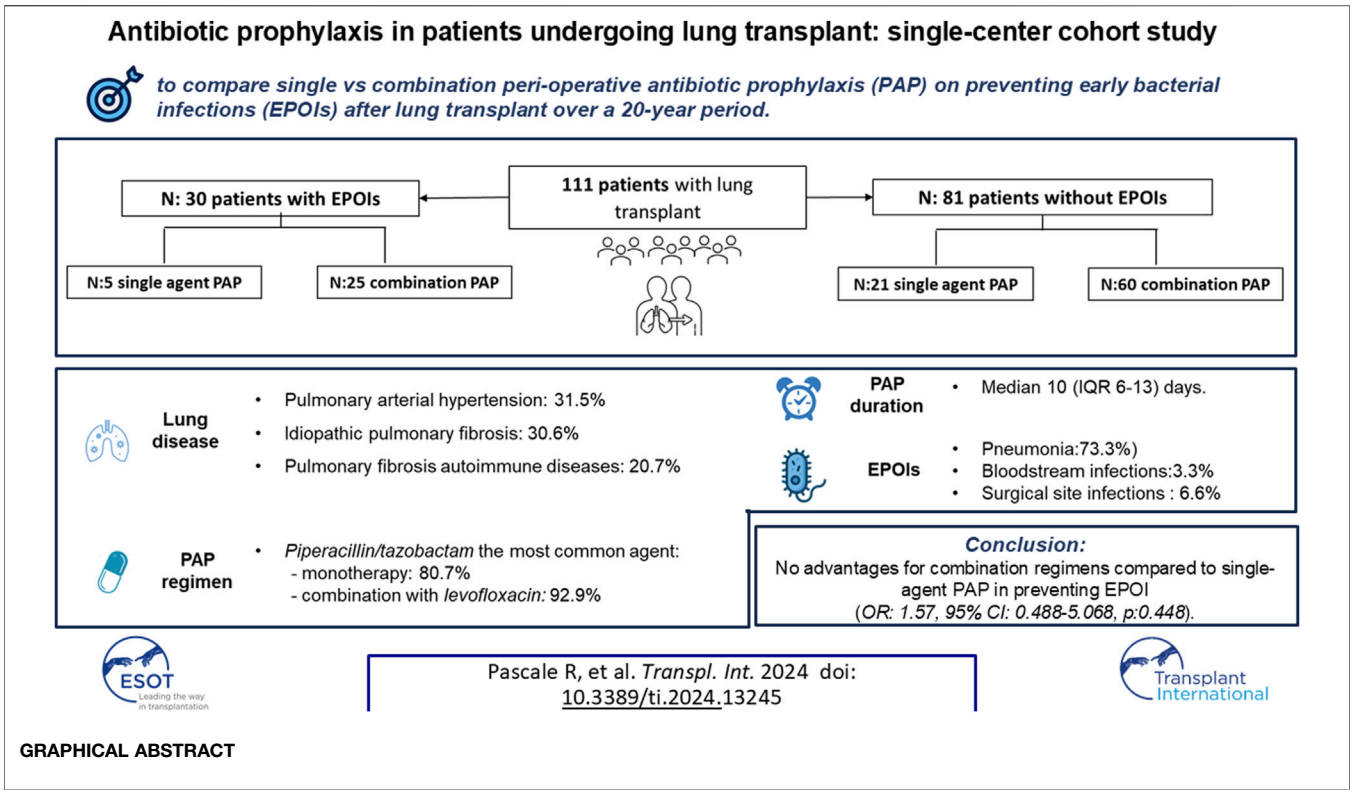
INTRODUCTION

Bacterial infections are clinically relevant complications in lung transplant recipients (LuTRs) causing chronic lung allograft dysfunction and high rates of mortality, especially within the first year after transplant [1, 2]. Infectious episodes occurring in the first 30 days following lung transplantation (LuT) are due to microorganisms deriving from



GRAPHICAL ABSTRACT

the donor lung or pre-existing recipient flora [3]. Indeed, even though native lungs are removed, colonization of the grafts from recipients colonizing strains often rapidly occurs [4–6]. While some experts advise against the use of the organs with microorganism isolation or detection, others support it, if it is combined with at least 24 h of antibiotic therapy according to susceptibility patterns of recovered microorganisms [7]. This last approach is supported by retrospective studies showing no difference in overall survival of recipients of infected/colonized lungs, compared to recipients of uninfected lungs [8], even in case of multi-drug resistant organisms (MDRO). All this considered, antibiotic prophylaxis is routinely administered in LuTRs [8, 9]. International guidelines recommendations are generic and predominantly based on cardiac procedures and no formal recommendations to guide antimicrobial selection in LuT surgery are currently available [10]. Therefore, antibiotic regimens for peri-operative antibiotic prophylaxis (PAP) are based on clinical judgment, bacterial infection and/or colonization present in the donor and/or recipient and knowledge of the local epidemiology, inducing high heterogeneity, both for drug choice and treatment duration, in clinical practice between centers [7].

