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Liver transplantation: A single IS drug to protect the kidneys?

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DOI: 10.3389/ti.2025.13801

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DOI: 10.3389/ti.2025.14024

Fernanda Ortiz, Lorna Marson, Rachel Thomas, Andreas Kousios, Elvana Rista, Carmen Lefaucheur, Sanem Cimen, David Cucchiari, Gianluigi Zaza, Lucrezia Furian and Baris Akin on behalf of the European Kidney Transplant Association (EKITA)

As the number of living donors continues to increase, it is paramount to ensure their safety. This comprehensive review highlights the uncertainties of living donors' long-term follow-up, with recommendations and evidence-based targets for managing comorbidities after kidney donation.

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DOI: 10.3389/ti.2025.13992

Anastasia Georgiou, Weiyi Tan, Mihnea I. Ionescu, Isla L. Kuhn and Zoe Fritz

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DOI: 10.3389/ti.2025.13800

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Anti-spike monoclonal antibody therapy had potential benefit in the prevention and treatment of COVID-19 in lung transplant recipients, with a reduction in COVID-19 disease onset and severity. Monoclonal antibodies may be effective against other pathogens, which warrants further investigations.

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72 Mono-HOPE Versus Dual-HOPE in Liver Transplantation: A Propensity Score-Matched Evaluation of Early Graft Outcome

DOI: 10.3389/ti.2025.13891

Dominik Thomas Koch, Micol Tamai, Malte Schirren, Moritz Drefs, Severin Jacobi, Christian M. Lange, Matthias Ilmer, Hanno Nieß, Bernhard Renz, Jens Werner, Markus Guba and Dionysios Koliogiannis

A Propensity Score-matched comparison of liver transplantation following dual-HOPE (N=90) versus mono-HOPE (N=93) revealed no improvement in patient or graft survival, NAS, or hospital length of stay. Thus, additional hepatic artery cannulation may offer no significant benefit.

Letter to the Editor

82 Proteomic Analysis of Transbronchial Biopsy Tissue Reveals a Distinct Proteome and Mechanistic Pathways in High-Grade Eosinophilic Inflammation After Lung Transplantation

DOI: 10.3389/ti.2025.14080

Eisa Tahmasbpour, Ashleigh Philp, Tabitha Cree, Vanathi Sivasubramaniam, Claire Thomson, Marshall Plit, Anjaneyaswamy Ravipati, Mark Raftery and David R. Darley

We performed a whole proteome analysis coupled with advanced bioinformatics platforms to elucidate mechanistic pathways in which graft eosinophilia is linked to enhanced risk of chronic lung allograft dysfunction independent of concurrent acute cellular rejection.


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TRANSPLANT TRIAL WATCH
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Transplant Trial Watch

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

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Keywords: randomised controlled trial, systematic review/Meta-analysis, liver transplantation (LT), kidney transplantation (KT), BK polyomavirus

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.

SYSTEMATIC REVIEW

Benefits of Hypothermic Oxygenated Perfusion Versus Static Cold Storage in Liver Transplant: A Comprehensive Systematic Review and Meta-Analysis.

by Feng, G. Y., et al. Journal of Clinical & Experimental Hepatology 2024; 14(3): 1.

Aims

To comprehensively evaluate whether hypothermic oxygenated perfusion (HOPE) offers significant benefits over static cold storage (SCS) in adult liver transplantation, focusing on graft outcomes, complications, and patient prognosis.

Interventions

The control group of donor livers preserved using SCS compared with the intervention group of donor livers preserved using HOPE.

Participants

They included 11 studies (4 RCTs, 4 prospective non-randomized, 3 retrospective), totalling 1,765 adult liver transplant recipients: HOPE in 532 patients and SCS in 1,233 patients. Donor grafts included donation after brain death (DBD), extended criteria donor DBD, and donation after circulatory death (DCD).

Outcomes

Primary Outcomes: early allograft dysfunction (EAD), primary non-function (PNF), acute rejection and one-year graft loss Secondary Outcomes: one-year mortality, biliary complications, vascular complications, major postoperative complications (Clavien-Dindo grade ≥ IIIa or ≥ IIIb) and additional descriptive outcomes (peak liver enzymes, ICU/hospital stay) where reported.

Follow-Up

Follow-up varied across studies, with most tracking outcomes up to one-year post-transplant.

CET Conclusion

by John Fallon

The authors conducted a robust and comprehensive systematic review and meta-analysis, with 11 studies of at least moderate quality, 4 small to moderate sized RCTs, 3 of which were multi-centre

Transplant Trial Watch

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and 7 cohort studies on of which was a large retrospective study with 121 livers having undergone HOPE. The analyses demonstrate a significant reduction in EAD: HOPE substantially decreased early allograft dysfunction (pooled OR ~0.36) and A lower graft loss rate: one-year graft loss was significantly less frequent with HOPE (pooled OR ~0.57). With regards complication profiles HOPE was associated with fewer Clavien-Dindo ≥IIIa complications and tended to reduce biliary complications, acute rejection, and vascular complications (though sensitivity analyses revealed some heterogeneity among studies). As has been seen in the kidney and is consistent among liver studies HOPE is particularly beneficial for DCD Grafts: Subgroup analysis showed HOPE recipients with DCD grafts had reduced biliary complications, one-year mortality, and acute rejection. As with all analyses of this nature, they are limited by the quality of underlying studies, in this case the are a reasonable number of randomised studies, and across the studies a low heterogeneity for certain important outcomes such EAD which provides strong evidence. There is, of course, moderate of high levels for some complications due to variability in study design and populations, however this does not weaken the overall message. Overall, the evidence supports a notable advantage of HOPE in reducing ischemia-reperfusion injury and improving early and some longer-term outcomes in liver transplantation, especially for higher-risk grafts such as DCD. This being said, there is no large multi-centre/multi-national RCT which could definitively demonstrate the need for ubiquitous HOPE, especially in marginal grafts.

Trial Registration
PROSPERO - CRD4202343074.

Funding Source
Non-industry funded.

RANDOMISED CONTROLLED TRIAL

Insights From the BKEVER Trial Comparing Everolimus Versus mycophenolate Mofetil for BK Polyomavirus Infection in Kidney Transplant Recipients.

by Caillard, S., et al. Kidney International 2024 [record in progress].

Aims
This study aimed to examine whether the administration of everolimus (EVR) was more effective in facilitating the clearance of BK polyomavirus (BKPyV) infection in comparison to standard immunosuppression reduction in kidney transplant recipients.

Interventions
Participants were randomised to either the mycophenolate mofetil (MMF) group or the EVR group.

Participants
130 kidney transplant recipients.

Outcomes
The primary outcome was the proportion of patients that were able to achieve BKPyV clearance. The secondary outcomes were the assessment of BKPyV replication kinetics, the incidence of biopsy-proven BKPyVN, rate of rejection, change in kidney allograft function, the incidence of donor-specific antibodies (DSAs) and treatment safety.

Follow-Up
2 years following randomisation.

CET Conclusion
by Simon Knight

This multicentre randomised controlled trial investigated the role of everolimus in the management of kidney transplant recipients with BK virus infection. 130 kidney recipients with BK viraemia were randomised to standard immunosuppression reduction versus a switch from MMF to everolimus. BK virus clearance was actually higher in the MMF arm, despite similar CNI trough levels. This is an interesting and well-designed study, although a lack of blinding and a fixed randomisation block size might have affected allocation concealment. Intent-to-treat analysis is used. It should be noted that patients with established BK virus nephropathy were excluded. Given the antiviral properties of mTOR inhibitors, the results are surprising. The authors hypothesise that higher overall immunosuppression or insufficient levels of everolimus to exert an antiviral effect may provide an explanation.

Jadad Score
3.

Data Analysis
Strict intention-to-treat analysis.

Allocation Concealment
Yes.

Trial Registration
ClinicalTrials.gov - NCT03216967.

Funding Source
Non-industry funded.

CLINICAL IMPACT SUMMARY

by Simon Knight

Previous studies have suggested that mammalian target of rapamycin inhibitors (mTORi) may have antiviral

properties, potentially giving them a role in management of infections post-transplant [1]. mTORi enhance the quantity and quality of memory CD8 T-cells following viral infection or vaccination [2], and when used *de novo* in kidney transplant recipients appear to reduce the risk of CMV and BK viral infection [3].

The role of mTORi in the management of established viral infection post-transplant is less clear. Current management of BK virus post-transplant centres around reduction in immunosuppression, with no compelling evidence for the use of antiviral agents [4].

The multicentre BKEVER trial investigated the efficacy of switching from mycophenolate mofetil (MMF) to everolimus, with reduced dose calcineurin inhibitor (CNI), compared to standard MMF and CNI reduction in kidney transplant recipients with BK viraemia [5]. 130 patients were randomised across 16 transplant centres. Contrary to the author's hypothesis, BK viral clearance was actually higher in the MMF group at 6 months (81.3% vs. 55.7%) with numerically higher rejection rates in the everolimus group and no difference in graft survival.

These results are difficult to explain, but the authors postulate that there may have still been a higher overall immunosuppressive load in the everolimus group despite similar trough CNI levels. The frequency of rejection episodes would argue against this. An alternative explanation is that the everolimus levels achieved were not sufficient to exert an antiviral effect.

Whatever the explanation, the results of this study suggest that the use of mTORi at the doses used in this study for the management of established BK virus infection is ineffective.

Clinical Impact

4/5.

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

SK has received consultancy fees from OrganOx Ltd for assistance in clinical study design.

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

GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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IN MEMORIAM
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In Memoriam Frans H. J. Claas

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Keywords: histocompatibility and immunogenetics, transplantation, highly sensitized patients, HLA, transplant immunology

Frans Claas, one of the most influential transplant immunologists and histocompatibility experts of his time, unexpectedly passed away on Sunday the 2nd of February 2025, aged 73. He died while on a vacation trip in South Africa with his wife Ilse and dear friends Ronald and Dienne Bontrop.

Frans Claas was born on 6 October 1951 in Eindhoven, a city in the province of North Brabant in the south of the Netherlands. He was born into a very Catholic family, resulting in his first potential career choice of becoming a pope. Alternative career choices were professional football (Frans was goalkeeper at RKVV Tongelre, and almost made it to professional club MVV Maastricht), or biology. After successfully finishing his Gymnasium education in 1970, Frans eventually decided to study biology at Leiden University, for which he took his final exam in 1976. During the last 2 years of his education he was already a student assistant in the laboratory of Jon J. van Rood at the Academic Medical Center in Leiden. After obtaining his biology degree he continued working in this lab and started his PhD studies. He successfully defended his PhD thesis entitled "The Interaction of Drugs and γ-Type Endorphins with Polymorphic Cell Membrane Antigens" on 29 May 1985. Following, he took over the end responsibility of the HLA laboratory, achieving the status of National Reference Center for Histocompatibility Testing. He also became Director of the Eurotransplant Reference Laboratory. On 13 December 1996 Frans became Professor on the Immunogenetics of Transplantation at Leiden University.

Frans was an exceptional scientist, and the true embodiment of the collaborative spirit that has characterized the histocompatibility and immunogenetics field throughout the years. For him, the advancement of science and the wellbeing of patients was always more important than personal benefit or recognition. His pioneering spirit is exemplified by the publication from 1988 where Frans introduced a totally new concept to increase the chance of transplantation for highly sensitized patients [1]. By extensive antibody screening (at that time solely by complement-dependent cytotoxicity (CDC) assays), he showed that it was possible to define "acceptable mismatches" to which a negative crossmatch could be predicted. This work culminated into the still highly successful Eurotransplant Acceptable Mismatch Program [2], in which more than 2000 highly sensitized patients have been transplanted to date.

In his efforts to extend the possibilities for highly sensitized patients Frans became one of the founding fathers of the field of what is now often called "molecular mismatch" analysis. In the early 2000s, Frans teamed up with Rene Duquesnoy, who had just introduced his HLAMatchmaker concept [3]. They showed that additional acceptable antigens for highly sensitized patients could be defined by extrapolating negative CDC antigen reactivity to untested HLA class I antigens by triplet (predecessor of eplet) sharing [4]. Following, his group was the first to show that an increased level of HLA triplet mismatches was associated with an increased chance of *de novo* donor-specific antibody (dnDSA) formation, and that antigen mismatched, but triplet matched transplants did not result in dnDSA formation [5], a finding that is still replicated in studies today. With the transition of triplets to eplets and the start of the HLA Epitope Registry [6], his team made significant contributions to the antibody verification of eplets by developing human HLA-specific monoclonal antibodies [7–9]. His work on differential immunogenicity of HLA mismatches was not limited to solid organ transplantation. His team also explored the role of molecular mismatch in the setting of

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FIGURE 1 | Frans Claas at Leiden University Medical Center.

hematopoietic stem cell transplantation. They showed that HLAMatchmaker analysis was not informative for the cytotoxic T cell precursor (CTLp) frequency [10]. Paradoxically, more amino acid mismatches at the alpha-helices and beta-sheet resulted in less formation of donor reactive $CD8^+$ T cells, a finding explained by the necessity of some level of resemblance between mismatched HLA and self-HLA for direct allo-recognition [11]. Linked to these observations were the seminal studies on heterologous immunity, in which cross-reactivity of virus-specific T cells with allogeneic HLA could explain the relatively high frequency of T cells with direct alloreactivity [12, 13].

Frans (**Figure 1**) was one of the few scientists in histocompatibility that explored the setting of pregnancy for understanding naturally occurring immunological tolerance to a haploidentical situation. Through the years his group explored the unique T cell signature in the human placenta, related to either good or complicated pregnancy outcomes [14–16]. More recent work using mass cytometry highlighted the potential role of myeloid cells in the human placenta [17, 18]. In his research, Frans did not evade controversial subjects, as evidenced by a paper in which a correlation between oral sex and the low incidence of the pregnancy complication preeclampsia was shown, with the hypothesis that soluble HLA could induce immunological tolerance [19].

Frans' legacy is enormous, with over 600 peer-reviewed papers published. He was member of several advisory committees and consensus meetings [20, 21]. His scientific merits have been recognized by receiving several prestigious awards, including the ASHI distinguished scientist award in 2006, the EFI Ceppellini Award in 2015, and the ASHI Rose Payne Distinguished Scientist Award in 2015. Upon his retirement in 2017 Frans was knighted as a Knight of the Order of the Netherlands Lion by the King of the Netherlands for the impact of his work on society.

Besides his scientific achievements, what his colleagues remember most about Frans is that he was a wonderful human being. He showed interest in everybody, regardless of their knowledge, skillset, or origin. He felt a great deal of responsibility to help scientists from all over the world to improve their knowledge and skills. The lab in Leiden continuously hosted colleagues from all over the world, such as India, Australia, Israel and China, just to name a few. His collaborative spirit was tangible in the lab in Leiden, and beyond. His social skills were second to none, as he took interest in everyone and was always willing to give advice. Moreover, he surely knew how to have a good time. Wherever there was a dance floor, Frans was there to be found. He loved to have a drink with his many friends and talk about science, but also about life outside of science. Frans was an avid runner and completed numerous marathons, with the most notable being the Bordeaux Médoc Marathon, which combined two major passions of Frans.

We hope that his memory will inspire others to selflessly advance science for patient benefit. Finally, we would like to remember Frans by one of his life mottos, "Carpe Diem," which rings true even more since Frans is no longer with us.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

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

GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Role of a Porcine Herpesvirus, PCMV/PRV, in Xenotransplantation

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Keywords: orthotopic pig heart transplantation, porcine cytomegalovirus/porcine roseolovirus, virus safety, xenotransplantation, survival time

A Forum discussing:

Progress in Orthotopic Pig Heart Transplantation in Nonhuman Primates
by Längin M, Bender M, Schmoeckel M, Reichart B (2024) Transpl Int. 37:13607. doi: 10.3389/ti.2024.13607

INTRODUCTION

Xenotransplantation using pig organs may be associated with the transmission of porcine viruses that could cause disease in recipients. A well-known example is the porcine cytomegalovirus, which is actually a porcine roseolovirus, hence abbreviated as PCMV/PRV. This virus is related to human herpesviruses 6 and 7 and is not closely related to human cytomegalovirus, which causes significant complications in allotransplantation [1]. PCMV/PRV has been shown to drastically reduce the survival time of porcine organs in non-human primates (for review, see [2]). The virus was also transmitted to the first patient in Baltimore who received a pig heart; it replicated exponentially to high titers in the transplanted pig heart and likely contributed to the patient's death [3]. Therefore, the transmission of PCMV/PRV and other potentially zoonotic porcine viruses should be prevented.

Längin et al. highlighted the progress in orthotopic pig heart transplantation in non-human primates [4]. Since the first study in 1994, it has been possible to increase the survival time of orthotopically transplanted pig hearts from 39 to 59 to 195 and finally to 264 days. In addition to advancements in multiple genetically modified donor pigs, organ preservation, new immunosuppressive and immunomodulatory drugs, and growth inhibition of the transplanted organ, the authors discussed the virological safety of xenotransplantation. Unfortunately, in this context, Längin et al. [4] cited an abstract from the International Xenotransplantation Association Conference in San Diego in 2023 without critical commentary. In the abstract, Zhang et al. [5] claimed that their investigations found no difference in survival times of pig heart transplants from PCMV/PRV-positive versus PCMV/PRV-negative donor animals in baboons. In these 12 donor pigs, PCMV/PRV was tested only by PCR; six animals (50%) were positive, but no differences in transplant or recipient survival were observed [6]. This study warrants critical scrutiny because it contradicts all previous findings and could lead to an underestimation of the risks posed by PCMV/PRV.

THE RISK POSED BY PCMV/PRV

As reported as early as 2014, PCMV/PRV significantly reduced the survival times of pig kidneys transplanted into baboons and cynomolgus monkeys [6, 7]. Kidneys infected with PCMV/PRV survived no longer than 14 days, whereas virus-free organs survived up to 53 days. Similarly, the absence of PCMV/PRV was a key factor in prolonging the survival time of orthotopic pig heart

Forum

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transplants in baboons: pig hearts infected with PCMV/PRV never lasted beyond 30 days, while virus-free transplants survived up to 195 days [8].