We aim to carry-out a retrospective observational study to investigate different regimens of PAP used in our center over 20-year period, and their impact on preventing early bacterial infections and donor derived infection after LuT. The results obtained from our study will contribute to increasing knowledge about the prophylaxis regimens that can be adopted in hospitals with a similar clinical and microbiological epidemiology.

MATERIALS AND METHODS

Study Design and Setting

Retrospective, monocentric observational cohort study including all adult patients who underwent LuT at IRCCS Azienda Ospedaliero-Universitaria di Bologna from 1st January 2002 to 31st August 2023. During the study period, LuTRs antibiotic prophylaxis regimens were established by Transplant Intensivists and Pneumologists who managed the patients in the immediate peri-transplant period, according to usual practice and internal guidelines.

All enrolled patients are followed from time of LuT to 30 days after (or until death, whichever occurred first). Data were retrospectively collected from medical charts and microbiology archives. Data were collected using a dedicated REDCap electronic case report form (eCRF) hosted by IRCCS Azienda Ospedaliero-Universitaria di Bologna [11]. The study was conducted according to declaration of Helsinki and Good Clinical Practice guidelines and approved by the local Ethics Committee (no 676/2023/Oss/AOUBo).

Population

All adult (≥18 years) patients who underwent LuT receiving PAP during the study period were screened for inclusion. Patients were

excluded in case of lack of clinical and/or laboratory data regarding type of early postoperative bacterial infections (EPOIs).

Procedures

During the study period PAP regimen was composed by piperacillin-tazobactam administered with 9 g as loading dose followed by 4.5 g every 6 h in combination with levofloxacin 500 mg every 12 h [12–14]. This PAP regimen was chosen to provide two drugs with potential activity against *Pseudomonas* spp while awaiting donor/recipient culture results. PAP duration was continued until results of perioperative cultures. In case of positive recipient and/or donor cultures, PAP was tailored and extended for 10–14 days. In case of penicillin-drug allergy or intolerance, piperacillin/tazobactam was replaced by cefepime or meropenem. Levofloxacin was not administered in case of drug allergy, presence of a contraindication (history of epilepsy, connective disease, QT prolongation), or according with clinical judgement. When available, the pre-transplant recipient colonization status, at upper or lower respiratory tract, was used to target the antibiotic prophylaxis.

After transplantation, lower respiratory tract samples were taken when patients had clinical signs or symptoms of respiratory tract infection or rejection. During all the study period,in clinically stable patients, post-transplant bronchoscopy was performed after 48 h post-transplantation and subsequently every week for the first month. During each procedure, bronchoalveolar lavage and transbronchial biopsy were sent for microbiological cultures.

Variables and Definitions

Primary endpoint was diagnosis of EPOIs, defined as any bacterial infection diagnosed according to US Centers for Disease Control and Prevention (CDC) criteria [15] within 30 days from LuT. Among EPOIs, donor derived events were included and defined as any bacterial infection caused by the same microorganism isolated from the donor and the recipient [16].

PAP was defined as the antibiotic regimen administered at time of LuT before susceptibility report of donor cultures were available. Changes in antibiotic treatment according with recipient/donor cultures were recorded as well as the overall duration of PAP. PAP was mainly classified as single-agent or combination regimen.

The other variables were age and sex, co-morbidities summarized by the Charlson Comorbidity score [17], information on LuT (transplant date, graft Number; graft function during first 24 h). Immunosuppressive drugs used as induction and maintenance regimen were recorded. Donor and recipient colonization were inferred from respiratory samples. Infection etiology was also classified according to the causative species into Gram positives and Gram negative rods. According to the definitions of CDC [18] all strains from donors/recipients were categorized as Oxacillin-resistant (OxaR) or Vancomicin Resistant (VR) for Gram positive and Carbapenem resistance (CR), third generation cephalosporin resistance (ESCR), β-lactam/β-lactamase inhibitor (BL/BLIR) and fluroquinolone resistance (FQR) for Gram negatives. For the latter, Magiorakos criteria (non-MDR, MDR, XDR or PDR) and the new definition of *"difficult to treat resistance"* (DTR) were also used [19, 20].

Microbiology

Clinical samples collected during the study period were analysed following routine diagnostic workflow in the bacteriology laboratory, Unit of Microbiology. Since 2010, donor derived samples collected at the time of organ removal were referred to our center to be analyzed. Before that time, all donor cultures were performed at donor center and results subsequently provided at Transplant Unit. Results of any other microbiological samples previously analyzed at the donor center were provided to our center through the regional transplant coordination network.

Statistical Analysis

For descriptive analysis, categorical variables were presented as frequencies and percentages, continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR) according to normal or non-normal distribution. The clinical and demographic characteristics of the two subgroups of the study population were described and compared using bivariate tests such as t-test or Mann-Whitney test for continuous variables, chi-square or Fisher's exact test for categorical variables.

A multivariable binary logistic regression analysis was performed to investigate independent predictors of EPOIs considering type of PAP regimen (single-agent vs. combination) as main exposure variable along with all the other variables showing a $p < 0.05$ at univariable analysis, including male gender, Charlson Comorbidity Index, Tacrolimus as maintenance regimen, idiopatic pulmonary fibrosis as leading cause for lung transplant and primary graft non function. A second model to assess the impact of PAP duration on EPOIs development was done in which patients on PAP at the time of infection diagnosis were excluded. For this analysis we used the cutoff of PAP duration ≤6 vs. >6 days considering that in most cases cultures results of donor and recipient samples were available and communicated within 6 days of transplantation. SPSS 21.0 was used for all analyses, with significance level set at $\alpha = 0.05$.

RESULTS

Overall, 112 patients receiving LuT were screened for inclusion, 1 patient was excluded for lack of data and 111 were analysed (**Figure 1**). The main characteristics of study population are shown in **Table 1**. Of them, 64 (57.5%) were male, with a median age of 50 years (IQR 39–59), median Charlson Index was 2 (IQR: 1–4). The most frequent underlying lung disease leading to LuT was pulmonary arterial hypertension (35, 31.5%), followed by idiopathic pulmonary fibrosis (IPF) (34, 30.6%), pulmonary fibrosis associated with autoimmune diseases (23, 20.7%) and emphysema and chronic obstructive pulmonary disease (COPD) (14, 12.6%). Patients with cystic fibrosis were absent in our