How, then, can the findings of Zhang et al. [5] be explained? False-negative PCR results may occur when the virus is no longer detectable in tested samples because it has entered latency, a hallmark of herpesviruses like PCMV/PRV [9]. Conversely, false-positive PCR results - such as the one from the donor animal whose recipient survived 225 days - are harder to interpret and are most likely due to contamination during PCR. Unfortunately, the PCR methodology was not described in detail in the abstract. Retesting could help resolve the discrepancies between Zhang et al.'s results [5] and previously published data [2, 6–8]. Additional immunological screening for antibodies against PCMV/PRV in donor pigs - a preferred method for detecting latent PCMV/PRV infection [9] - or testing recipient baboons for PCMV/PRV, as the virus should be present in all organs even after short survival times as shown by us [10], could also provide clarity. We would be happy to offer our expertise and methodologies to support these investigations.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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CONFLICT OF INTEREST

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

GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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ORIGINAL RESEARCH
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Indications and Long-Term Outcomes of Using Mycophenolate Mofetil Monotherapy in Substitution for Calcineurin Inhibitors in Liver Transplantation

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Switching the use of calcineurin inhibitors (CNIs), as basal immunosuppression in liver transplantation (LT) patients, for that of mycophenolate mofetil monotherapy (MMF-MT) is currently considered a good measure in recipients with chronic kidney disease (CKD) and other CNI-related adverse effects. We analyzed a retrospective cohort series of 324 LT patients who underwent long-term follow-up and were switched from CNI immunosuppression to MMF-MT due to CKD and other CNI-related adverse effects (diabetes, hypertension, infection). The median time on MMF-MT was 78 months. The indication for MMF-MT was CKD alone or associated with CNI-related adverse effects in 215 patients, diabetes in 61, hypertension in 42, and recurrent cholangitis in 6. Twenty-four (7.4%) patients developed non-resistant acute rejection post-MMF-MT, and 48 (14.8%) patients experienced MMF-related adverse effects, with MMF-MT withdrawn in only 8 (2.5%) patients. In the comparison between the pre-MMF-MT period and the last outpatient review, using a repeated measures model and taking each patient as its own comparator, we demonstrated a significant increase in GFR and significant decrease in creatinine and ALT values, remaining the other variables (diabetes, hypertension, and hematological and AST) within similar levels. Five-year survival post-MMF-MT conversion was 75.3%. MMF-MT significantly improved renal function, was well tolerated, and had a low rejection rate.

Keywords: mycophenolate mofetil, tacrolimus, cyclosporine, immunosuppression minimization, liver transplantation, chronic kidney dysfunction

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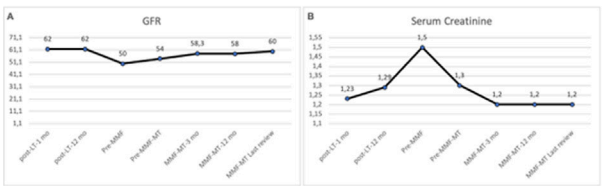
Abbreviations: ALT, alanine amino transferase; AST, aspartate amino transferase; BMI, body mass index; CKD, chronic kidney disease; CNI, calcineurin inhibitor; DBD, donation after brain death; GFR, glomerular filtration rate; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil; MT, monotherapy; MPA, mycophenolic acid.

Indications and long-term outcomes of using mycophenolate mofetil monotherapy in substitution for calcineurin inhibitors in liver transplantation

We analyzed a retrospective cohort series of 324 LT patients who underwent long-term follow-up and were switched from CNI immunosuppression to MMF-MT due to CKD and other CNI-related adverse effects. Twenty-four (7.4%) patients developed non-resistant acute rejection post-MMF-MT, and 48 (14.8%) patients experienced MMF-related adverse effects, with MMF-MT withdrawn in only 8 (2.5%) patients

Months from LT to MMF-MT initiation	67 (5-338)
Months on MMF-MT	78 (1-231)
Indications of conversion to MMF-MT	
CKD alone	88 (27.2%)
CKD + Hypertension	55 (17%)
CKD + Hypertension + Diabetes mellitus	46 (14.2%)
CKD + Diabetes mellitus	26 (8%)
Diabetes mellitus	61 (18.8%)
Hypertension	42 (13%)
Recurrent biliary infection	6 (1.8%)



Mycophenolate mofetil monotherapy improve significantly renal function showing good tolerance and low rates of rejection and mycophenolate mofetil withdrawal due to adverse effects.

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GRAPHICAL ABSTRACT |

INTRODUCTION

Currently, calcineurin inhibitors (CNIs) are the standard therapy for maintenance immunosuppression in patients who undergo liver transplantation (LT), with a preference for tacrolimus over cyclosporine [1]. However, CNI drugs are often associated with several adverse effects, such as: nephrotoxicity, chronic kidney disease (CKD), neurotoxicity, diabetes, arterial hypertension, cardiovascular complications, hyperlipidemia, hyperuricemia, hepatocellular carcinoma (HCC) recurrence, *de novo* malignancies and infections [2–7]. The use of tacrolimus is associated with improved renal function than the use of CyA [4], especially when a low dose of tacrolimus is combined with mycophenolate mofetil (MMF) [8–10]. Conversely, some immunosuppressive changes have been introduced to prevent or reduce the adverse effects related to CNIs, such as the minimization or substitution of CNIs for either MMF monotherapy (MT) or the mTORi-MT regimen [11–13]. The term "immunosuppression minimization" is defined as the lowest dose of immunosuppressive drugs compatible with a rejection-free state and the absence of clinically adverse effects [14, 15].

Mycophenolic acid (MPA) is the pharmacokinetically active product of MMF with potent inhibitory effects on *de novo* purine synthesis and T and B lymphocyte proliferation. Nevertheless, several adverse effects have also been associated with the use of MMF, such as myelotoxicity (anemia, leukopenia, and thrombocytopenia) and gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal pain, hemorrhage) [16–19], as well as teratogenicity [20]. Despite these drawbacks, switching from CNIs to MMF-MT is currently considered a good measure to improve kidney function in patients who develop post-LT CKD [16, 18, 19, 21–24], hypertension [16, 21, 22, 25], and diabetes mellitus [17, 22]. The presence of hypertension, with a prevalence of approximately 70% in LT patients, increases the risk of chronic kidney disease (CKD) and cardiovascular disease development and is associated with a higher mortality risk more than 1 year after LT [26].

The aim of this retrospective study is to describe our experience switching CNI immunosuppression to that with MMF-MT in LT patients who develop CNI-related adverse effects throughout a long-term follow-up. To our knowledge, this study is the largest single-center study reported using MMF-MT in LT patients.

PATIENTS AND METHODS

Population and Study Design

Between April 1986 and June 2022, we performed a total of 2,204 LTs at our institution. For this study, we recorded the data of 324 LT recipients among a total of 1,697 who underwent LT between January 1997 (the first patient included in MMF-MT) and June 2022 and were subsequently converted from immunosuppression with combined CNI-MT or CNI + MMF

to MMF-MT. In this retrospective single-center cohort study, we analyzed the impact of MMF-MT on toxicity or adverse effects (CKD, hypertension, diabetes mellitus, and recurrent biliary infection) in patients previously undergoing immunosuppression with CNIs and the incidence of rejection and adverse effects related to the use of MMF-MT.

The inclusion criteria for conversion from CNI-MT to MMF-MT were as follows: patients >18 years usually with more than 2 years of follow-up after LT, stable liver graft function and the absence of acute rejection in the last year before MMF-MT conversion. This study was closed on December 2023, and all patients were followed for at least 1.5 years after conversion to MMF-MT. Medical history of liver retransplantation, previous renal transplant, and hepatocellular carcinoma recurrence were considered exclusionary for this study. Informed consent for MMF-MT was obtained from all patients included in this study.

This research was performed in accordance with the ethical guidelines of the 1964 Helsinki Declaration and its later amendments and was approved by our Institutional Review Board (Research Registry no 24/025). The need for local clinical research ethics committee approval was waived because of the retrospective nature of the research.

Baseline Data

The following patient data were retrospectively collected: age, sex, body mass index (BMI), Child–Pugh and MELD scores, presence of arterial hypertension or diabetes, LT indications, pre-LT recipient laboratory values, type of donors and graft steatosis, type of CNI, rate and grade of post-LT acute rejection, median time elapsed from LT to initiation of MMF-MT and median time on MMF-MT, indications of conversion to MMF-MT, rate of post-MMF-MT acute rejection and therapy, adverse effects related to MMF-MT, causes of MMF-MT withdrawal, and the need for dialysis and kidney transplant during the follow-up of MMF-MT patients.

Determinations were taken of post-MMF-MT laboratory parameters (serum glucose, hematological, kidney and liver function values), doses of MMF and blood levels of MPA throughout the follow-up at different periods [pre-MMF-MT (combined CNI-MMF), 3, 6, and 12 months post-MMF-MT, and at the end of the study]. Comparisons between the variables (diabetes, hypertension, and hematological, kidney and liver function) of pre-MMF-MT patients and the final outpatient review of MMF-MT patients were performed. The sample was divided into two eras (first era: 1999–2011; second era: 2012–2023), that were compared regarding acute rejection, adverse effects, causes MMF-MT withdrawal and patient survival was performed between both groups of patients.

Variable Definitions

CKD was defined as a GFR <60 mL/min/1.73 m^2 or markers of kidney damage, or both, of at least 3 months in duration, and estimation of the GFR was performed according to the CKD-EPI equation [27]. Arterial hypertension was defined as a systolic blood pressure >140 mmHg and/or a diastolic blood pressure >90 mmHg on three consecutive measurements within three to 6 months [28]. A diagnosis of diabetes mellitus was established if fasting plasma glucose was ≥126 mg/dL or if 2 h plasma glucose levels were ≥200 mg/dL, according to the ADA criteria [29]. Anemia was defined as hemoglobin <8 g/dL; leukopenia was defined as a white blood cell count <2,500/mm^3; and thrombocytopenia was defined as a platelet count <60,000/mm^3. The diagnosis of acute rejection was performed by liver graft biopsy or empirically by alteration of liver function tests. Acute rejection was classified according to the Banff grades [30].

Immunosuppression

The initial immunosuppressive regimen comprised CNI (cyclosporine or tacrolimus) and steroids with or without MMF. Steroids were discontinued between 3 and 6 months post-transplantation. The dose of tacrolimus was adjusted to achieve target blood trough levels of 10–15 ng/mL for the first month, 7–9 ng/mL within the first year, 5 ng/mL between the 2nd and 4th years, and between 4 and 5 ng/mL thereafter. The dose of oral cyclosporine was adjusted to maintain blood trough levels between 200 and 300 ng/mL for the first month and between 150 and 200 thereafter.

In the presence of severe adverse effects associated with CNIs, such as renal dysfunction, diabetes, and hypertension, MMF was introduced to reduce CNI levels by half. Conversion from CNI to MMF-MT was performed on long-term follow-up recipients with stable liver function, starting at a dose of 500 mg of MMF twice daily, which was subsequently increased up to 1 g twice daily, followed by a gradual reduction in CNI until complete withdrawal. For patients on MMF-MT, MMF was administered at a dose capable of maintaining MPA levels between 2–4 ng/mL. Currently, the period from the introduction of MMF to CNI withdrawal is between 1 and 2 months, with posterior review in the outpatient clinic at 15, 30, and 90 days and routine follow-up every 6 months thereafter.

Patients on MMF-MT who showed liver dysfunction or biopsy-proven acute rejection grade I/II were initially treated with increasing doses of MMF (up to 1 g/12 h) to achieve MPA levels between 2–4 ng/mL or with 0.5–1 g of methylprednisolone intravenously for 3 days. Tacrolimus, cyclosporine or mTORi were reintroduced in cases of resistant acute rejection. In the presence of moderate-severe adverse effects, MMF was reduced or withdrawn and CNI was reintroduced. The dose of MMF was adjusted according to the protocol based on blood levels and liver function.

Statistical Analysis

Qualitative variables are expressed as absolute numbers, and relative frequencies are expressed as percentages. Associations were analyzed via the chi-square test or Fisher's exact test, when applicable. Most quantitative variables did not have a normal distribution according to the Kolmogorov–Smirnov test; therefore, all the quantitative variables are expressed as medians and percentiles and are expressed between 0 and 100. The relationships between quantitative variables were analyzed via the Mann–Whitney U test. A repeated measures model was used, taking each patient as its own comparator, in order to evaluate different key parameters pre and post MMF-MT.

TABLE 1 | Characteristics of recipients and donors converted from CNI to MMF-MT.

Pre-LT variables	n = 324
Age (yr)	55 (19–70)
Sex (M/F)	242/82 (74.7%/25.3%)
Body mass index	26.9 (14.5–46)
Child–Pugh score	
A	32 (9.9%)
B	166 (51.2%)
C	126 (38.9%)
MELD score	15 (6–35)
Hypertension	50 (15.4%)
Diabetes mellitus	79 (24.4%)
LT indications	
Alcoholic cirrhosis	150 (46.3%)
Hepatitis C virus cirrhosis	133 (41%)
Hepatocellular carcinoma	81 (25%)
Hepatitis virus B cirrhosis	43 (13.3%)
Pre-LT laboratory values of recipients	
Serum creatinine (mg/dL)	1.1 (0.5–1.9)
GFR (mL/min/1.73 m^2)	70.2 (36–111)
Serum glucose (mg/dL)	109 (81–290)
Bilirubin (mg/dL)	2.15 (0.9–41)
Na (mEq/L)	135 (128–144)
K (mEq/L)	4.3 (3–5)
Cholesterol (mg/dL)	136 (83–274)
Leukocytes/mm^3	5,100 (2,100–16,000)
Hemoglobin (g/dL)	12.6 (10–15.1)
Platelets/$mm^3 \times 10^3$	73 (20–243)
Type of donors	
Donation after brain death	289 (89.2%)
Donation after circulatory death	16 (4.9%)
Split-liver	9 (2.8%)
Living donor	7 (2.2%)
Pediatric	3 (0.9%)
Steatosis	
No	61 (18.8%)
Microsteatosis	75 (23.1%)
Macrosteatosis	138 (42.6%)
N/A	50 (15.4%)
Grade of macrosteatosis	
Mild (<30%)	101 (31.1%)
Moderate (30%–60%)	35 (10.8%)
Severe (>60%)	2 (0.6%)

GFR, glomerular filtration rate; MELD, model for end-stage liver disease.

TABLE 2 | Pre- and post-MMF-MT rejection, adverse effects and MMF withdrawal.

Post-LT CNI immunosuppression	
Tacrolimus-based	252 (77.8%)
Cyclosporine-based	72 (22.2%)
Post-LT acute rejection	113 (34.9%)
Number of episodes	
1	90 (27.8%)
≥2	23 (7.1%)
Grade of rejection	
I	47 (14.5%)
II	59 (18.2%)
III	7 (2.1%)
Months from LT to MMF-MT initiation	67 (5–338)
Months from MMF initiation to MMF-MT	18 (0–170)
Months on MMF-MT (last outpatient review)	78 (1–231)
Indications of conversion from CNI to MMF-MT	
CKD alone	88 (27.2%)
CKD + Hypertension	55 (17%)
CKD + Hypertension + Diabetes mellitus	46 (14.2%)
CKD + Diabetes mellitus	26 (8%)
Diabetes mellitus	61 (18.8%)
Hypertension	42 (13%)
Recurrent biliary infection	6 (1.8%)
Pre-MMF-MT (CNI immunosuppression)	
Tacrolimus + MMF	220 (67.9%)
Tacrolimus	8 (2.5%)
Cyclosporine + MMF	91 (27.8%)
Cyclosporine	5 (1.5%)
Post-MMF-MT acute rejection	24 (7.4%)
Diagnosis by liver biopsy	14 (4.3%)
Grade I	8 (2.5%)
Grade II	5 (1.5%)
Grade III	1 (0.3%)
Diagnosis by liver dysfunction	10 (3.1%)
Acute rejection therapy	
Tacrolimus	20 (6.2%)
Cyclosporine	1 (0.3%)
mTORi	3 (0.9%)
Adverse effects	48 (14.8%)
Diarrhea	18 (5.6%)
Vomiting	6 (1.9%)
Leukopenia	19 (5.9%)
Anemia	3 (0.9%)
Asthenia	2 (0.6%)
Causes of MMF-MT withdrawal	42 (12.9%)
De novo tumors	13 (4%)
Rejection	8 (2.5%)
Liver dysfunction (no liver biopsy)	6 (1.8%)
Liver retransplantation	4 (1.2%)
Kidney transplantation	3 (0.9%)
Adverse effects	8 (2.5%)
Diarrhea	5 (1.5%)
Leukopenia	3 (0.9%)

CKD, chronic kidney disease; CNI, calcineurin inhibitor; LT, liver transplantation; MMF-MT, mycophenolate mofetil monotherapy.

Survival analysis was performed via the Kaplan–Meier estimator and the log-rank test. A p value of <0.05 was considered to indicate statistical significance. Statistical analysis was performed via SPSS Statistics, version 25 (SPSS, Inc., Chicago, IL, United States).

RESULTS

Recipient and Donor Characteristics

From January 1997 to June 2022, a total of 1,697 patients underwent LT and were immunosuppressed with CNI. A group of 324 patients was initially treated with CNI standard immunosuppression (252 with tacrolimus-based and 72 with cyclosporine-based). The median recipient age was 55 (19–70) years, and the median MELD score was 15 (6–35). Alcoholic cirrhosis, hepatitis C virus (HCV) cirrhosis and HCC were the most frequent indications for LT.

Concerning pre-LT laboratory variables, the median serum creatinine value was 1.1 (0.5–1.9) mg/dL, and the median GFR was 70.2 (36–111) mL/min/1.73 m^2. Livers from donation after brain death (DBD) were used in 289 (89.2%) patients, and livers from donors with uncontrolled circulatory death (uDCD) were

used in 16 (4.9%) patients. The remaining characteristics of the recipients and donors are detailed in **Table 1**.

Pre- and Post-MMF-MT Characteristics

Immediately after LT, tacrolimus-based immunosuppression was used in 252 (77.8%) patients vs. the 72 (22.2%) who received cyclosporine-based immunosuppression. One episode of acute rejection after LT occurred in 90 (27.8%) patients, and two or more episodes in 23 (7.1%), with rejection grades I-II appearing in 106 (32.7%) patients.

The median time from LT to the initiation of MMF-MT was 67 (5–338) months, whereas the median time from the initiation of the combined MMF-CNI or CNI-alone regimen to CNI withdrawal and switch to MMF-MT was 18 (0–170) months. The overall median follow-up time of patients on MMF-MT was 68 (1–231) months.

The indication for switching from CNI to MMF-MT was CKD in 215 (66.4%) patients (CKD on its own in 88 patients and associated with hypertension in 55 patients, diabetes and hypertension in 46 patients, and associated with diabetes in 26 patients), diabetes mellitus on its own in 61 (18.8%) patients, hypertension in 42 (13%) patients, and recurrent biliary infection in 6 (1.8%) patients.

Just before shifting from tacrolimus to MMF-MT, 228 (70.3%) patients were on tacrolimus immunosuppression (associated with MMF in 220 patients and monotherapy in 8 patients), and 96 patients were on cyclosporine immunosuppression (associated with MMF in 91 patients and monotherapy in 5 patients).

Twenty-four (7.4%) patients experienced acute rejection after conversion from CNI to MMT-MT; 14 (4.3%) patients were diagnosed by liver biopsy (grade I/II in 13), and 10 (3.1%) were empirically diagnosed by liver dysfunction. All patients responded completely to rejection therapy (steroids and reintroduction of tacrolimus [20 patients], cyclosporine [1 patient], or mTORi [3 patients]). Forty-eight (14.8%) patients developed adverse effects related to MMF-MT, with the most common diarrhea (5.6%), vomiting (1.9%), and leukopenia (5.9%).