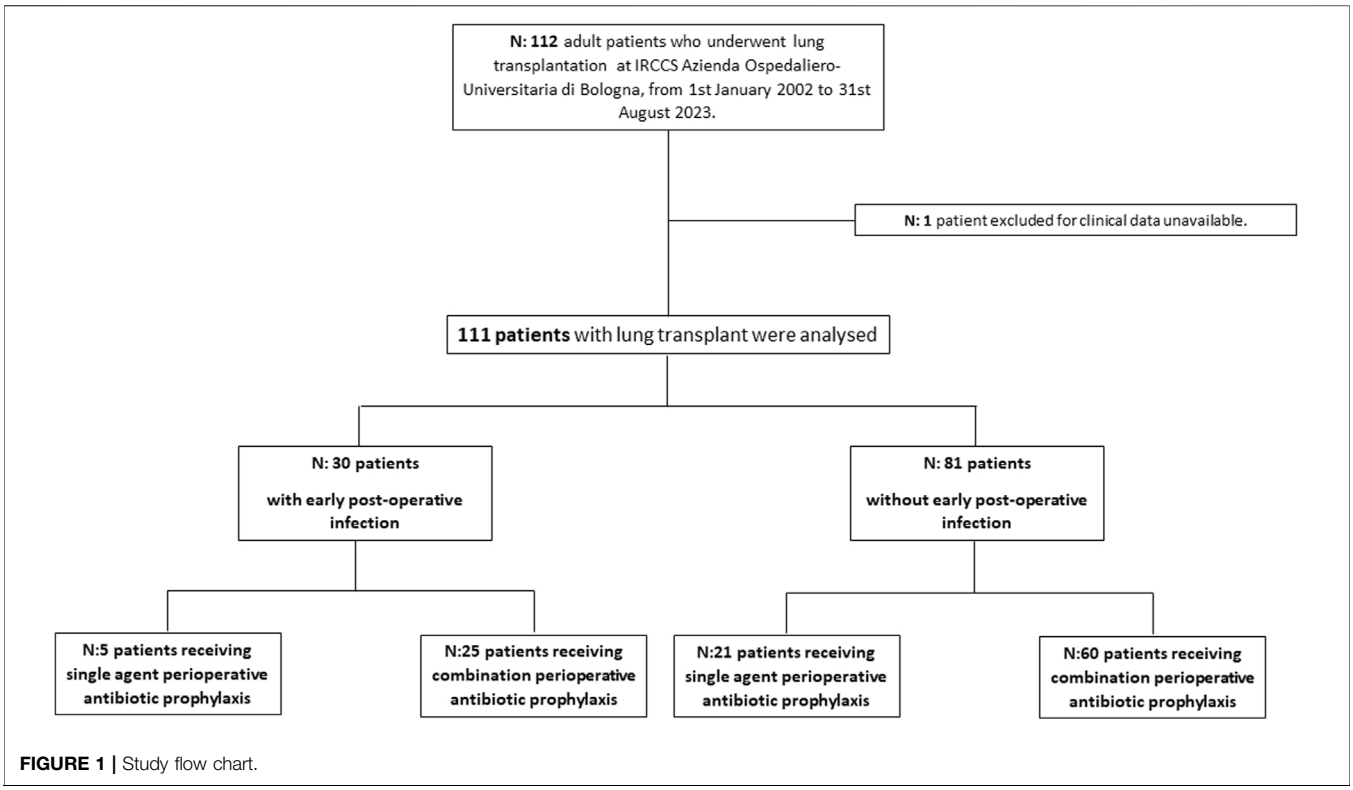


FIGURE 1 | Study flow chart.

cohort. Primary graft non function was experienced by 15 (14%) patients.

Recipient BAL colonization was found in 16 (14.4%) patients, data shown in **Supplementary Table S1**. Donor characteristics are summarized in **Table 1**: median age at the time of donation was 48 years (IQR: 31–55). Mainly were donation after brain death (DBD) (107, 96.4%). Infectious risk was considered as "*non-standard*" in 22 (21.4%) donations and ≥1 positive sample from BAL and blood was obtained from 59 (53.2%) donors. Data about donor/recipient BAL colonization are shown in **Supplementary Table S1**.

PAP consisted of single-agent or combination regimens in 26 (25.2%) and 85 (74.8%) LuTR, respectively (**Figure 2**).

Piperacillin/tazobactam was the most common agent used either as monotherapy (n = 21, 80.7%) as combination with levofloxacin (n = 79, 92.9%). Among all, 11 patients did not receive piperacillin/tazobactam as backbone of peri-operative antibiotic prophylaxis (PAP), 8 due to drug allergy/intolerance (of which 2, 1 and 5 of them received meropenem, levofloxacin alone and cefepime, respectively) and 3 due to surgeon decision. Levofloxacin was not administered in 8 patients (in 3 cases due to reported allergy to fluoroquinolones and in 5 patients due to other contraindications - history of epilepsy n = 2, QT prolongation n = 2, connective tissue disease n = 1). Vancomycin was administered as part of the PAP regimen in two recipients due to MRSA colonization of the respiratory samples in the pre-transplant period. The median duration of antibiotic prophylaxis was 10 days (IQR 6–13). No differences were found in PAP duration according to donor sample and recipient colonization (**Supplementary Table S2**).

MDRO colonization after LuT is reported in **Supplementary Table S3**. No differences were found regarding MDRO colonization in patients with PAP ≤6 days or >6 days (9, 32.1% vs. 15, 19.2%, p = 0.161). No *Clostridioides difficile* infection was found in the entire patient cohort.

EPOIs were diagnosed in 30 (27%) patients: 22 (73.3%) pneumonia, 1 (3.3%) bloodstream infections (BSI) and 2 (6.6%) surgical site infections. The median time to EPOIs was 10 days (IQR 6–23) from LuT. Overall, 13 patients with EPOIs were still on PAP at the time of infection diagnosis and therefore the antibiotic treatment was changed and targeted based on antimicrobial susceptibility of the pathogens. Enterobacterales were the main pathogens, none had a DTR profile. Two EPOIs were considered as donor derived events, data shown in **Supplementary Table S4**. Trend of LuT performed and related EPOIs devolopment during the study period is showed in **Supplementary Figure S1**. Comparison of patients with and without EPOIs is shown in **Table 1**. Patients with EPOIs were more frequently male (22, 73.3% vs. 42, 51.9%, p = 0.042) with older age (54, IQR: 46–63 vs. 48, IQR: 36–59, p = 0.029) with more frequently IPF (14, 46.7% vs. 20, 24.7%, p = 0.026) as underlying lung disease. No differences were found as regard single or combination PAP regimens administered. There were no differences in 30-day mortality (4, 13.3% vs. 14, 17.3%, p 0.616). However, patients with EPOIs had more longer length of stay (LOS) in ICU (15 days, IQR: 6–26 vs. 11 days, IQR: 6–24, p:0.001) and ICU readmission rates (9, 30% vs. 6, 7.4%, p = 0.002), longer duration of mechanical ventilation (9 days, IQR: 7–17 vs. 4 days, IQR: 2–9, p < 0.001) and more

TABLE 1 | Characteristics of patients receiving lung transplant and comparison of patients with and without bacterial infection after lung-transplant.

	Cases with available data	Total of patient 111 (%)	Patients without bacterial infection 81 (%)	Patients with bacterial infection 30 (%)	p-value
Demographics					
Age (years), median (IQR)	111	50 (39–59)	48 (36–59)	54 (46–63)	0.029
Gender (male)	111	64 (57.5)	42 (51.9)	22 (73.3)	0.042
Underlying Lung Disease					
Idiopatic pulmonary fibrosis	111	34 (30.6)	20 (24.7)	14 (46.7)	0.026
Pulmonary fibrosis associated with autoimmune diseases	111	23 (20.7)	17 (21.0)	6 (20.0)	0.909
Emphysema/COPD	111	14 (12.6)	11 (13.6)	3 (10.0)	0.614
Pulmonary arterial hypertension	111	35 (31.5)	27 (33.3)	8 (26.7)	0.502
Chronic Thromboembolic Pulmonary Hypertension	111	1 (0.9)	1 (1.2)	0 (0.0)	0.541
Other	111	10 (9.0)	9 (11.1)	1 (3.3)	0.204
Underlying diseases					
Myocardial infarction	111	6 (5.4)	4 (4.9)	2 (6.7)	
Congestive heart failure	111	45 (40.5)	28 (34.6)	17 (56.7)	0.035
Peripheral vascular disease	111	7 (6.3)	4 (4.9)	3 (10.0)	0.330
Cerebrovascular disease	111	3 (2.7)	2 (2.5)	1 (3.3)	0.803
Connective tissue disease	111	13 (11.7)	12 (14.8)	1 (3.3)	0.095
Diabetes mellitus	111	13 (11.9)	7 (8.9)	6 (20.0)	0.109
Charlson index, median (IQR)	111	2 (1–4)	2 (1–3)	3 (2–4)	0.006
Donor information					
Age at the time of donation median (IQR)	111	48 (31–55)	48 (31–56)	48 (34–55)	0.750
Donation after circulatory death (DCD)	111	3 (2.7)	1 (1.2)	2 (6.7)	0.117
Donation after brain death (DBD)	111	108 (96.4)	79 (97.5)	28 (93.3)	0.292
Infectious donor risk					0.423
Standard	103	81 (78.6)	62 (80.5)	19 (73.1)	
Non standard	103	22 (21.4)	15 (19.5)	7 (26.9)	
Cause of donor death					0.362
Trauma	111	34 (30.6)	26 (32.1)	8 (26.7)	
Cerebrovascular	111	69 (62.2)	49 (60.5)	20 (66.7)	
Other	111	8 (7.2)	6 (7.4)	2 (6.7)	
Transplant information					
Days from inclusion list to transplant, median (IQR)	111	235 (83–508)	237 (83–534)	154 (76–349)	0.307
Single-lung	111	16 (14.4)	9 (11.1)	7 (23.3)	0.103
Double-lung	111	95 (85.6)	72 (88.9)	23 (76.7)	0.103
Heart + Lung	111	4 (3.7)	3 (3.8)	1 (3.4)	0.941
Ischemia Time (hours) median (IQR)	85	5.4 (4.35–6.1)	5.1 (4.3–6.4)	5.8 (4.8–6.1)	0.188
Primary graft non function	111	15 (14.0)	12 (15.2)	3 (10.7)	0.558
Delayed graft function	111	1 (0.9)	1 (1.3)	0 (0.0)	0.550
Induction regimen					
Bolus of steroids	111	104 (93.7)	75 (92.6)	29 (96.7)	0.433
Antylimphocyte globulin	111	11 (9.9)	7 (8.6)	4 (13.3)	0.463
Basiliximab	111	56 (50.5)	41 (50.6)	15 (50.0)	0.954
Maintenance regimen					
Cyclosporine	111	11 (9.9)	6 (7.4)	5 (16.7)	0.147
Azathioprine	111	13 (11.7)	9 (11.1)	4 (13.3)	0.746
Tacrolimus	111	73 (65.8)	59 (72.8)	14 (46.7)	0.010
Mycophenolate	111	37 (33.3)	29 (35.8)	8 (26.7)	0.365
Everolimus	111	1 (0.9)	1 (1.2)	0 (0.0)	0.541
Steroids	111	84 (75.7)	64 (79.0)	20 (66.7)	0.178
Etanercept	111	28 (25.2)	23 (28.4)	5 (16.7)	0.206
Positive Donor Derived Samples	111	59 (53.2)			
BSI	*59*	*3 (10.1)*	*1 (1.2)*	*2 (6.7)*	0.117
BAL	*59*	*56 (94.9)*	*41 (50.6)*	*15 (50.0)*	0.954
Recipient colonization	111	17 (77.3)			
CPE Rectal colonization	*16*	1 (0.9)	0 (0.0)	1 (3.3)	0.099
BAL	*16*	16 (14.4)	12 (14.8)	4 (13.3)	0.844
Perioperative Antibiotic prophylaxis					
Mono - regimen	111	26 (23.4)	21 (25.9)	5 (16.6)	0.306
Piperacillin/tazobactam	111	21 (80.7)	17 (80.9)	4 (80)	0.181
Levofloxacin	111	2 (7.7)	1 (4.7)	1 (20)	0.250
Meropenem	111	2 (7.7)	2 (9.5)	(0.0)	0.473