MMF-MT withdrawal was performed in 42 (12.9%) patients, due to *de novo* tumors in 13 (4%) patients (substitution of MMF-MT by mTORi monotherapy), biopsy-proven rejection in 8 (2.5%), liver dysfunction in 6 (1.8%), liver retransplantation in 4 (1.2%), kidney retransplantation in 3 (0.9%) and adverse effects in 8 (2.5%). With respect to side effects, MMF-MT withdrawal was performed in 5 (1.5%) patients with persistent chronic diarrhea despite a change from MMF to mycophenolate sodium salt and in 3 (0.8%) patients with leukopenia (**Table 2**). The remaining patients with adverse effects improved with a reduction in MMF dosage.

Dosage of MMF and Monitoring of MPA Levels Through Follow-Up

The dosage of MMF was adjusted according to MPA plasma levels, resulting in great variability among patients. The overall daily dose of MMF and median MPA plasma levels in patients on combined CNI-MMF therapy (just before conversion to MMF-MT) and in MMF-MT patients after 3, 6, and 12 months and at the last outpatient review (median period of 78 months) are detailed in **Table 3**, where it can be observed that MPA median plasma levels were similar in the pre-MMF-MT period or combined CNI-MMF [2.6 (0.1–15 ng/dL)] and at the last outpatient review [2.7 (0.2–15) ng/dL; $p = 0.527$].

Comparison of Characteristics Between Pre-MMF-MT and Final Review

The frequency of diabetes and hypertension and laboratory values of hematological, renal and liver function during long-term follow-up are shown in **Table 4**. In the comparison of the median values of variables between the pre-MMF-MT period (combined MMF-CNI or CNI alone) and the last outpatient review on MMF-MT (median of 78 months), only the median GFR value was significantly greater in the last review on MMF-MT [56 (15–126) mL/min/1.73 m^2 vs. 61 (7–134) mL/min/1.73 m^2; $p = 0.001$], whereas the frequency of diabetes and hypertension and laboratory values of hematological variables, serum creatinine and liver function (AST and ALT) did not show significant differences between the two periods (**Figures 1**, **2**). The 6 patients who were switched to MMF-MT due to biliary infection did not experience any new episodes of recurrent biliary cholangitis. On the other hand, using a repeated measures model, taking each patient as its own comparator, we found a statistically significant increase in GFR, statistically significant decrease in creatinine and statistically lower value of ALT at the last outpatient review in comparison with the pre-MMF-MT period (combined MMF-CNI or CNI alone) (**Table 4**).

Concerning comparison between both eras, we observed a significantly higher incidence of hypertension ($p = 0.019$) and diabetes mellitus ($p = 0.023$) before LT in the first era, and a significantly higher incidence of HCC ($p < 0.001$) in the second era, showing significant differences ($p < 0.001$) between the eras regarding indications of conversion to MMF-MT (**Table 5**).

The overall actuarial patient survival rates at 1, 3, 5, and 10 years after the onset of MMF-MT were 95.7%, 86.5%, 75.3%, and 54.6%, respectively (**Figure 3**). The actuarial patient survival rate at 1, 3, 5, and 10 years after the onset of MMF-MT were 93.8%, 82.3%, 70.1%, and 51.9%, respectively, in era 1, whereas in the second era patient survival rate was 97.9%, 91.8%, 80.9%, and 64.3%, respectively. ($p = 0.089$) (**Table 5**).

DISCUSSION

The use of CNIs within the first 12 months after LT is a risk factor for renal failure [31], with a cumulative incidence of advanced CKD (GFR ≤29 mL/min) of 8% at 1 year and 18.1% at 5 years [32]. Renal function should improve more notably when the CNI is completely withdrawn than when it is partially withdrawn [33–35]. The substitution of CNI drugs for MMF-MT has been indicated mainly to halt or improve CKD and other CNI-induced adverse effects [16, 18, 19, 21–23, 33–35]. Other less frequent indications for shifting to MMF-MT were neurological or

TABLE 3 | Overall daily doses of MMF and monitoring of MPA levels during follow-up.

MMF dose (mg/d)	Pre-MMF-MT (CNI-MMF)	MMF-MT (3-mo)	MMF-MT (6-mo)	MMF-MT (12-mo)	[a]MMF-MT (median: 78-mo) (last outpatient review)
500	8 (2.5%)	4 (1.2%)	2 (0.6%)	7 (2.2%)	7 (2.2%)
750	3 (0.9%)	4 (1.2%)	4 (1.2%)	8 (2.5%)	18 (5.6%)
1,000	101 (31.2%)	54 (16.7%)	47 (14.5%)	51 (15.7%)	110 (33.9%)
1,250	4 (1.2%)	15 (4.6%)	13 (4%)	20 (6.2%)	15 (4.6%)
1,500	68 (20.9%)	89 (27.5%)	78 (24.1%)	86 (26.5%)	60 (18.5%)
1,750	3 (0.9%)	11 (3.4%)	13 (4%)	12 (3.7%)	4 (1.2%)
2,000	100 (30.9%)	130 (40.1%)	139 (42.9%)	109 (33.6%)	99 (30.6%)
N/A	37 (11.4%)	17 (5.2%)	28 (8.6%)	31 (9.6%)	11 (3.4%)
MPA median levels (ng/mL)	2.6 (0.1–15)	3.3 (0.4–13)	3.3 (0.5–12)	3 (0.5–19)	2.7 (0.2–15)

[a]Comparison between MPA levels in the pre-MMF-MT period and the last outpatient visit (p = 0.527). CNI, calcineurin inhibitor; MMF-MT, mycophenolate mofetil monotherapy; MPA, mycophenolic acid.

TABLE 4 | Comparison of variables between the pre-MMF-MT period and last review[a].

Diabetes mellitus	OR	p	CI 95%
Pre-MMF-MT	1.387	0.569	0.450 to 4.276
Last review	1.869	0.117	0.525 to 15.537
Hypertension			
Pre-MMF-MT	0.429	0.179	0.395 to 1.249
Last review	0.376	0.416	0.239 to 2.723
Leukocytesx 10^3			
Pre-MMF-MT	−140	0.695	−842 to 5,617
Last review	310	0.389	399 to 1,016
Hemoglobin			
Pre-MMF-MT	0.299	0.347	−0.032 to 0.923
Last review	0.013	0.967	0.613 to 639
Platelets			
Pre-MMF-MT	492	0.938	0.118 to 12.836
Last review	467	0.460	0.772 to 17.071
AST			
Pre-MMF-MT	−4.015	0.084	8.575 to 0.545
Last review	−4.077	0.080	8.648 to 0.494
ALT			
Pre-MMF-MT	−8.817	0.001	−14.243 to 3.391
Last review	−12.295	0.000	−17.734 to 6.855
GFR			
Pre-MMF-MT	4.223	0.000	2.233 to 6.213
Last review	6.920	0.000	4.924 to 8.917
Creatinine			
Pre-MMF-MT	−0.418	0.009	−0.733 to −0.104
Last review	−0.375	0.020	−0.691 to −0.059

ALT, alanine amino transferase; AST, aspartate amino transferase; GFR, glomerular filtration rate; MMF-MT, mycophenolate mofetil monotherapy.
[a]Comparison between pre-MMF-MT and last review using a repeated measures model taking each patient as its own comparator.

cardiovascular complications, risk of tumor recurrence [19], and metabolic disorders [18]. The most frequent indications for LT in our series were alcoholic cirrhosis, HCV, hepatitis B virus (HBV) and HCC, and tacrolimus was the most commonly used immunosuppressor, with an overall rate of acute rejection of 34.6% after LT. As in other reported studies [2–7], the main reasons for conversion from CNIs to MMF-MT in our study were the presence of CKD on its own or in association with diabetes or arterial hypertension and other adverse effects related to the use of CNIs, such as the presence of isolated diabetes, hypertension, or recurrent biliary infection.

Some researchers are reluctant to switch CNIs for MMF-MT in patients with previous history of graft rejection using CNIs [34], but the usual practice of other researchers is to switch CNI for MMF-MT in patients in the absence of acute rejection for 6–15 months before conversion [16, 17, 19, 36], the presence of stable liver function [16, 17, 21], and the absence of anemia, leukopenia and thrombocytopenia [36].

According to several studies, the time elapsed from LT to the onset of MMF-MT was between 27–81 months [16, 17, 19, 21, 22, 37–39], whereas in our experience, it corresponded to a median period of 72 months. The period of conversion from MMF-CNI to CNI withdrawal and the initiation of MMF-MT has been reported to last from 2 weeks to 9 months [16–19, 21, 25, 37, 40]; to 19 months in our experience. However, following our long-term experience, our period from the introduction of MMF to complete CNI withdrawal has been reduced to 1–2 months, with routine follow-up at 15, 30, and 90 days to detect occasional acute rejection or adverse effects.

The mean follow-up period of several studies of patients on MMF-MT is between 12 and 48 months [16–19, 21, 22, 38, 39], whereas our median follow-up time for patients on MMF-MT has reached 78 months.

Conversion from CNIs to MMF-MT is usually performed with an initial dose of 500 mg/12 h, reaching a dose of 1 g/12 h for 2–4 weeks simultaneously with a gradual reduction in CNI, usually by 25% at a time, until complete withdrawal [16, 17, 23, 25, 35]. Several authors have advised on maintaining MPA plasma levels between 1 and 3.5 ng/mL [41] or between 2 and 4 ng/mL, adjusting the MMF dosage according to the degree of renal dysfunction and monitoring of MPA plasma levels [21, 35, 39, 42, 43] because impaired renal function is correlated with a decrease in the clearance of MPA metabolites, which consequently increases the plasma concentration of MPA metabolites and augments immunosuppression [44]. Although MMF-MT may be a risk factor for liver rejection [45], we agree with other experiences that monitoring MPA levels can improve the management of immunosuppression [46] and may even limit the risk of rejection or drug toxicity [19, 23, 38, 45]. Thus, with MPA level monitoring, we adjusted the MMF doses between 500 and 2,000 mg/d to obtain

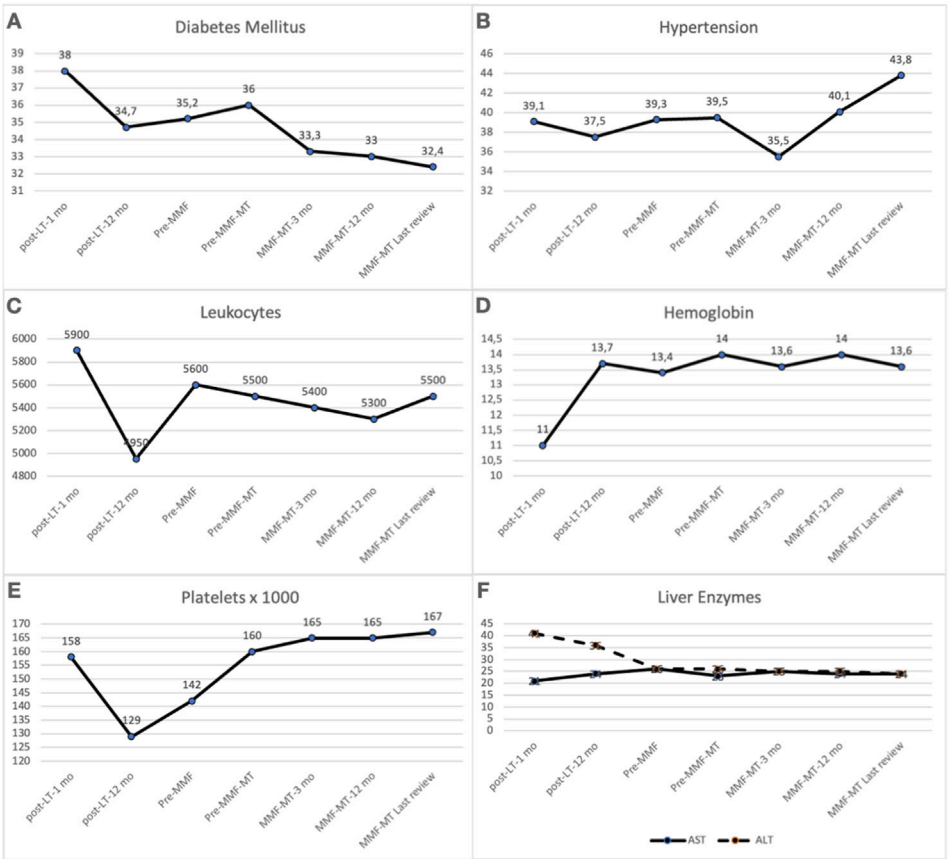

FIGURE 1 | Comparison between the pre-MMF-MT period (combined MMF-CNI or CNI alone) and the final period of MMF-MT (last outpatient review) regarding the frequency of diabetes mellitus **(A)** ($P = 0.603$) and hypertension **(B)** ($P = 0.141$) and the median values of leukocytes **(C)** ($P = 0.391$), hemoglobin **(D)** ($P = 0.115$), platelets **(E)** ($P = 0.210$), AST **(F)** ($P = 0.471$) and ALT **(F)** ($P = 0.106$). *ALT, alanine amino transferase; AST, aspartate amino transferase; CNI, calcineurin inhibitor; GFR, glomerular filtration rate; MMF-MT, mycophenolate mofetil monotherapy.

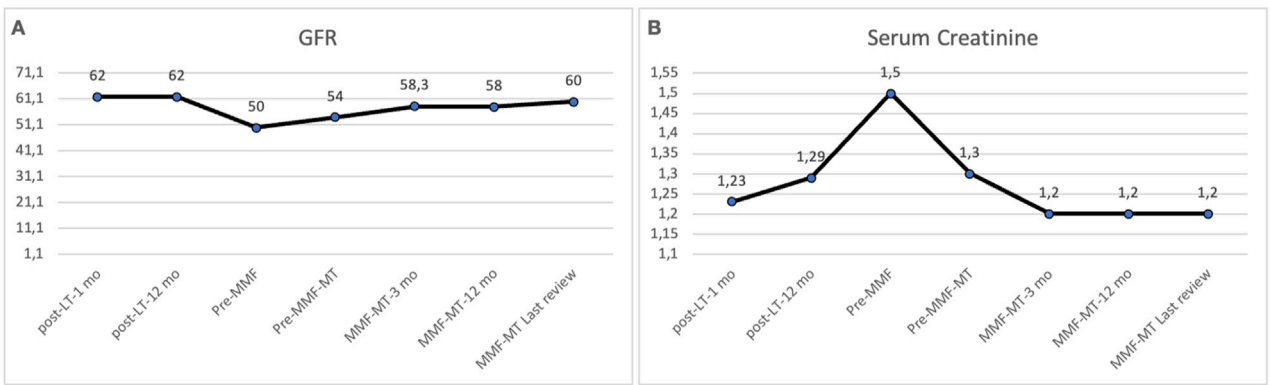

FIGURE 2 | Comparison of renal function between the pre-MMF-MT period (combined MMF-CNI or CNI alone) and the final period of MMF-MT (last outpatient review). The median values of the GFR **(A)** increased significantly at the end of the study (56.5 mL/min/1.73 m^2 vs. 61 mL/min/1.73 m^2; $p = 0.001$). The median serum creatinine **(B)** value decreased at the end of the study, but the difference was not statistically significant ($p = 0.112$). *CNI, calcineurin inhibitor; GFR, glomerular filtration rate; MMF-MT, mycophenolate mofetil monotherapy.

TABLE 5 | Results according to eras of LT recipients converted from CNI to MMF-MT.

	First Era (1999–2011) (n = 161)	Second Era (2012–2023) (n = 163)	*P*
Age (yr)	54 (22–70)	56 (19–70)	
Sex (M/F)	111(68.9%)/50 (31.1%)	131 (80.4%)/32 (19.6%)	0.018
Hypertension	33 (20.5%)	17 (10.4%)	0.019
Diabetes mellitus	32 (19.9%)	47 (28.8%)	0.023
MELD Score	15 (7–23)	15 (6–35)	
LT indications			
Alcoholic cirrhosis	67 (41.6%)	83 (50.9%)	0.093
Hepatitis C virus cirrhosis	63 (39.1%)	70 (42.9%)	0.485
Hepatocellular carcinoma	24 (14.9%)	57 (35.4%)	<0.001
Hepatitis virus B cirrhosis	24 (15%)	19 (11.7%)	0.388
Steatosis			0.062
No	24 (14.9%)	37 (22.7%)	
Microsteatosis	42 (26.1%)	33 (20.2%)	
Macrosteatosis	71 (44.1%)	67 (41.1%)	
N/A	24 (14.9%)	26 (15.9%)	
Indications of conversion from CNI to MMF-MT			<0.001
CKD alone	42 (26.1%)	46 (28.2%)	
CKD + Hypertension	18 (11.2%)	37 (22.7%)	
CKD + Hypertension + Diabetes mellitus	30 (18.6%)	16 (9.8%)	
CKD + Diabetes mellitus	10 (6.2%)	16 (9.8%)	
Diabetes mellitus	26 (16.1%)	35 (21.5%)	
Hypertension	31 (19.2%)	11 (6.7%)	
Recurrent biliary infection	4 (2.5%)	2 (1.2%)	
Post-MMF-MT acute rejection	11 (6.8%)	13 (7.9%)	0.694
Diagnosis by liver biopsy	6 (3.7%)	8 (4.9%)	
Grade I	3 (1.8%)	5 (3.1%)	
Grade II	2 (1.2%)	3 (1.8%)	
Grade III	1 (0.6%)	0 (0%)	
Diagnosis by liver dysfunction	5 (3.1%)	5 (3.1%)	
Adverse effects	26 (16.1%)	22 (13.5%)	0.667
Diarrhea	7 (4.3%)	11 (6.7%)	
Vomiting	4 (2.5%)	2 (1.2%)	
Leukopenia	13 (8.1%)	6 (3.7%)	
Anemia	1 (0.6%)	2 (1.2%)	
Asthenia	1 (0.6%)	1 (0.6%)	
Causes of MMF-MT withdrawal	26 (16.1%)	16 (9.8%)	0.460
De novo tumors	11 (6.7%)	2 (1.2%)	
Rejection	4 (2.5%)	4 (2.4%)	
Liver dysfunction (no liver biopsy)	3 (1.9%)	3 (1.8%)	
Liver retransplantation	2 (1.2%)	2 (1.2%)	
Kidney transplantation	2 (1.2%)	1 (0.6%)	
Adverse effects	4 (2.5%)	4 (2.4%)	
• Diarrhea	3 (1.9%)	1 (0.6%)	
• Leukopenia	1 (0.6%)	3 (1.8%)	
Actuarial patient survival after MMF-MT			0.089
1-y	93.8%	97.9%	
3-y	82.3%	91.8%	
5-y	70.1%	80.9%	
10-y	51.9%	64.3%	

median MPA levels between 2.5 and 3.3 ng/mL, maintaining 135 (38.6%) patients without rejection on a dose ≤1,000 mg/d of MMF at the last outpatient review. The monitoring of MPA levels allows the minimization of immunosuppression and prevents MMF-related adverse effects. However, AUC is considered the goal standard for measuring MPA levels [47], although in our experience it has been very impractical owing to the time and number of determinations it requires, especially among our high volume of patients, many of whom do not live in our city. Therefore, due to its simplicity and the need for only one determination per visit, it was decided in our center to use MPA levels.

Due to the mentioned risk of acute rejection, it is advisable to not attempt MMF-MT in poor MMF absorbers, which have been defined as patients with MPA levels <0.5 ng/mL after daily intake of ≥1,000 mg/d MMF or MPA levels <1 ng/mL after daily intake of 1,500 mg/d [48].

Substitution of CNIs by MMF-MMF has been associated with a rate of acute rejection ranging from 4% to 21.4% [16–19, 21, 22, 25, 37, 38, 48, 49]. Our rate of acute rejection was 7.4%, and as other researchers [23] have reported, diagnosis was performed either by liver biopsy or empirically by alteration of liver function. All our patients with acute rejection responded successfully with

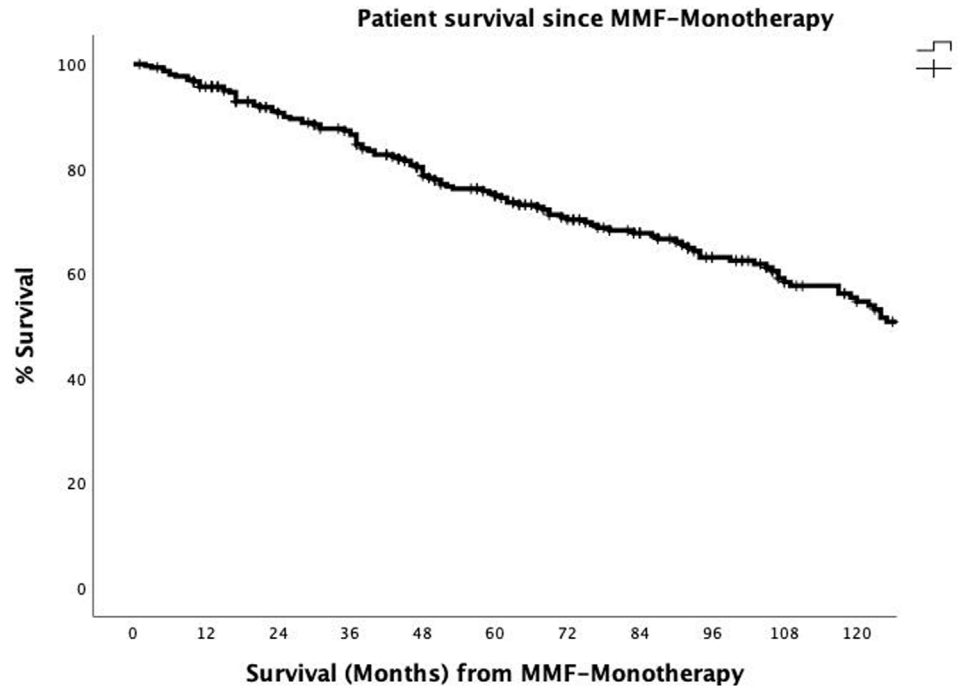

FIGURE 3 | The actuarial patient survival rates after conversion from CNI immunosuppression to MMF-MT (mycophenolate mofetil monotherapy) at 1, 3, 5, and 10 years were 95.7%, 86.5, 75.3%, and 54.6%.

steroids and/or reintroduction of CNI or mTORi monotherapy, and no patients developed chronic rejection. However, late acute liver rejection can occur, and close follow-up during the first year after MMF-MT is advised, as has been previously reported [33].

The development of adverse effects is frequently related to MPA plasma levels higher than 4 ng/mL [41]. There is great variability in MMF-MT-induced side effects, ranging from an incidence between 4.3% and 57% [16, 17, 19, 21, 25, 37], although they are usually controlled by a reduction in the MMF dose [16, 18, 21, 35, 43], with the need for MMF-MT withdrawal in only 2%–11.8% of patients who show gastrointestinal symptoms, pancytopenia or pruritus [17, 19, 22, 25, 39]. In addition, gastrointestinal adverse effects can be improved by switching from MMF to enteric-coated mycophenolate sodium [50, 51]. In our study, 48 (14.8%) patients developed MMF-MT-induced adverse effects, but conversion to CNI was only performed in 8 (2.5%) patients due to failure to control severe diarrhea with enteric-coated mycophenolate sodium or leukopenia. The remaining adverse effects of patients improved when the dose of MMF decreased without the need to return to CNIs. Other reasons for MMT-MT withdrawal in our experience were the presence of *de novo* tumors (13 patients), biopsy-proven rejection or liver dysfunction (14 patients), liver retransplantation (4 patients) and kidney transplantation (3 patients).

Serum creatinine levels improved significantly in between 78.6% and 89% of the patients who were converted from CNIs to MMF-MT [16, 21, 25]. Similarly, replacement of CNIs with MMF-MT significantly increased the mean value of the GFR in patients with CKD [18, 19, 21, 22]. In our study, the comparison between the median values of the GFR in the pre-MMF-MT (CNI therapy) period and the last outpatient control, with a median value of 78 months between the two periods, revealed a significantly greater value of the GFR in the last control (56.5 vs. 61 mL/min/1.73 m^2). The median serum creatinine value also improved at the last outpatient visit, but the difference was not statistically significant. However, when a repeated measures model was used taking each patient as its own comparator a significant increase of GFR and a significant decrease of serum creatinine and ALT values were demonstrated not showing significant differences regarding the rates of diabetes, hypertension, and values of hematological variables and AST.

In addition, the rates of diabetes mellitus and hypertension and the median values of hematological parameters (hemoglobin, leukocytes and platelets), serum glucose and liver transaminases did not significantly differ between the two periods. Notably, the 6 patients who were converted to MMF-MT due to recurrent cholangitis did not experience any more infection episodes after conversion. Five-year patient survival after conversion from CNI to MMF-MT was reported to be between 70% and 90% in 3 studies [19, 23, 35], and our 5-year patient survival rate was 75.3%. In the comparison of the results after conversion to MMF-MT in both eras we did not find significant differences regarding to the rates of acute rejection, adverse effects and causes of MMF-MT withdrawal, finding a higher patient survival rate in the second era, although statistically unsignificant.

This study has several limitations, such as its retrospective nature, long duration, and single institution design; consequently, it is subject to bias. Future multicenter prospective randomized studies with large samples are necessary to confirm our results.

In conclusion, MMF-MT can be safely used in LT patients with CNI-related adverse effects, such as CKD, hypertension, diabetes and biliary infection. Monitoring of MPA levels allows the reduction of the MMF dose and its adverse effects. The acute rejection rate was low, with a good response to CNI reintroduction or mTORi therapy, and the GFR, creatinine and ALT transaminase improved significantly through long-term follow-up. Comparison of the results between 2 eras did not show significant differences. A good tolerance of MMF-MT and a low rate of MMF-MT withdrawal have been shown.

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

This study was approved by the institutional review board (approval number 24/025) and was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent participate in this study was not required due to the retrospective nature of the study.

AUTHOR CONTRIBUTIONS

Study conceptualization and design (CJ-R, IJ, AMQ, and AMM). Acquisition of data (all authors). Data analysis (CJ-R, IJ, AMQ, OC, CL, FC, and CM-A). Data interpretation (CJ-R, IJ, AMQ, AMM, AG-S, JC, CL, CM-A, and AN). Writing of the original draft (CJ-R, IJ, and AMQ). Reviewing and editing (all authors). Supervision (CJ-R, IJ, and AMQ). All authors approved the submitted version.

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CONFLICT OF INTEREST

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

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.13790/full#supplementary-material

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REVIEW
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Heart Transplantation and Donation After Circulatory Death in Children. A Review of the Technological, Logistical and Ethical Framework

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Heart transplant for adults following Donation after Circulatory Death (DCD) is well established in many parts of the world, including the United Kingdom (UK). Small child DCD hearts have now been recovered in the UK and internationally utilising novel technologies. Despite these recent advances, extension of this practice to pediatric cardiac transplantation has been slow and difficult despite the severe shortage of donors for children leading to a high number of deaths annually of children waiting for heart transplant. This is in direct contrast with the thriving UK programme of adult DCD heart transplant and pediatric DCD donation for non-cardiac organs. There has been insufficient action in addressing this inequality thus far. Barriers to development of a pediatric cardiac DCD programme are multifaceted: ethical concerns, technological paucity, financial and logistical hurdles. We describe the background, live issues, current developments and how we are driving resources toward a sustainable DCD programme for small children in the UK to provide valuable insights to other countries of the elements and principles at play. This is a call to responsible bodies to take urgent and achievable actions to establish an equitable paediatric DCD cardiac programme for donors, recipients and their families.

Keywords: pediatric organ donation, pediatric heart transplantation, donation after circulatory death (DCD), hypothermic organ perfusion, *ex-situ* heart perfusion

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INTRODUCTION

Controlled donation after circulatory death (DCD) is a well-established practice in the United Kingdom (UK), now accounting for 46% of all deceased donor organs. Since the year 2000, the UK has carried out over 8000 DCD donations providing for over 20,000 recipients [1]. In 2015, the UK was one of the first nations to commence cardiac DCD transplantation and has performed almost 300 heart transplants from

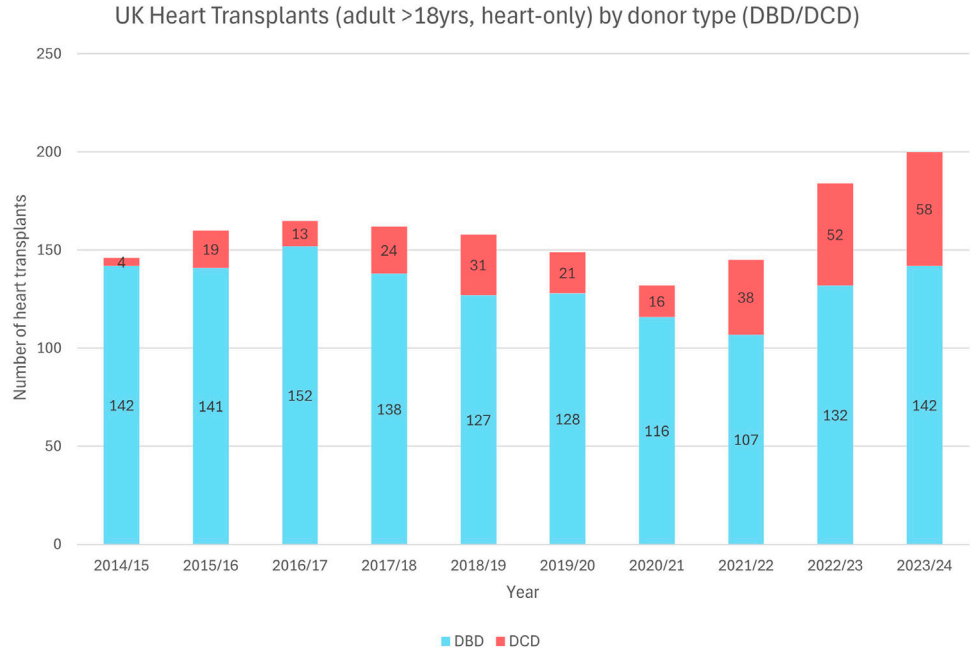

FIGURE 1 | UK heart transplantations (adult >18 years, heart alone) by donor type (DBD/DCD) demonstrating the increasing DCD heart utilization in adults over the past decade (2014–2024).

DCD donors (see **Figure 1**) with recipient outcomes comparable to those following Donation after Brain Death (DBD) transplantation [2–4]. Last year, 29% of UK adult heart transplants were made possible by DCD donation and this has given rise to a year-on-year increase in the total number of heart transplants performed [1].

So, what of children? Since commencing in 2013, a total of 200 children (<18 years) in the UK have become DCD donors contributing at least 1 transplantable organ, accounting for almost 40% of UK pediatric donations [1]. However, Paediatric DCD heart donation and transplantation remains a rare event. Only 28 of the 297 UK DCD heart transplants have occurred in recipients <18 years, exclusively in older children and adolescents. Meanwhile, each year, 10–15 children die waiting for a heart in the UK [1]. The DCD pediatric donor pool, accessible for children of any size awaiting liver and kidney, remains inaccessible to small children in need of a heart. Waitlist mortality remains excessively high, in part due to current barriers to smaller DCD heart donors.

We seek here to examine the present technological, logistical and ethical obstacles to achieving a functional cardiac DCD program in children and provide a synopsis of the ethical, clinical and legal framework that already exists to provide the solution to these obstacles. We hope to encourage progress in our own country and provide valuable insight to others considering a cardiac DCD pediatric program.

PAEDIATRIC CARDIAC DONATION

Over the past decade, although paediatric DBD donors have reduced in numbers overall, the proportion of DBD hearts retrieved has increased (**Figure 2A**). The majority of paediatric DBD donations include cardiac, demonstrating a willingness from donor families to donate the heart. Conversely, paediatric DCD organ donations rarely include the heart, and numbers have remained low since the introduction of the paediatric DCD cardiac retrieval in 2017 (**Figures 2A, B**) [1].

As yet, pediatric DCD cardiac donation remains an uncommon occurrence with only fifteen children <16 years old donating DCD hearts (**Figure 3**) [1]. These children were predominantly adolescents with a median donor weight of 60 kg (IQR 50–70 kg). The leading restriction is that the *ex-situ* normothermic preservation technology used in the UK–the Organ Care System (TransMedics OCS™) – only permits DCD heart retrieval from donors >50 kg which excludes most children from DCD heart donation. The practice of size mismatching enables a 20 kg child to receive a heart from a 50 kg DCD donor, but smaller children are acutely disadvantaged by the donor weight criteria.

Adult data shows that enabling DCD cardiac donation can add significantly to the organ pool (**Figure 1**). **Figures 2A**, **B** suggest there have been a significant number of missed opportunities for heart donation from DCD donors, particularly in the younger age categories.

It is not possible to determine the number of true potential heart donors from this retrospective cohort. Historically, DCD cardiac donation has not been explored in children <50 kg due to lack of technology to retrieve the heart. As such many potential donors did not undergo echocardiography to determine organ suitability, nor were families approached for consent for heart recovery. One could assume that since families consented to

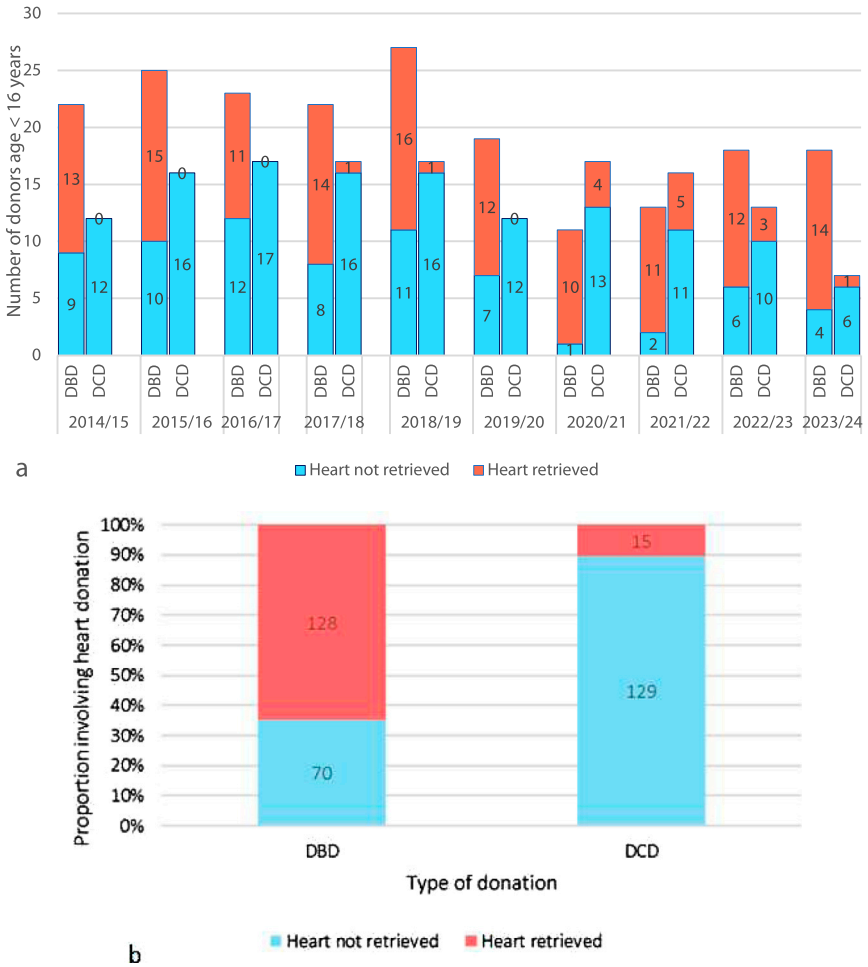

FIGURE 2 | (A) An annual breakdown of the past decade of UK pediatric (aged <16 years) solid organ donors by donor type (DBD/DCD) and categorized into heart retrieved and heart not retrieved. **(B)** Total number of DBD and DCD pediatric donors (<16 years) in the past 10 years (2014–2024) categorized into heart retrieved and heart not retrieved) [1].

donation of other organs, then a number of these DCD donors, represented by blue on **Figures 2A**, **B**, may have fulfilled criteria of consent, organ condition and ischemic time. A potential cardiac donor represents a missed opportunity for both donor and recipient patients and their families.

WHAT IS THE CLINICAL NEED?

At any given time, there are 40–50 children waiting for a heart-alone transplant in the two national centres across the UK (Freeman Hospital, Newcastle; Great Ormond Street Hospital London – FRH/GOSH). 40% of these children are below 25 kg and therefore unsuitable for DCD hearts utilising TransMedics OCS™.

Many of these children are supported mechanically by ventricular assist devices which require the smaller child to remain an inpatient whilst waiting for an organ. Children on these devices are vulnerable to death, stroke, infection, organ failure and chronic pain. Psychosocial disruption for the child, parents and siblings is frequent. Financial costs to the National Health Service are very high. The median waiting period for a heart is 193 days (95% CI 158–258), with younger children waiting the longest [1]. The significant limiting factor for transplantation is the shortage of organs and consequently, 25% of children will die whilst awaiting an organ [1]. Furthermore, in the current climate of organ scarcity, the more complex transplant candidates are denied access to listing as well as mechanical support due to negligible chance of ever being transplanted.