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of patients receiving lung transplant and comparison of patients with and without bacterial infection after lung-transplant.

	Cases with available data	Total of patient 111 (%)	Patients without bacterial infection 81 (%)	Patients with bacterial infection 30 (%)	p-value
Cefepime	111	1 (3.8)	1 (4.7)	0 (0.0)	0.619
Combo - regimen	111	85 (76.6)	60 (74.1)	25 (8.3)	0.306
Vancomicin-Cefepime	111	5 (5.9)	2 (3.3)	3 (12.0)	0.099
Piperacillina/tazobactam_levofloxacin	111	79 (92.9)	58 (96.6)	21 (84.0)	0.099
Meropenem_levofloxacin	111	1 (1.2)	0 (0.0)	1 (4)	0.099
Total Duration of PAP (median, IQR)	110	10 (6–13)	10 (6–14)	9 (6–10)	0.138
Duration of PAP ≤6 days	110	29 (27.1)	20 (25.6)	9 (31.0)	0.577
Recipient colonization after lung transplant	110	25 (22.7)	13 (16.2)	12 (40.0)	0.008
BAL	*25*	20 (18.0)	9 (11.1)	11 (36.7)	0.002
Rectal (CPE)	*25*	4(3.6)	3 (3.7)	1 (3.3)	0.926
Urinary	*25*	4 (3.6)	3 (3.7)	1 (3.3)	0.504
Time of colonization from Tx	*25*	15 (6–41)	17 (6–42)	10 (4–36)	0.695
Outcome					
ICU Readmission	111	15 (13.5)	6 (7.4)	9 (30.0)	0.002
ICU LOS	109	15 (6–26)	11 (6–24)	21 (15–33)	0.001
Duration of MV	110	6 (3–12)	4 (2–9)	9 (7–17)	<0.001
Renal Replacement Therapy	111	41 (36.9)	22 (27.2)	19 (63.3)	<0.001
Continous Renal Replacement Therapy	111	38 (34.2)	21 (25.9)	17 (56.7)	0.002
Days of Continous Renal Replacement Therapy median (IQR)	*36*	12 (8–21)	*10 (5–20)*	16 (11–21)	0.002
Re-IOT	106	17 (15.3)	10 (12.8)	7 (25.0)	0.132
Re-hospitalization	94	5 (4.5)	3 (4.5)	2 (7.4)	0.567
Death 30 days	111	18 (16.2)	14 (17.3)	4 (13.3)	0.616

Abbreviations: BAL, bronchoalveolar lavage; BSI, bloodstream infection; COPD, chronic obstructive pulmonary disease; CPE, carabapenem producing enterobacterales; DBD, donation after brain death; DCD, donation after circulatory death; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; MV, mechanical ventilation; OI, orotracheal intubation; PAP, Perioperative antibiotic prophylaxis.