The clinical need exists not only in the realm of the recipient, but also in that of the donor. Organ donation brings a unique opportunity to find meaning in bereavement. Donations which are unable to proceed can bring disappointment to families [5, 6]. Many families gain comfort from knowing that their child's death gave life to another child. Whilst most donor families do not meet their recipient, some do and report joy at hearing their child's heartbeat again [7]. The heart, as is well recognised, has a special emotional significance for many.

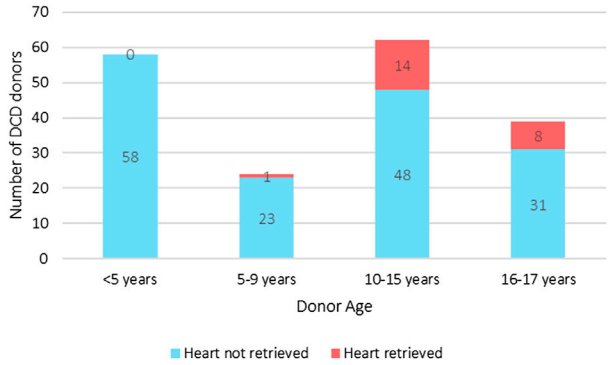

FIGURE 3 | UK pediatric DCD all solid organ donation with and without heart retrieval, and heart donation categorized by age groups (2014–2024). The median weight of the heart donors was 60 kg (IQR 50–70 kg) [1].

THE HISTORY OF PEDIATRIC DCD HEART TRANSPLANTATION

The first human heart transplanted by Christiaan Barnard in 1967, was from a DCD donor. After the establishment of brain-death criteria in 1968, virtually all donor hearts for the next 36 years were recovered from DBD donors until the beginning of the next millennium when DCD, or "non-heart beating donation" as it was known at the time, gained new interest.

In 2004, teams in Denver, Colorado performed three DCD infant heart transplants with 100% survival [8]. The circumstances surrounding the diagnosis of death ignited controversy and stimulated necessary robust debate on how donor death is determined [9].

It was subsequently shown, in large animal models, that even after the obligatory warm ischaemic insult during the standard DCD donation process, reperfusion of the retrieved *ex-situ* heart with oxygenated blood could provide transplantable organs [10].

In 2014, modern adult cardiac DCD transplantation commenced in Sydney with the use of direct recovery and reperfusion with oxygenated blood via *ex-situ* normothermic preservation utilising the TransMedics OCS™. The UK followed suit in 2015, led by the Papworth team and included a small number of older adolescents [11]. In 2019, clinical ethics panels from the two UK pediatric cardiac centres convened to discuss and approve cardiac DCD in children, and from 2020, children have been both cardiac DCD donors and recipients utilising the OCS (within the weight limitation of >50 kg) [12].

The process of DCD organ recovery, including withdrawal of life-sustaining treatment (WLST), stand-off period and limitations on functional warm ischemia are identical for children as for adults and are clearly outlined in **Figure 4**.

In the past 5 years, teams across the globe have worked on advancing the technological options for supporting and expanding pediatric cardiac DCD donation [13–16]. There are now viable technologies to support the hearts of <50 kg donors with techniques of Normothermic Regional Perfusion *in situ* (NRP) and Hypothermic Oxygenated Perfusion *Ex-situ* (HOPE) having both been adopted internationally to permit cardiac DCD retrieval [13–22].

UK transplant centers seeking approval for these techniques have encountered previously resolved ethical concerns. These concerns, amidst other barriers which we seek to highlight in this paper, are preventing life-saving transplants from going ahead and need to be urgently resolved.

WHAT ARE THE CURRENT BARRIERS TO CARDIAC DCD IN PAEDIATRICS IN THE UK?

It is widely acceptable, and medically feasible, for a child to receive a DCD donated heart, yet there are barriers when it comes to children becoming cardiac DCD donor. These barriers fall under three main categories: technological, resource and logistics, and ethical.

Introduction of New Technologies

It is important to clarify that pediatric hearts are already being donated in the UK with the use of Direct Retrieval (DR) and normothermic *ex-situ* perfusion using the Transmedics OCS™. This technology is not able to perfuse hearts from donors <50 kg and consequently, due to permissible weight mismatching, for recipients >20 kg. The small-donor advancing field is focused on three alternative strategies: DR followed by *ex-situ* normothermic perfusion, DR followed by Hypothermic Organ Perfusion *Ex-situ* (HOPE), and *in situ* Thoraco-Abdominal Normothermic Regional Perfusion (TA-NRP).

Normothermic *Ex-Situ* Perfusion

The OCS™ is available for DCD heart recovery in donors >50 kg, with the main limiting factors being the aortic connector and concerns of perfusion pressure in smaller hearts. This system is utilised following DR for all DCD heart retrieval in the UK presently, including those of child donors >50 kg with excellent outcomes [4, 23, 24].

In the drive to extend normothermic *ex-situ* perfusion to the child population, a collaboration between Royal Papworth Hospital and Great Ormond Street Hospital has resulted in "The mOrgan™" (**Figure 5**). This technology allows retrieval of any size heart down to a donor of 3 kg. Significant steps have been made toward operationalising the use of this device. Although experimental, this device was approved by regulatory bodies in March 2022 for a named patient on compassionate grounds. The named patient received 5 offers of hearts from pediatric DCD donors <40 kg, although none were suitable primarily due to logistics. Before a suitable DCD donor was identified, the child received a DBD donor heart. Despite clinical need and enthusiasm, the use of the mOrgan™ has not yet expanded beyond this case due to ongoing regulatory challenges, although a clinical trial is planned. To date, there are no published pre-clinical or clinical data for this device. Given the notable success of normothermic technology in the adult cardiac DCD programme, there is great enthusiasm for the potential the mOrgan offers to children.

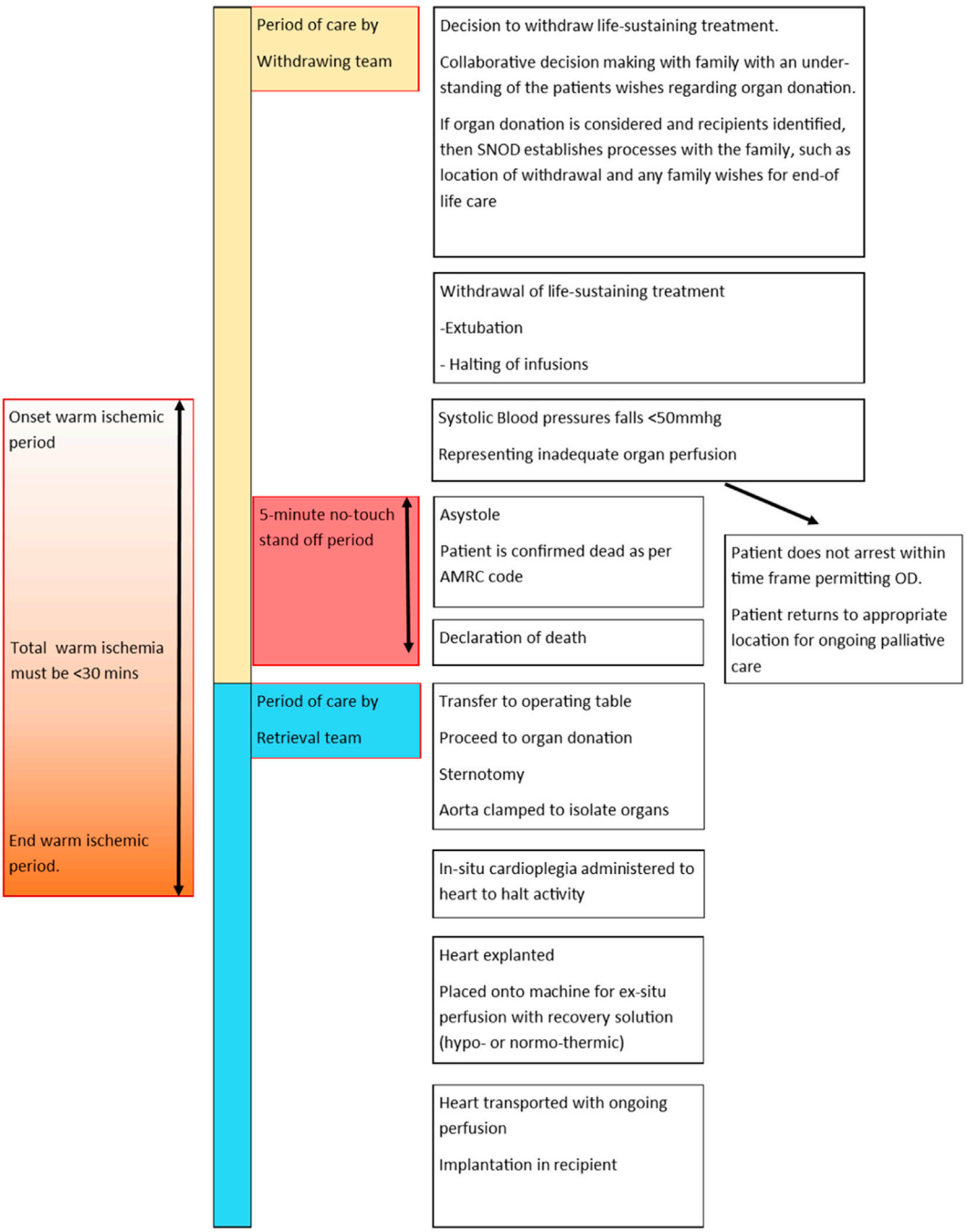

FIGURE 4 | An infographic tracking the process of donation by circulatory death. In the UK a five-minute stand-off period is required following asystole. Recovery of the heart requires a functional warm ischemic time (from SBP<50 mmg or age-dependent pediatric equivalent) to onset of cardioplegia) to be less than 30 min.

Hypothermic Organ Perfusion *Ex-Situ* (HOPE)

Concurrently, the Newcastle team have been working toward utilising technology which permits the retrieved DCD heart to be re-perfused via Hypothermic Organ Perfusion Exsitu (HOPE) utilising the XVIVO Heart Assist Transport™ (**Figure 5**) [25, 26]. The XVIVO™ has been used on compassionate grounds for small child donors in the UK in both DBD and DCD pathways.

This approach uses small quantities of bank blood incorporated into a hyper-osmolar, potassium-rich hypothermic solution. It is thought that the avoidance of donor blood, together with low pressure allowed by the hypothermia avoids progressive myocardial oedema. Following cardiac DCD, continuous HOPE of the *ex-situ* donor heart is initiated.

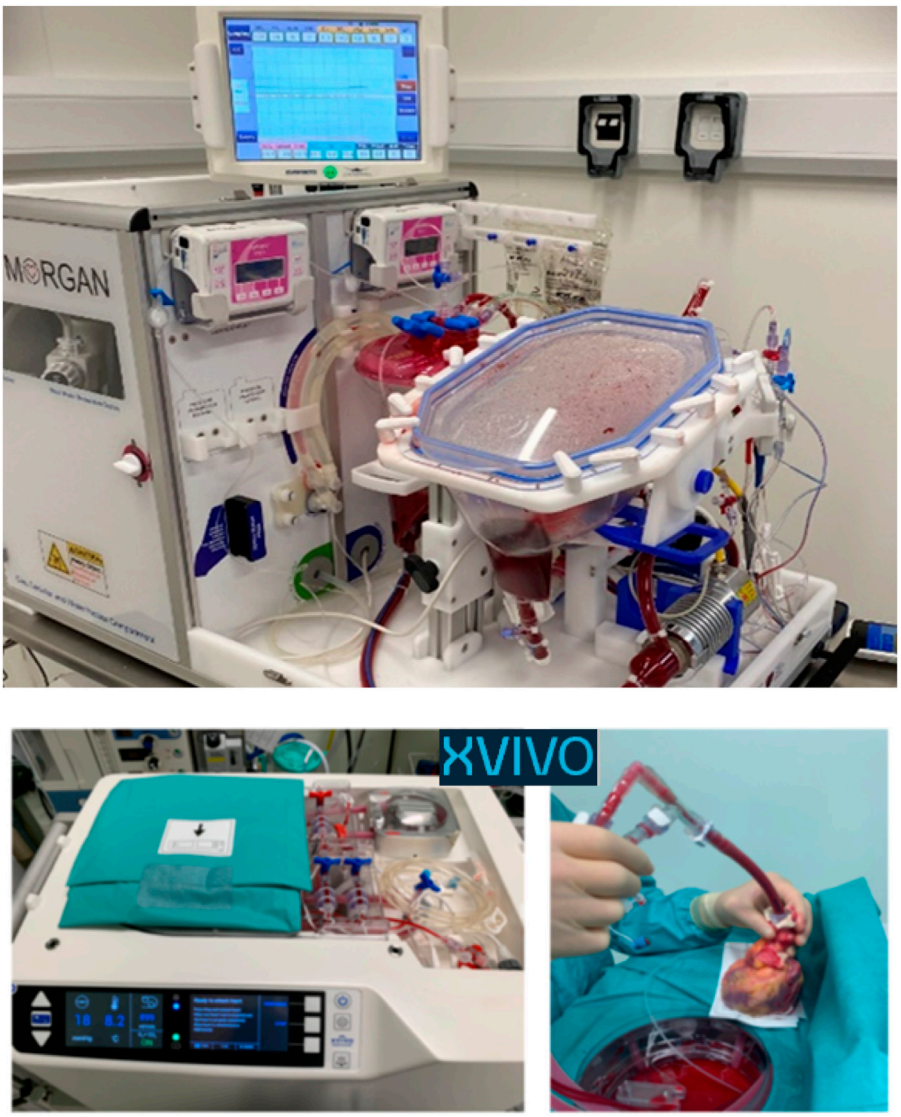

FIGURE 5 | The two *ex-situ* perfusion technologies currently available to facilitate child DCD heart donation. The mOrgan utilizes normothermic continuous perfusion, and the XVIVO utilizes hypothermic continuous perfusion. Both devices are unlicensed and applications for their use have been under compassionate waiver.

Pre-clinical animal and human studies demonstrated restoration of metabolic performance and successful DCD heart transplantation with XVIVO™ [25, 27]. In the pre-clinical human studies, function of the DCD heart and biochemical normalisation of energy stores after reperfusion was comparable to the DBD heart [25]. Importantly, the animal studies compared DR + HOPE against NRP + HOPE, and NRP followed by cold static storage. The DR + HOPE had the best outcome, with better function than NRP followed by HOPE [27]. This may reflect the advantage of the initial perfusion being with hypothermic (8°C) blood and the avoidance of donor blood with associated cytokine and complement activation [28].

HOPE has been utilised to maintain prolonged perfusion, up to 12 h in DBD hearts with great success [29–31]. Additionally, the corresponding author reports using XVIVO for a small child DBD heart preservation (donor 15 kg) for 291 min perfusion with excellent clinical outcome following transplantation [26].

The Belgium group have published three cases of successful adult DCD heart transplant using XVIVO™ with excellent short-term outcomes [32]. In their ongoing programme, eight cases have been performed, including one adolescent case, with 100% 30-day survival (personal communication). Whilst the data for HOPE in DCD hearts appears promising, the early limitation was the size of the cannula. A collaboration between the Newcastle team and XVIVO led to development of a 14 mm cannula extending the opportunity to donate to small children and even infants.

Subsequently, in November 2024, humanitarian approval was given for a small child as the first UK DCD heart retrieval utilising direct procurement and XVIVO technology for recovery (lead clinician, corresponding author LK). Case reporting of this single case is pending, however early clinical outcomes are excellent with preserved ventricular function, no mechanical support requirement and full functional recovery of the child.

Since the XVIVO™ holds the heart in cold, static diastole with continuous low-pressure oxygenated perfusion, there is limited potential for ongoing assessment during perfusion. On the OCS™ or mOrgan™, the heart can be seen beating and serial lactate measurements can be performed. Whilst it is not possible to see the heart beating on XVIVO™, it is possible to measure lactate – the significance of which is debated. It is a poor predictor of cardiac function [33], particularly within a metabolically isolated organ [34]. There are similar questions regarding the validity of measuring function by eye-balling an unloaded beating heart.

More informative predictors of organ function are found in the donor medical history, the comorbidities, clinical status and mechanism of death. Total and warm ischemic time, the dying process and technical details are critical. The transplanting team must have confidence that a well-functioning heart exposed to a rigidly limited warm ischemic time and rapid retrieval process will be a good heart within the limitations of whichever *ex-situ* perfusion technology is used. The liver and kidney teams have taken this approach with excellent results – viewing donor management and organ preservation as a whole, rather than depending upon poorly validated techniques and biochemical markers [35–37].

Early evidence demonstrated by successful DCD recovery in UK and Belgium [32], in addition to small child DBD heart recovery [26] supports the hope that the XVIVO system is the solution for expanding paediatric DCD heart donation from children previously excluded, even down to organ recovery from neonates.

Thoraco-Abdominal Normothermic Regional Perfusion (TA-NRP)

In TA-NRP, an ECMO circuit is used to restore thoracic and abdominal oxygenated blood circulation within the donor body post-death) whilst isolating the brain from circulation [38]. The heart recommences beating and following a suitable period to allow metabolic recovery *in situ*, the heart can be assessed and retrieved using cardioplegia and cold-static-storage. Although TA-NRP, which permits perfusion and recovery of both abdominal and thoracic organs has been utilized in the UK historically, the thoracic component of TA-NRP was halted in 2020 due to ethical concerns and is subject to ongoing international debate for both adult and child donors [18, 38–41].

Abdominal-NRP (A-NRP), with the thorax isolated from the circulation, continues to be utilised in the UK to recover abdominal organs. Presently, in cases where A-NRP is adopted, the heart is recovered utilising DR and normothermic *ex-situ* perfusion with the OCS device.

TA-NRP-facilitated DCD heart transplant is practiced in Spain and the United States including neonatal donation [13–16]. Benefits for the organ and to the recipient are clear from the Spanish body of work which reports reduced warm ischaemic damage and superior assessment of organ viability [14, 15]. There are early reports of improved longer term survival following TA-NRP in comparison to DR-OCS although this is based upon small numbers [42]. Similar data is anticipated from centers in the USA which have adopted TA-NRP as the predominant method of cardiac DCD [43].

Reperfusion of the thoracic circulation, especially the restarting of the heart after death inside the body of the donor, raises controversy surrounding violation of the "dead donor rule." There is additional concern over potential cerebral flow during recirculation resulting in the theoretical risk of restoring sentience in the donor. Inadvertent cerebral perfusion following death may result in an uncontrolled catecholamine storm with subsequent profound detrimental effect on all organs. Recent clinical research in human DCD donors has shown that perfusion pressure within the Circle of Willis does not increase upon initiation of TA-NRP with utilization of additional techniques to isolate the brain [44].

Nonetheless, these ethical concerns have led to a halt of TA-NRP in a number of European countries. A recent international consensus statement provides an excellent review of TA-NRP, the ethical dilemmas and the potential way forward [45]. In the UK, we await data from a validation study in Papworth and Cambridge University Hospital, regarding the prevention of cerebral perfusion, which will help inform ethical deliberation and professional consensus.

Logistics and Resource Barriers

The DCD process depends upon a multifaceted, complex sequence: donor identification, referral to the Specialist Nurse in Organ Donation (SNOD), discussion with relatives, consent and often coronial approval, donor management for withdrawal of life-sustaining treatment, diagnosis of death, retrieval of organs, safe mounting of the organ onto the device, transfer, implantation and post-death care of the donor.

While much of the infrastructure required to support this process is well established at an individual hospital and national level, there are aspects of pediatric cardiac DCD which need attention.

Identification and Care of Donors

Reaching agreement with families to donate depends greatly on the attitudes and beliefs of healthcare staff. Where pediatric DCD has been adopted (UK, United States, Spain, Netherlands, Belgium, France) there is a positive attitude toward DCD donation across the disciplines and an understanding that donation contributes positively to a family's grieving process [46–50]. Negative perceptions center around the complexity of the DCD process, poor knowledge of DCD protocols, perceiving withdrawal as professional failure, protection of children, fear that the donor feels pain and legal repercussions [46–54].

Child death and organ donation are highly sensitive, emotional topics. While the "lifesaving" act of donation can

have a positive effect on grieving families, there is reported discomfort amongst healthcare providers in holding discussion regarding DCD which may impact upon donor referral and consent [46, 54].

The traditional approach to family-centred care and differences in end-of-life practice may conflict with what is needed for DCD [55]. DCD organ donation requires consideration of location and environment to minimise organ ischemic time. The concept of a witnessed, monitored death in an anaesthetic room adjacent to the operating theatre (the typical location for DCD in the UK), followed by an expedient move to theatre can be confronting to healthcare workers and donor families. These facts are discussed with the donor family as part of consent for donation and are justified by the guiding principle of "parental consent" and "overall benefit" when making decisions about end-of-life care [56, 57]. The family are always afforded the opportunity to be present and their privacy respected [58].

Decision-making is collaborative, with the healthcare team supporting the family. Whether a child has indicated willingness (e.g., by organ donor registration or through conversation) or has not expressed a view then pediatric clinicians are adept and accustomed to working collaboratively to reach a decision of best interests.

Understanding the reasons for families to decline DCD is helpful for recognizing how logistics and practicalities influence decision-making. In 2022-3, families of sixty-two dying children were approached regarding DCD organ donation. 44/62 (71%) of families were non-consenting. The most common reason was that parents wished to stay with their child after death or that their child had suffered enough. These reasons are also seen in DBD. A greater number approached for DCD felt the donation process to be too prolonged when compared to DBD [59].

Bespoke strategies are required to develop the environment and protocols to support staff in embracing pediatric DCD as part of end-of-life care [56]. In the UK, The Pediatric and Neonatal Deceased Donation Strategy embeds organ donation as a routine end-of-life choice for every family facing the death of their child [60]. The multidisciplinary leadership course "Child and Infant Deceased Donation" trains clinical teams to confidently use the national strategy recommendations within their practice, to transform cultures and develop policy through local leadership.

The impact of such robust national recommendations is illustrated in all-age DCD donation statistics in the UK which followed government strategies in 2008 and 2013 to increase deceased donation [61, 62]. The number of families approached from 2007 to 2012 increased by 4% for DBD (1,055 to 1,100) but increased by 420% for DCD (349 to 1,816), resulting in a 154% increase in the number of DCD donors (200 to 507) over the same 5 years [1].

Since 2010, more families in the UK consent to DCD each year than to DBD [1]. This increase is a direct result of a cultural shift in ICU attitude and behaviours toward DCD, empowered by nationally endorsed strategic planning and recommendations [59, 61–63]. Staff involved need to be educated about the process and confident of the legal framework for DCD pediatric organ donation provided primarily by the Human Tissue Act 2004 and follow-up guidance [56, 64, 65].

Infrastructure and Resources for Organ Recovery

The UK National Organ Retrieval Service (NORS) was established by NHSBT in 2010 to provide a 24-h national service for deceased donation. Two specialist pediatric teams in the UK retrieve hearts from DBD donors <40 kg. The established DCD programme only retrieves hearts from donors, including children, over 50 kg. Currently, only one of the specialist pediatric retrieval teams has the additional expertise to retrieve DCD hearts. A formally commissioned, national DCD heart programme is awaited. Until the DCD heart retrieval service is sustainably funded and formally commissioned, there is a financial and logistical barrier to new technologies.

Cardiac DCD retrieval is a resource-intensive endeavour requiring theatre space, personnel, devices and disposables and often private air-travel. However, it must be weighed against the cost of mechanically supporting a child on the heart transplant waiting list. The cost of a Ventricular Assist Device (VAD) supported pediatric journey to heart transplant is upwards of US$700,000 [66]. Investment in processes to increase the number of donor hearts available and improve organ utilisation rates is in itself, a viable financial argument.

In 2018, a commitment was made to ensure consistently available expertise and skill to retrieve organs from all pediatric patients including small infants. While this did not specify DCD, the recommendations do state that ongoing clinical governance processes should review specific challenges, and ongoing training needs to achieve this commitment [59]. In 2023, as work toward viable technology and infrastructure progressed, the UK National DCD Pediatric Working Group was convened to establish the logistical barriers to cardiac DCD in children, including the necessary collaboration and training required to establish a complete retrieval team.

It is inevitable that both pediatric heart recovery teams will need to be DCD trained in order to sustain a safe cardiac DCD programme for children, however, the limitation of national sustainable funding for the DCD heart service is impeding the progression of any pediatric DCD heart programme.

Ethical Barriers

There is considerable variability in ethical perspectives on DCD organ donation across the globe [19, 40, 41, 67–76]. Focusing on countries with an established deceased donation programme, those who question DCD heart donation raise concerns related primarily to the diagnosis of death, the permissibility of restarting the heart and whether DCD, particularly TA-NRP, involves breaching of the dead donor rule [77–79]. The acceptance of the ethics of DCD heart donation in adult practice within the UK is demonstrated by the breadth of professional, legal and ethical documents available from The Department of Health, Royal Colleges, the General Medical Council, the National Institute for Health and Care Excellence (NICE), the UK Donation Ethics Committee (UKDEC), the Intensive Care Society, NHS Blood and Transplant (NHSBT) and the British Transplant society [9, 45, 56–58, 62, 65, 80–89].

Progress on the technological front to facilitate pediatric DCD has led to situations in the UK where previously settled ethical concerns have been questioned again. Although notably the questions raised have been no different when it comes to children, it is only that there is a new audience confronting the ethics for the first time. Given the acceptance by the medical community and society for adult cardiac DCD, it could be considered unethical and even discriminatory to deny the opportunity for transplant in children based upon the same ethical principles. As stated by NICE, the GMC, The Royal College of Pediatrics, NHSBT, the Pediatric Intensive Care Society, and UKDEC, organ donation should be a routine component of a child's end of life care and as such it should be considered in any child in whom the decision has been made for withdrawal of life support [56, 65, 83, 86–89].

In 2015 UKDEC published a position paper on ethical issues in pediatric organ donation [56]. Nine recommendations reinforce the importance of facilitating donation where a family wishes to. The positives of child organ donation are well documented. For many, the single positive outcome of their tragedy is their child's potential to save others [59]. Empowering families to explore their feelings and take control of decisions around donation can have a significant effect on meaning-making and healing [90].

Ethical dilemmas in DCD lie in the grounds of potential conflict between what is right for the individual as a dying patient, what is right for the individual as an organ donor and for the family who are giving their consent. With the widespread ethical, legal and professional support, resulting in nearly 10,000 DCD donations in the UK over the last 24 years [1], we must acknowledge that though new technology can raise new questions, the fundamental questions have been met with robust and reflective ethical answers and this is a practice widely accepted by families and clinicians in the UK and our international peer nations.

SUMMARY AND A CALL TO ACTION

The emergence of technology dedicated to the *ex-situ* perfusion of small hearts has been long-awaited and now requires prioritisation in order that children can have the same opportunity for a life-saving transplant as adults. HOPE has now been utilised in the UK for a small child DCD heart donation and transplant with excellent result and as such it is time to address all barriers to ensure equitable access for children. We can no longer deny DCD hearts to children on the basis of lack of technology.

Logistical barriers of donor identification and care, organ retrieval and resources can be overcome. There is however an urgent need to communicate the message to decision-makers about cardiac DCD technology, that the fundamental ethics of DCD are already well established. Cardiac DCD is embedded practice in adults in the UK and there is no rational argument for difference in pediatric practice. Indeed, it would seem to be unethical to withhold life-saving technology from children who need it. A 25% mortality on the transplant waiting list is unacceptable when a solution exists, and which would be available to children if they were just a few years older. We have a responsibility to children and families, who are donating other organs using DCD processes, to allow them to donate the heart too.

We call upon the Department of Health, Royal College of Paediatrics and Child health, The British Transplant Society, NHSBT, and international equivalents to demand urgent action to:

- Ensure that no child dies unnecessarily due to failure to provide appropriate services analogous to those available to adults and older children.
- Build the logistical framework to facilitate pediatric cardiac DCD within the already established ethical, legal and professional frameworks.
- Provide education and training of all staff involved in this complex process.
- Ensure a sustainable organ retrieval service in order that no organ is lost due to skill deficit by training both pediatric retrieval centers to undertake cardiac DCD.
- Apply the new technologies under appropriate surveillance, safety monitoring and rigorous reporting to the clinical community across both paediatric heart transplant centres in the UK.
- Urge NHS commissioners to recognise the financial benefit of employing technology to increase the donor pool for young children on the waiting list and seek sustainable funding for DCD paediatric heart recovery.
- Demand due process from the regulatory health authority to allow for compassionate use of technology to prevent further loss of life due to delay.

AUTHOR CONTRIBUTIONS

LK conceptualized and wrote the manuscript. LK, JB, DG, and ES developed the concepts and key message. All authors contributed according to their fields of expertise, to reviewing and editing the manuscript and approved the final submitted version. Following LK as first author, all other authors are listed in alphabetical order and share equal contribution.

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CONFLICT OF INTEREST

JD has received support for expenses from XVIVO perfusion AB (Mölndal, Sweden) to attend a symposium. SL is the chief investigator and fellow creator of the mOrgan *ex-situ* Langendorff perfusion device. The device is owned by Royal Papworth Hospital and is being prepared for clinical trial.

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

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MINI REVIEW
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Evaluating Risk in Kidney Living Donors

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Kidney donation is a safe procedure for carefully screened donors. The growing shortage of organs and improved survival rates among recipients of living donor transplants have broadened the criteria for acceptable living donors, including older individuals and those with pre-existing health conditions. Consequently, ensuring both the short- and long-term safety of living donors is of paramount importance. The primary objectives are to prevent the need for kidney replacement therapy, major cardiovascular events, or premature death. Lifelong monitoring of living donors is essential to facilitate early treatment for preventable illnesses. To this end, annual follow-up is generally recommended, which should minimally include an assessment of blood pressure, body mass index, kidney function, albuminuria, lifestyle factors, and general wellbeing. However, the management of these risk factors and treatment targets in this population remain inadequately defined. Recommendations for genetic counseling in cases of living-related donation also remain inconsistent. The aim of this mini-review is to address the challenges in evaluating the evidence on the long-term consequences of kidney donation, particularly concerning the risk of developing end-stage kidney disease, cardiovascular mortality, gestational complications, and hypertension. This article aligns with the ESOT call for action to promote living kidney donation and EKITA's mission.

Keywords: end-stage kidney disease, cardiovascular disease, kidney transplant, living donor, hypertension

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INTRODUCTION

Globally the number of individuals with end-stage kidney disease (ESKD) has increased with a growing number of patients waiting for a kidney transplant. Even in countries with the highest transplant activity, around 10 patients die every day waiting for a kidney [1]. One way to improve patients' prognoses is to increase the number of living donor (LD) transplants. Compared to transplants from deceased donors, LD kidney transplants significantly improve recipients' long-term physical, biochemical, and psychological outcomes [2]. These benefits are maintained even in older

LD grafts as they improve graft and patient survival compared to both standard criteria donor and extended criteria donor kidneys or remaining on dialysis [3].

A nephrectomy inevitably results in some health detriment to the voluntary donor, at least in the short term. Potential kidney donors are thoroughly informed about the associated risks. A multidisciplinary team assesses their suitability for the procedure following an extensive health examination [4], and final approval from local authorities. Studies indicate that 86%–98% of kidney donors would choose to donate again [2, 5]. The health risks to the donor are minimal compared to the significant benefits to the recipient.

LD rates increased by 7.8% in 2023 compared to 2022, although with a marked variation in global rates. LD activity has varied across Europe and within countries in the past decade [1] (**Figure 1**). The variance in the activity is evident not only between countries but also between institutions within the same country. This can be explained by different legal frameworks, socioeconomic, cultural, and religious backgrounds of potential donors, and concerns about the donor candidate's age and comorbidities influencing acceptance criteria. As the number of global LD kidney transplants increases, it is beholden on the transplant community to continually reassess risk to donors, particularly as the criteria for eligibility for living donation expands; with an increasing number of older donors, or acceptance of co-morbidities that would not have been exclusions 10 years ago. This is the purpose of this literature review.

Challenges in Interpreting Literature About Living Kidney Donors' Long-Term Consequences

Live donors represent a unique subset of the population before and after donation. After nephrectomy, kidney donors should be healthy individuals albeit with only one functioning kidney. Defining a comparable population is challenging; thus, risk assessments in the literature should be approached critically. Nowadays, surgical complication rates are low thanks to development of surgical techniques. Recovery from nephrectomy is typically swift, with discharge occurring approximately 2-3 days post-procedure and a return to normal life within 3–6 weeks. However, it is equally important to evaluate the long-term health impacts of kidney donation, particularly the donor's risk of progressing to end-stage kidney disease (ESKD) or increased cardiovascular risk due to reduced kidney function. It is also necessary to assess whether kidney donation causes psychological harm or reduces quality of life. When compared to the general population, kidney donors tend to have better survival and health outcomes; likely because donors are well-screened healthy individuals, whereas the general population includes individuals with various pathologies [6]. Conversely, compared to individuals who could have donated a kidney but did not, the risks for kidney donors seem to be higher, although there is still controversy [7]. Significant challenges in comparisons arise from varying acceptance criteria for kidney donation, incomplete follow-up data, insufficient registry data, and inadequate consideration of genetic predisposition, smoking, biometric, or socioeconomic parameters in the comparison group. A particular problem is data scarcity on long-term donor outcomes (i.e., studies of more than 15–20 years of follow-up), which makes risk assessment for younger potential donors difficult.

Risk of Progressing to End-Stage Kidney Disease

After nephrectomy, the number of nephrons is reduced by half. Serum creatinine rises, and the estimated glomerular filtration rate (eGFR) immediately drops after around 50% reduction in kidney mass [8]. Unlike unilateral nephrectomy in individuals with comorbidities, the LD remaining kidney has adequate kidney functional reserve capacity, which enables compensatory, adaptive hyperfiltration, typically increasing its function in the months post donation. About a year after nephrectomy, kidney function stabilizes at approximately 60%–65% of the initial pre-operative function. Similarly, eGFR decreases after surgery regardless of baseline levels, age, and

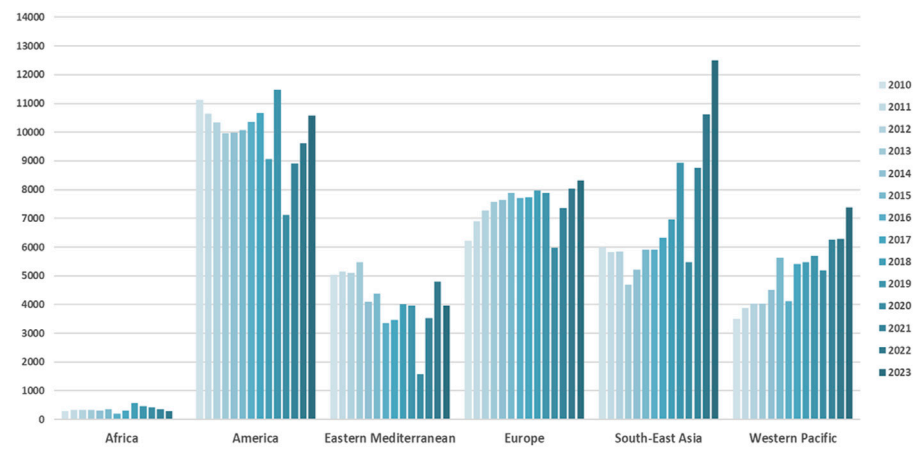

FIGURE 1 | Trends in living kidney donation worldwide. Source: www.transplant-observatory.org.

gender, remaining stable long-term, as in healthy non-donors [9]. The annual eGFR decline was 0.35 mL/min/1.75 m^2 in donors compared to 0.85 mL/min/1.75 m^2 in healthy controls in a retrospective matched cohort study of 604 Canadian donors from 2002 to 2016, a difference attributed to donor glomerular hyperfiltration in the first five years post donation. A Dutch registry-based analysis confirmed these findings, although it was noted that in approximately 13% of donors, the expected increase in eGFR post-nephrectomy was not observed [10]. These findings suggest that in some individuals the kidney functional reserve capacity is decreased, perhaps due to factors such as low nephron mass and low birth weight, preventing enhanced function in the remaining kidney, The risk of progressing to ESKD after kidney donation is minimal, occurring in less than 1:200 donors (0.5%) [11]. This risk is significantly lower than in the general (unscreened) population. Muzaale reported on the long-term follow-up of 96,217 kidney donors in the United States, comparing the outcomes to a control population of 20,024 participants from the NHANES III study [12]. Ninety-nine of 96,217 donors (0.1%) developed ESKD on average 8.6 years after donation compared to 36 of 96,217 (0.04%) matched healthy non-donors. Based on this, the estimated risk of ESKD 15 years after donation was 30.8 per 10,000 donors and 3.9 per 10,000 controls. On further analysis of the same registry data, 10 per 10,000 donors developed ESKD within 10 years post donation, primarily due to glomerulonephritis. Twenty-five years post-donation, 85 out of 10,000 donors had developed ESKD, mainly due to diabetes and hypertension [13].

Mjøen reported on the long-term kidney function of 1,901 Norwegian donors, comparing transplant registry data to 32,621 individuals who could have but did not donate a kidney [14]. The average follow-up was 15.1 years for donors and 24.9 years for non-donors. The risk of ESKD was 11.38 times higher in kidney donors. Notably, this elevated risk is based on only nine donors requiring kidney replacement therapy 18.7 years after donation, with seven of these recipients being first-degree relatives of the donors. Similarly, in the U.S. study [12], the authors found that 67% of donors who developed ESKD were biologically related to their recipients. In contrast, most controls had no family history of kidney disease.