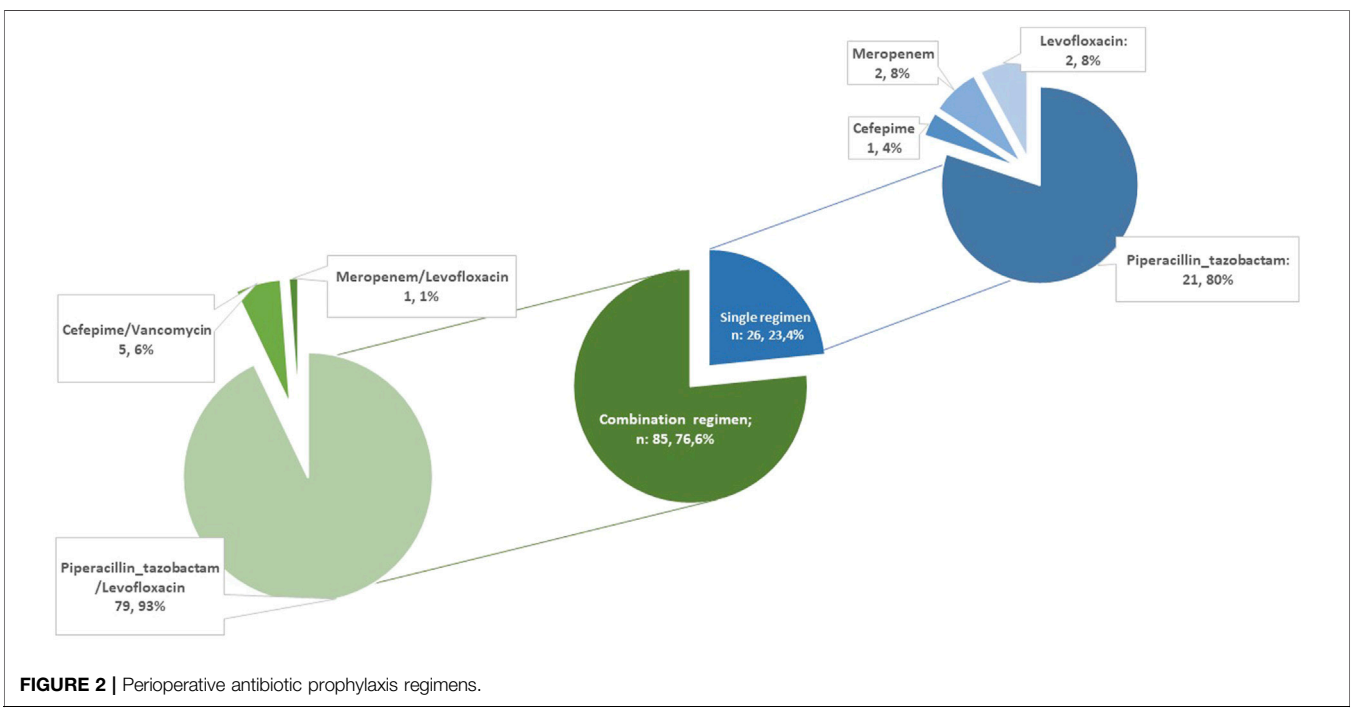


FIGURE 2 | Perioperative antibiotic prophylaxis regimens.

frequently need of renal replacement therapy (19, 63.3% vs. 22, 27.2%, p < 0.001).

The multivariable analysis of risk factors for EPOIs is showed in **Table 2**, panel A. No advantages were found for combination regimens compared to single-agent PAP in preventing EPOI (OR: 1.57, 95% CI: 0.488–5.068, p:0.448). The model was adjusted for male gender, Charlson Comorbidity Index, Tacrolimus as maintenance immunosuppresive regimen, idiopatic pulmonary

TABLE 2 | Multivariable binary logistic regression of: total EPOIs development at 30 days after lung transplantation (*Panel a*); EPOIs in patients without PAP at the time of infection diagnosis (*Panel b*).

Panel a	**OR**	**IC 95%**	**P**
Male gender	0.736	0.241–2.244	0.590
Idiopatic pulmonary fibrosis as leading cause for lung transplant	1.436	0.517–3.984	0.487
Primary graft non function	0.304	0.062–1.488	0.142
Charlson comorbidity index	1.236	0.916–1.667	0.167
Tacrolimus as mantainance regimen	0.295	0.095–0.918	0.035
PAP combination regimens	1.573	0.488–5.068	0.448
Panel b	**OR**	**IC 95%**	**P**
Male gender	0.854	0.194–3.756	0.834
Idiopatic pulmonary fibrosis as leading cause for lung transplant	0.466	0.111–1.955	0.297
Primary graft non function	0.149	0.013–1.671	0.123
Charlson comorbidity index	1.391	0.937–2.064	0.102
Tacrolimus as mantainance regimen	0.324	0.076–1.376	0.127
PAP combination regimens	5.606	0.643–48.901	0.119
Duration of PAP ≤6 days	2.165	0.596–7.863	0.240

Abbreviations: OR, odds ratio; IC, confidence intervals; PAP, perioperative antibiotic prophylaxis.

fibrosis as leading cause for lung transplant and primary graft non function. To investigate the impact of PAP duration of EPOIs development, we excluded from analysis patients with ongoing antibiotic prophylaxis at infection diagnosis (13 of 30, 43%). The remaining 17 patients developing EPOIs were included in the model. PAP duration ≤6 days was used as main exposure variable. We didn't find a significantly impact of PAP duration (OR:2.165, 95% CI: 0.596–7.863, p: 0.240) (**Table 2**, panel B). The multivariable analysis of risk factors for EPOIs was repeated by selecting only patients treated with piperacillin/tazobactam in monotherapy and in association with levofloxacin confirming no advantages for combination regimen compared to single-agent PAP in preventing EPOI and neither significantly impact of PAP duration (**Supplementary Table S5**, panel A and B).