Assessing the genetic predisposition to kidney disease is advisable in selected cases when donor and recipient are first-degree relatives [13]. When the recipient's kidney disease is known, specific cases in which genetic testing might be considered include Alport's, aHUS, hereditary focal and segmental glomerulosclerosis, Fabry's, and autosomal dominant polycystic kidney disease. However, this approach remains a matter of debate and there is wide variation in clinical practice [15]. There is concern in the transplant community about the lack of prospective data evaluating the risk of ESKD in donors of African ancestry with a high-risk APOL 1 genotype. A retrospective study found that donors with high-risk APOL1 genotypes had significantly lower pre-donation and post-donation eGFR. However, the rate of eGFR decline was comparable to APOL1-matched non-donor controls [16].

Risk of Hypertension

Several adaptive compensatory mechanisms develop post-nephrectomy; kidney plasma volume increases, resulting in glomerular growth and accentuated hyperfiltration. However, hyperfiltration does not cause high glomerular pressure or damage in kidney donors, although albuminuria may occur [17]. A key question is whether nephrectomy affects the prevalence of hypertension. Studies indicate that the prevalence of hypertension increases after kidney donation, with risk varying from zero to a threefold increase. Meta-analyses suggest donor blood pressure rises by 5 mmHg compared to healthy controls [18]. Despite extensive research, varying methodologies challenge the possibility of drawing definite conclusions, as outlined in **Table 1**.

Hypertension raises the risk of progressing to ESKD and cardiovascular events; these are reduced if blood pressure is maintained below 130/80 mm Hg after donation [19] because mean blood pressure over 140/80 increases the risk of progressing to ESKD fourfold [12]. The risk of hypertension increases when risk factors such as obesity, smoking, genetic predisposition, older age, and low eGFR accumulate [20]. Weight gain increases the risk of hypertension more in kidney donors than in controls. However, both obese donors and non-donors had a similar hypertension incidence [21].

A BMI >30 doubles the relative risk of ESKD compared to BMI <30 at 15-year follow-up. However, the incidence of ESKD in these groups remain very low (40 cases in BMI >30 vs. 20 cases if BMI <30 out of 10,000 donors) [11].

TABLE 1 | The complexity in the evaluation of hypertension risk factors.

Blood pressure measurement technique before donation	Home vs. office vs. 24-h measurements. All these methods have been indistinctly applied, without consensus on the most suitable for this population
Hypertension diagnosis before donation	Hypertension does not preclude donation if well-controlled with 2 drugs at the most. The acceptance of a donor candidate is affected by age. The detection of organ damage is a contraindication
Familiar risks	Not recorded in most registries
Smoking	Insufficient data captured in the registries
Comorbidities	Dyslipidemia, abnormal glucose metabolism, or overt diabetes have not been considered in association with hypertension
Overweight	Weight changes after donation have not been systematically reported
Length of follow-up	Most studies report the results from the first 10 years after donation, but long-term data is scarce
Data based on registries	Some registries retrieve data from hospital charts, others from pharmacy repositories, or rely on patients' reports

Risk of Death

A recent meta-analysis of over 900 studies found a perioperative mortality rate of 0.01% with low incidence of intraoperative complications (2.3%). With the current laparoscopic nephrectomy technique, the rate of infections, bleeding, and reoperations are quite low. Among these complications, infections are most common and easily treatable [22]. A recent analysis of 164,593 kidney donations reported a death rate 90 days post-surgery less than 1 event per 10,000 donations. Perioperative mortality after living donation declined substantially in the past decade. The risk was higher for male donors and donors with a history of hypertension [23].

Studies in Sweden [24] and the United States [25] have shown that survival is better for live donors compared to the general population. However, when the comparison group consists of healthy individuals from the general population, it is less clear if kidney donation has a detrimental effect on long-term cardiovascular mortality. The previously mentioned U.S. [12] and Norwegian [14] studies present conflicting findings. In Mjøen's study, the mortality risk ratio was 1.3 for LD compared to controls, and the cardiovascular mortality risk ratio was 1.4. Muzaale reported no increase in long-term mortality risk for donors compared to controls. Both studies face several methodological challenges; for example, in the Norwegian study, the control group consisted of younger individuals, living in rural areas who smoked less and had no family history of kidney disease.

Particular attention should be given to how cardiovascular risk factors change after kidney donation. A small number of studies examined the changes in metabolic factors post-donation [26]. In an Israeli study, LD had higher increases in BMI, triglycerides, type 2 diabetes, and incidence of metabolic syndrome, compared to controls over a five-year follow-up period. Blood pressure was similar between LD and healthy individuals, but paradoxically, cardiovascular events were more common in healthy individuals. A U.S. study also reported similar levels of blood pressure, HbA1c, albuminuria, and lipoproteins in LD and healthy controls after 9 years of follow-up. Noteworthy, LD had higher levels of parathyroid hormone and uric acid, probably because of decreased kidney mass [27].

Maternal and Fetal Risks After Kidney Donation

A recent systematic review compiled the results of 16 studies over a 35-year period, including 1,399 post-donation pregnancies [28]. These studies employed different methodologies, and only six of them included a control group. Based on the available evidence, eight clinical practice guidelines, three consensus statements, and four expert-opinion papers were published between 2010 and 2020. The general conclusion is that the occurrence of hypertension during pregnancy increased from 1% to 9% pre-donation or matched controls to 4%–12% post-donation. Pre-eclampsia also increased from 1% to 3% pre-donation or in non-donors to 4%–10% post-donation. The recommendations universally state that women should be counseled about the increased risk of gestational hypertension or pre-eclampsia. Additionally, it should be stressed that, according to the literature, most women had uncomplicated pregnancies post-donation, and the aspiration to have a child should not be seen as a contraindication for donation. In most studies, fetal and neonatal outcomes after kidney donation are like those in non-donor pregnancies.

Potential Psychological Consequences of Living Kidney Donation

Live kidney donors may find recovery is hindered by post procedure tiredness, although the majority recover within several months. While 14% of US kidney donors experienced persistent fatigue 1 year after donation, this rate was comparable to healthy controls [29]. Donors with a history of affective disorders, anxiety or lower levels of physical activity were identified as highest risk for persistent fatigue.

Type of surgery does not seem important, with both open and laparoscopic nephrectomy donors experiencing equal mental fatigue and reduced motivation. Although these symptoms had resolved by 3 months, the physical fatigue could persist for up to 12 months [30]. A Dutch study on health-related quality of life (HRQoL), also found that there was no difference in physical scores between pre- and 12 months post-donation [2] but mental scores varied significantly, declining from pre- to 6 months post-donation and then improving from 6 to 12 months. Predictors of greater fatigue included higher baseline fatigue, poorer baseline physical functioning, younger age, longer hospital stays, and greater influence of the recipient's condition.

Female donors are more affected. A German HRQoL study found similar QoL outcomes across genders, except for the mental component in SF-36, when 51–60-year-old females scored lower than both age-matched males and general female population [31]. This was corroborated by a Norwegian long-term study (217 donors) although fatigue levels were generally low. Here, higher QoL was associated with donors who received recognition whereas donors with regret reported generally elevated fatigue [32]. A Dutch 10-year study reported significant declines in physical function, pain, and general health (SF-36) at follow-up but unfortunately, the lack of a comparator makes it difficult to distinguish the impact of donation from general aging but reinforces the need for psychosocial support [33].

LONG-TERM FOLLOW-UP FOR KIDNEY DONORS

Ever since the first LD kidney transplant in Boston in 1954, the best approach to the care and management of living kidney donors has frequently been debated. As the practice expanded, it was recognized that the health status of kidney donors must be monitored throughout their lives to ensure treatment for preventable illnesses. In current guidelines, yearly living kidney donor follow-up is suggested which includes at the minimum the following: blood pressure, BMI, eGFR, albuminuria, health style, and general wellbeing review [34]. However, a personalized approach is recommended. Compliance with

TABLE 2 | Living donor follow-up checklist.

Variable	Target	To note
Blood pressure	<130/80	The drug of choice is usually on RAAS inhibitors and thiazides. Of crucial importance is a restriction on salt intake under 5g/day
LDL-cholesterol	<2.5 or <1.8 or <1.4	There are no recommendations for kidney donors. The target depends on the underlying conditions and eGFR. Statins are safe
HbA1c	<42 mmol/mol	In case the value is above the normal range, the usual treatment
Creatinine, eGFR	no target	Trends in eGFR should be considered
U-AlbCrea	<3 mg/mmol	A small amount of albuminuria may appear, but if the urine albumin/creatinine ratio is over 60 mg/mmol, a careful evaluation is warranted
Smoking	stop smoking	Usual recommendations
BMI	BMI <25	Usual recommendations
Lifestyle and wellbeing	healthy choices	Usual recommendations
Other important considerations		
Nephrotoxic drugs	Avoidance of NSAIDs. Advice to adjust drug doses to eGFR.	
Complications	Follow-up data and complications, especially severe infections, cardiovascular morbidity, cancer, or psychiatric, should be informed to the local transplant registry administrator	

this recommendation may be reduced due to the costs to healthcare organizations. In the US, the Organ Procurement and Transplantation Network requires transplant programs to submit 6-, 12-, and 24-month post-donation follow-up data to the national registry, but after this time point recovering follow-up care costs is billing the recipient's insurance, while in some cases the programs bill the donor, or the follow-up costs were covered by charitable funds. US researchers advocated for the revision of the Organ Acquisition Cost Center's policy to include follow-up costs as part of the commitment necessary for living donor care and safety, rather than solely for data collection [35].

Most of the available evidence of LD safety is based on registry data and therefore is only as valid as the reported follow-up, and may be limited, particularly for those who donated more than 20 years ago. Transplant registries are crucial for planning transplant activities, epidemiological analysis, organizing follow-up care, and evaluating outcomes. They are a critical tool for quality control, thus improving patient safety. Altogether, 115 transplant registries are identified worldwide in the International Registry in Organ Donation and Transplantation. Of them, only 16 reported living donor outcomes post-donation including organ function (n = 9) and death (n = 16) [36].

Transplant programs should ensure long-term surveillance of LD, but the dataset captured by different registries is diverse, and its harmonization has proved challenging [37]. Coordinated efforts to gather valuable information from different transplant registries have gained attention recently. In Europe, the European Society of Organ Transplantation launched a platform to host pan-European registries on transplant recipients and living donors. This initiative has the support of the European Commission [38]. Similar efforts are ongoing in the US. [39, 40]. Common barriers to data sharing include technical, economic, legal, and ethical issues [41]. Nevertheless, the efforts outweigh the benefits for patients with kidney disease and donors.

LD often receive care from primary healthcare, the private sector, and occupational health services. Valuable follow-up information emerging from these care providers could enhance the quality of the transplant registries. The digitalization of healthcare provides a unique opportunity for big data analysis, which may improve the understanding of LD clinical outcomes.

The Evolving Face of Living Kidney Donation

Kidney donation is a safe procedure for carefully screened donors. However, there is uncertainty about the risks of long-term risk when compared to healthy non-donors, especially after the first two decades post-donation. Organ shortage and improved recipient survival after LD transplant are pushing the limits for the acceptability of LD candidates, considering older living donors and those with comorbidities such as impaired glucose tolerance or diabetes without signs of nephropathy. In this context, while careful risk stratification and donor selection remain essential, the inclusion of these potential candidates in the pool represents a promising avenue for expanding living donation. Nevertheless, lifelong LD monitoring to detect treatable problems is paramount. The minimum data proposed to be systematically collected is shown in **Table 2**. Noteworthy, the targets for these parameters are based on expert opinions. There is no evidence of the impact of managing cardiovascular complications after LD on survival or risk for kidney replacement therapy.

Conclusion

This mini-review highlights the uncertainties of LD long-term follow-up, with recommendations and evidence-based targets for managing comorbidities after kidney donation. Further collaborative national and international efforts are needed to advance our knowledge and optimize follow-up care of living kidney donors.

AUTHOR CONTRIBUTIONS

Conceptualization: FO; data curation: FO, LM, RT, AK, ER, and BA; formal analysis: FO, LM, RT, AK, ER, CL, BA, GZ, and SC; LF

and DC; project administration: FO and BA; supervision: FO and BA; writing–original draft: FO, LM, RT, AK, ER, CL, BA, GZ, and SC; LF and DC; writing–review and editing: FO, LM, and RT. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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SYSTEMATIC REVIEW AND META-ANALYSIS
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Ethical Issues in Uncontrolled Donation After Circulatory Determination of Death: A Scoping Review to Reveal Areas of Broad Consensus, and Those for Future Research

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Uncontrolled donation after circulatory determination of death (uDCD) protocols are established in several countries with good outcomes. We reviewed the literature between 1997 and 2024 to identify ethical issues. 33 papers were identified. Several areas of continued ethical debate were delineated: the role of advanced life support techniques; the ethical acceptability of aortic occlusion balloons; the nature and timing of consent to organ preserving techniques; whether best interests can/should extend beyond individual bodily integrity in this context. Further empirical research and ethical analyses are needed in these domains. Broad consensus was identified on several issues including: decisions about termination of resuscitation and entry into a uDCD protocol should be made by different teams; at least 20–30 min of cardio-pulmonary resuscitation is required; a hands-off period of 5–7 min is required alongside continuous monitoring; organ preserving techniques should be as minimally invasive as possible; families should be approached early to discuss organ donation by trained staff; public knowledge and engagement about uDCD is poor and must be improved; transparency and informed consent are essential for potential uDCD organ recipients. To maintain transparency and encourage positive public engagement we propose a name change from uDCD to Organ Donation after Sudden Irreversible Cardiac Arrest (ODASICA).

Keywords: transplant, uncontrolled donation, cardiac arrest, ethical considerations, systematic literature review

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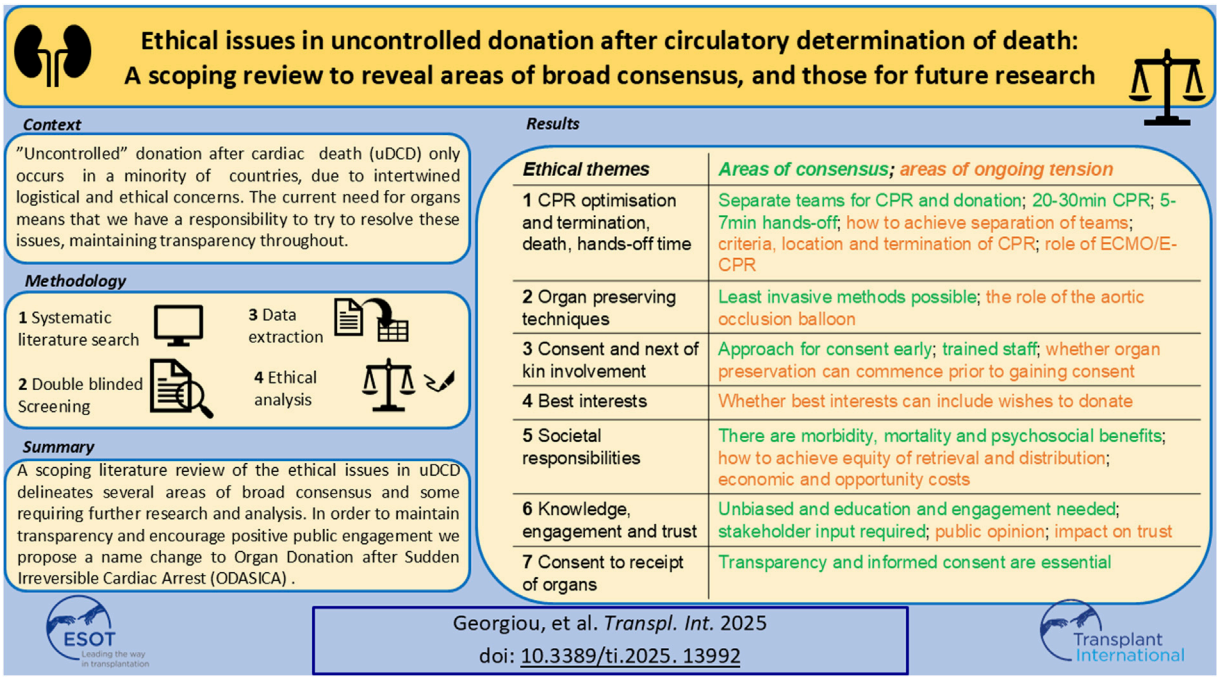
INTRODUCTION

Organ donation has widespread public support and can provide great comfort to families after the death of their loved ones [1–3]. However, only a small number become organ donors [4]. In the UK for example, less than 0.5% of people who die under the age of 80 years become organ donors [4], a key reason for this being that there is no mechanism for people who die following out-of-hospital cardiac arrest to donate; only those who die in a "controlled" donation after circulatory death



GRAPHICAL ABSTRACT

(cDCD) setting – on an intensive care unit, with planned withdrawal of treatment and immediate organ recovery – are eligible [5, 6].

So called "uncontrolled" donation after circulatory determination of death' (uDCD) is possible in other countries after a witnessed cardiac arrest [7]. Cardio-pulmonary resuscitation (CPR) is started, and all efforts are made to revive the individual for at least 30 min; this may include mechanical CPR which allows safe transport to hospital with ongoing regular compressions. Once in the hospital, the treating team assesses whether there are any further interventions which might be successful; if there are not, then, as with all cardiac arrests in which return of spontaneous circulation has not been achieved, CPR is stopped, and the patient is pronounced dead. There follows a hands-off period before the transplant team starts efforts to preserve the organs [8].

The challenge with uDCD is to ensure that, after the death of the patient, donor organs are rapidly preserved before they are irreversibly damaged due to ischemic injury while still providing sensitive care to donor families. In France and Spain, normothermic regional perfusion (NRP), a minimally invasive technique to preserve the organs *in-situ* after death, is used routinely to facilitate uDCD donation and the resulting kidney transplant outcomes have been excellent [9, 10].

uDCD has been introduced around Europe with notable success in France [11] and Spain [12]: around 1000 successful kidney transplants have been performed since 2015 [7, 9, 13]. It is also practiced in Italy [14, 15] the Netherlands [16], Portugal [17], and Poland [18] and has been developed in Belgium [19], Russia [20], the US [21, 22], Taiwan [23] Korea [24], Austria [25] and the Czech Republic [26, 27] with different protocols [28] and with varying degrees of success. Systematic reviews have examined specific elements of the process and the associated outcomes including of Extracorporeal Membrane Oxygenation (ECMO) [29], preservation techniques [30, 31] and graft outcomes [32].

Many overviews and editorials have been written on the challenges and ethical issues of both uDCD [33–39] and cDCD [40, 41]. Most ethical issues emerge from establishing the best way to act in the patient's best interests when survival is no longer possible; there is perceived conflict between ensuring best end-of-life care and ensuring opportunity to donate organs. **Figure 1** illustrates these points of conflict and ethical tension, alongside the uDCD process. See **Table SA** in the supplementary materials for a full Glossary and abbreviations associated with uDCD.