DISCUSSION

We analysed a large cohort of LuTRs to evaluate different PAP regimens used to prevent EPOIs, mainly with piperacillin/tazobactam as backbone. No differences were found as regard EPOIs development between combination or single agent PAP regimens. In addition, we observed a prolonged PAP not justified by donor/recipient culture results underlying the need of *ad hoc* strategies to limit the use of broad spectrum and unnecessary prolonged regimens.

The knowledge of the patient's infectious risk is crucial for an appropriate management of LuTRs in the perioperative period. It may be helpful to consider targeted PAP for patients who are colonized with MDROs and, conversely, to limit the use of high microbiological impact antibiotics (i.e., carbapenems) if alternatives available. Regarding this aspect, characteristics of patients in our cohort are peculiar. The most frequent lung diseases requiring transplantation, COPD/emphysema and cystic fibrosis, are poor represented in our study [21]. Patients with COPD and cystic fibrosis suffer frequently of bacterial infections with consequently prolonged broad-spectrum antibiotics exposition and higher risk of MDROs colonization [3, 9]. Conversely, patients with interstitial lung disease show low rates of bacterial complication with a reduced antibiotic exposure and MDROs colonization [22]. Indeed, in our cohort, the rate of MDROs recipient colonization and infection was very low and PAP regimen was almost always effective on antimicrobial susceptibility profiles of donor/recipient isolates. We noted that, among all interstitial lung diseases collected in our center, patients with IPF appeared to have the highest risk of developing infections. Further studies are needed to confirm this finding.

The choice of single or combination PAP regimens is left to referral clinicians. If drugs with activity against MDR Gram negative rods are almost universally used, a second antibiotic with activity against *Staphylococcus aureus* could be added, according with local epidemiological data. In a large survey on perioperative antibiotic therapy in LuT involving 99 centers worldwide, most of the participants reported PAP regimens covering Gram negative rods with activity against *Pseudomonas aeruginosa.* Only one-third of the centres targeted *S. aureus*, almost exclusively from the USA and against methicillin resistant *S.aureus* (MRSA) [7], with vancomycin as preferred drug. The low *S. aureus* rate and the absence of a clear benefit from using a combination regimen in our cohort, support the need to set PAP according with local epidemiology.

Finally, duration of PAP is another matter of debate. Ideally, PAP should be stopped as soon as cultures of the donor and the recipients are reported as negative to reduce the risk of MDROs selection and/or *C. difficile* infections [23]. However, it has been shown that PAP duration among transplant centers is very heterogeneous [7]. In our study, PAP duration was unacceptably too prolonged even in cases without donor/recipient positive cultures, deviating from internal guidelines. Although with few cases, our analysis shows that a prolonged PAP is not protective for EPOIs development, thus supporting the opportunity of shortening PAP duration. In this regard, it seems desirable to design and/or standardize *ad hoc* antimicrobial stewardship strategies to avoid unnecessary prolonged PAP in lung transplant recipients in our center [23, 24].

There are several limitations in this study. First, we collected data from a single-center cohort of LuTR over a 20-year study period, however PAP regimens and approach to EPOI diagnosis did not change across years. Furthermore, our patients suffered mainly from interstitial lung disease and cystic fibrosis was not represented. Both these limitations could limit the generalizability of our results. However, our findings could add evidence supporting prophylaxis with a single drug in LuTRs with non-cystic fibrosis/COPD as underlying disease. Moreover, the rate of donor derived events could have been be underestimated due to the lack of respiratory sample in around half of the donors. In addition, the limited sample size and the heterogeneity of PAP administration did not allow to infer any conclusion about the impact of prophylaxis duration on EPOIs development. Finally, the retrospective design of the study could have reduced the accuracy of data collection. However, we attempted to reduce this limitation by thorough data quality control.

Despite these limitations, our results suggest no advantages for combination regimens over a single-agent regimen in preventing EPOIs in LuTRs with interstitial lung diseases as underlying disease. However, further studies are needed to confirm this hypothesis.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by the CE AREA VASTA EMILIA ROMAGNA 676/2023/Oss/AOUBo. 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

RP, BT, and AA contributed to conceptualisation and design of the study; AA, ES, GD, FA, MB, SP, and SA contributed to acquisition of data; RP and MG performed the analysis; RP contributed to writing the original draft; MG, MP, and PV supervised the work. 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.2024.13245/full#supplementary-material

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