While many authors have identified ethical issues, there is insufficient empirical evidence or stakeholder engagement to develop a grounded understanding of normative claims, or what might be the "right" thing to do in several domains, particularly around conversations and consent. This contributes to a reluctance to initiate uDCD programs or even pilots, which itself creates an ethical issue given the shortage of organs for those who need them; around 5,000 people are waiting for a kidney transplant in the UK with an estimated 3 deaths per day are related to the shortage of donor organs [4], and over 100,000 are reported to be waiting in the USA [21, 42]. A uDCD program is predicted to allow the recovery of a significant number of organs per year; to not explore this route would be to deny these patients a life-saving donation and to deny others the opportunity to donate.

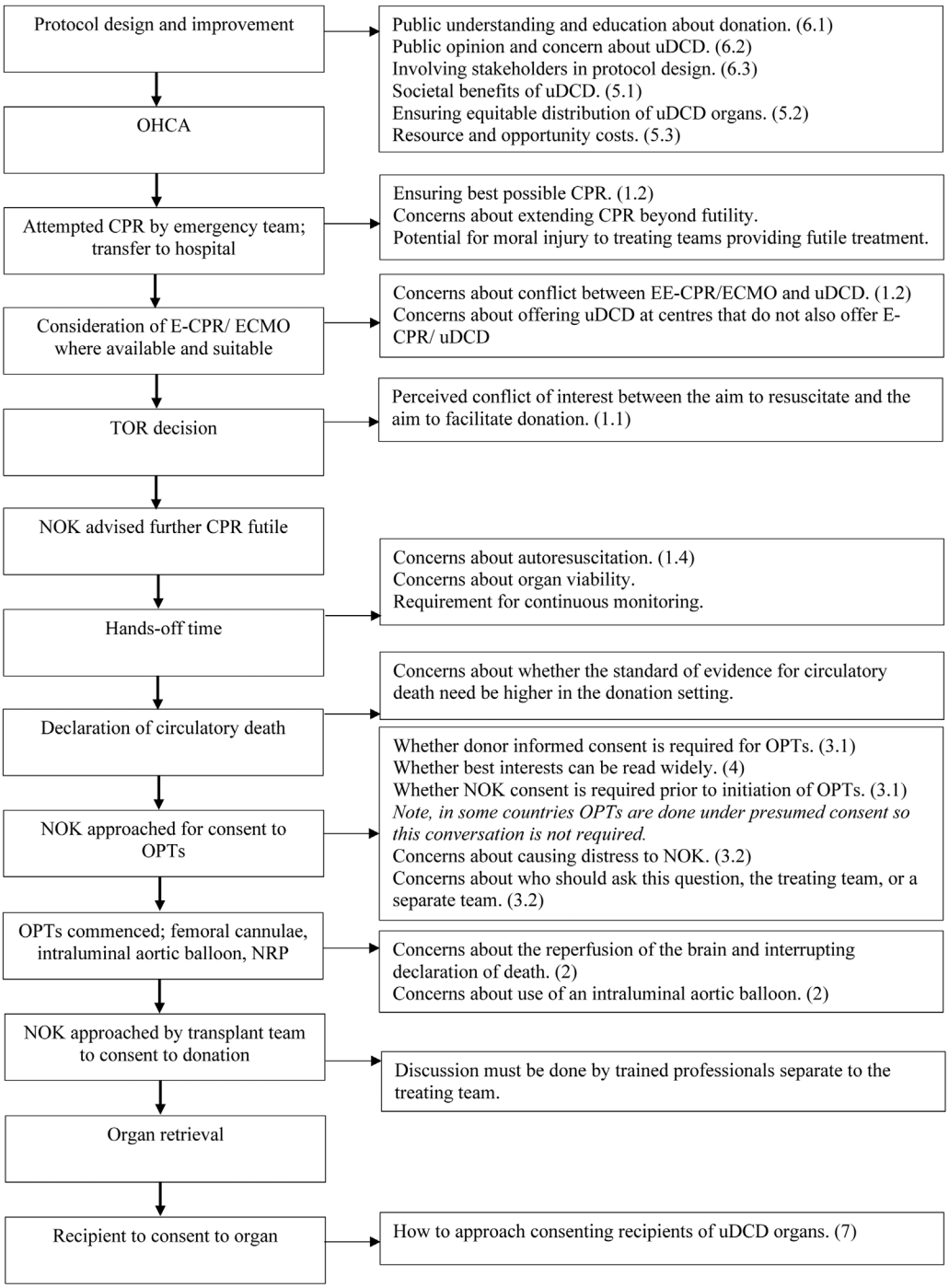


FIGURE 1 | A visual representation of the ethical issues associated with uDCD. On the left, going from top to bottom, are the stages of a typical uDCD protocol in chronological order. On the right are the ethical issues associated with each stage. The numbers in brackets refer to the paragraph in which the issue is discussed. This figure was derived from our synthesis of the results in this paper.

There appears, therefore, to be an ethical imperative to explore conducting uDCD; the International liaison Committee on Resuscitation recently conducted a thorough review of international protocols and concluded that "*All health systems should develop, implement, and evaluate protocols designed to optimize organ donation opportunities for patients who have an*

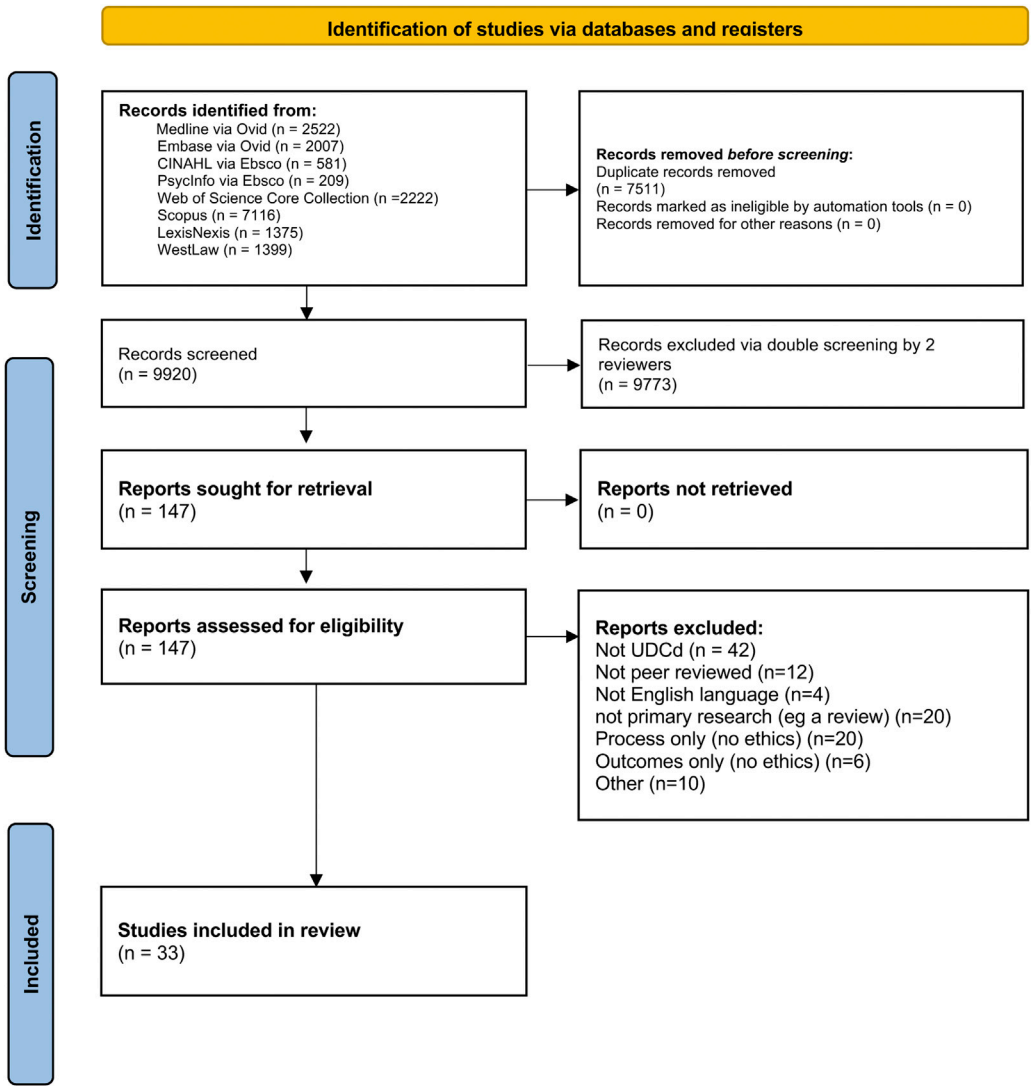


FIGURE 2 | PRISMA diagram combining data from initial and rerun searches.

out-of-hospital cardiac arrest and failed attempts at resuscitation" [43] but teams doing so must be fully informed its associated ethical issues so that they can address them within their protocols. Previous work has systematically delineated some specific issues: Bastami et al collated evidence surrounding healthcare providers' and the public's attitudes towards donation after cardiac death [44], Molina-Perez et al reviewed the role of families in deceased organ donation [45] and Schou et al reviewed ethical issues associated with extracorporeal life support [46] while Schiff et al have examined ethical issues associated with integrating ECMO and organ preservation in the USA [47]. However, there is no systematic review of original empirical studies or analyses on the ethical issues associated with uDCD.

We therefore undertook this review in order to (i) identify areas of ethical tension which need further research or stakeholder engagement and (ii) reveal areas of broad ethical consensus or empirical resolution. By doing this, we hope to be able to support those developing uDCD programs and direct researchers onto fertile ground.

METHODS

Search

We systematically reviewed the literature for original, peer reviewed, articles on the ethical issues associated with uDCD.

MEDLINE via Ovid, Embase via Ovid, CINAHL via Ebsco, Scopus, PsycInfo via Ebsco, LexisNexis, WestLaw and Web of Science Core Collection were searched using the following MeSH terms or other subject terms, and synonyms. The full search strategy can be found in the **Supplementary Appendix**, but can be summarized as: (1) out of hospital cardiac arrest terms OR uncontrolled AND (2) donation terms (adj5) AND (3) ethical OR legal terms The search was designed by a health librarian (IK) in

TABLE 1 | Inclusion and Exclusion criteria.

	Inclusion	Exclusion
Publication type	• Peer-reviewed • Journal, article, or chapter • Original analysis or data, e.g., original ethical analysis, empirical data pertaining to ethical issues about uDCD, or systematic ethical analysis • English language • Date from 01/01/1997 onward	• Not peer-reviewed • Opinion piece, commentary, review • No abstract • Not original analysis nor data (review article) • Systematic review (unless systematic ethical analysis)
Publication content	• uDCD • Ethics • Law • Policy analysis • Protocol analysis	• cDCD only • Pediatric (<18 years) organ donation • Non-human organ donation • Ethical issues relating to cellular level research • About process of donation only • About outcomes of uDCD only

TABLE 2 | Publication characteristics of included papers.

	n/ 33	%
Country	16	48
USA	3	9
Canada	3	9
UK	3	9
Spain	2	6
Switzerland	1	3
Belgium	1	3
Netherlands	1	3
Italy	1	3
Sweden	1	3
Denmark	1	3
Brazil		
Region	19	58
North America	13	39
Europe (continent)	1	3
Other		
Publication type	1	3
Systematic ethical analysis	14	42
Primary ethical analysis	3	9
Primary ethical and legal analysis	5	15
Empirical analysis of public perception	2	6
Empirical analysis of healthcare professional perception	1	3
Empirical analysis of public and healthcare professional perception	1	3
Empirical analysis of mass media campaigns	2	6
Commentary on a protocol	3	9
Primary ethical analysis and commentary on a protocol	1	3
Case study, ethical and legal analysis		
Date of publication	8	24
2001–2010	22	67
2011–2020	3	9
2021-May 2023		

collaboration with authors AG and ZF. Searches were run from 1st January 1997 until 1st April 2022 and re-run 30th May 2023 and again Sept 19th 2024. See **Figure 2** for the PRISMA flow diagram.

Screening

9,920 papers in total (7,605 in 2022, 1,035 in 2023 and 1,280 in 2024) were screened for inclusion/ exclusion, using the criteria shown in **Table 1**. Three authors, AG, MI and ZF, performed screening. Each paper was blindly screened by two of the three screening authors using Rayyan. The inclusion and exclusion criteria were applied to the title and abstract, and where the outcome was ambiguous, the full publication was read in full by all three members of the screening team and discussed until conflict was resolved.

We included two kinds of papers:

1. Papers which presented original peer reviewed ethical analysis (where ethical analysis is defined as: identifying questions regarding what is the "right" thing to do (or what we ought not to do); critically and reflectively examining [48, 49] different viewpoints; and presenting a reasoned argument, ideally with a normative conclusion of issues relating to uDCD) [50, 51].
2. Papers which presented empirical data pertaining to ethical issues about uDCD, in particular, studies examining perceptions of uDCD.

Systematic reviews were excluded from the review, although these papers were read as a further way of identifying relevant papers. Reviews, commentaries and opinion pieces were excluded. Papers which reported protocols, outcomes or processes of donation without ethical analysis were excluded. The nature of the included papers can be seen in **Table 2**.

Second Screening

All papers included on the basis of title and abstract were read in full by authors AG, MI and ZF. The inclusion/ exclusion criteria were applied blindly by each member. A full team meeting was held to agree final includes.

Re-Runs of Search

The search was re-run in May 2023 using the same method as above, and again in October 2024 following peer review. A fourth member of the research team, author WT, read all papers included from both searches in full to ensure consistency of application of inclusion and exclusion criteria. Any conflicts were discussed and resolved as a team.

Quality Assessment

In alignment with the PRISMA guidelines for scoping reviews, an assessment of whether quality assessment would be appropriate was undertaken [52]. Given the wide range and nature of articles identified, a formal quality assessment of included studies was not performed [53].

Data Extraction and Analysis

The final included papers were read in full by authors AG and ZF and data was extracted.

A excel spreadsheet was created for extraction of data relating to both publication characteristics (title, date, author(s), country, article type, participants, limitations and content. Framework analysis was undertaken [54]: an initial coding framework was created based on themes identified in the background literature (see **Supplementary Appendix** for data extraction proforma).

TABLE 3 | Proportion of papers addressing each ethical issue.

Ethical issue				n/33	%
1	Optimization and termination of CPR, declaration of death and hands-off time	1.1	Conflicts of interest between treatment and transplant teams	15	45
		1.2	Optimization and termination of resuscitation	11	33
		1.3	Declaration of death	15	45
		1.4	Hands-off time	8	24
2	The use of organ preserving techniques			19	58
3	Consent and involvement of next of kin	3.1	Informed consent to the use of organ preserving techniques	17	52
		3.2	The approach to the discussion of organ donation with next of kin	22	67
4	Best interests, and whether this can extend beyond strict medical benefit			8	24
5	Societal responsibilities	5.1	Societal benefits of uDCD	25	76
		5.2	Distributive justice	6	18
		5.3	Resource cost	11	33
6	Public and professional knowledge, opinion, engagement and trust	6.1	Public understanding, education, and transparency	21	64
		6.2	Public opinion and concerns about the uDCD process	21	64
		6.3	Involvement and engagement	23	70
7	Informed consent to the receipt of organs from uDCD donors			2	6

Having familiarized themselves with the data in each paper, and iterated the initial coding themes further, authors AG and ZF independently coded each paper.

Further themes were added upon data extraction and discussion among the authors, who together charted, mapped (see **Figure 1**) and interpreted the data.

Some themes were grouped together for ease of understanding, with sub-themes being created. For example, the themes of "consent" and "'relatives" were brought together under one heading, "consent and involvement of next of kin," with two sub-themes, "informed consent to the use of organ preserving techniques" and "the approach to discussion of organ donation with next of kin" having emerged. In another example, "optimisation and termination of resuscitation" emerged as an important theme.

The final coding framework comprised seven broad ethical themes, along with subthemes. The frequency with which each ethical theme was raised in the literature was documented.

RESULTS

Publication Characteristics

33 papers were included. **Table 2** shows publication breakdown by country of origin, region, publication type and date.

Ethical Issues

7 broad ethical themes, along with subthemes, were identified. **Table 3** shows the proportion of papers addressing each issue. We explore each of these themes below and summarize the results in **Table 4**, highlighting areas of broad consensus and areas of ongoing ethical tension.

Optimization and Termination of CPR, Declaration of Death and Hands-Off Time

An overarching ethical challenge that was identified throughout the literature was the perceived tension between maximizing the chances of successful resuscitation for the patient who has arrested and maintaining organ viability if resuscitative attempts were to fail.

Conflicts of Interest Between Treatment and Transplant Teams

Many authors recognized a potential for conflicts of interest (or perceived conflicts of interest) at several stages of the uDCD protocol; if one team, or several closely linked teams, make(s) decisions about resuscitation, termination of resuscitation (TOR), declaration of death and recruitment into the uDCD protocol, questions about the quality of resuscitation, whether all efforts were made to save the patient's life [8, 55] and about financial incentives [55, 56] are raised. Individual physicians may be placed in positions of conflict [55, 56] and perceived conflict of interest can erode trust in the donation system and medical system more broadly [57]. These concerns are reflected in quantitative data: Goudet et al found that a majority of healthcare respondents in their multicenter survey thought there is conflict of interest between saving lives and saving organs in the uDCD context [58].

Many proposed separating the roles [8, 21, 59, 60] although it was recognized this would not eliminate conflict if the teams are in contact [8, 21] and presents logistical and resource challenges [8, 21, 22, 59, 60].

Optimization and Termination of Resuscitation

It was universally accepted that CPR should not be terminated until it was clear that continuing would be futile for the patient. There is insufficient research to recommend a specific duration of resuscitation [61] and no internationally accepted guidance [58, 61–63] but most protocols mandate at least 20–30 min [8, 22].

Beyond traditional attempted CPR, several authors considered the role of Extracorporeal CPR (E-CPR) and Extracorporeal Membrane Oxygenation (ECMO) to ensure that optimal CPR had been delivered before TOR. Authors questioned whether doctors might be choosing between attempting E-CPR/ECMO (or directing a patient towards a center that provided this) and

TABLE 4 | Summary of results.

Ethical issue		Areas of consensus	Areas requiring further research
1 Optimization and termination of CPR, declaration of death and hands-off time	*1.1 Conflicts of interest between treatment and transplant teams*	Decisions about TOR and uDCD entry should be made by different teams	Ensuring true separation between teams
	1.2 Optimization and termination of resuscitation	At least 20–30 min of CPR.	Factors precluding TOR. Location of TOR. Role of E-CPR/ ECMO.
	1.3 Declaration of death		Standard of evidence of circulatory death
	1.4 Hands-off time	At least 5–7 min alongside continuous monitoring	
2 The use of OPTs		The least invasive methods possible should be used	Ethical acceptability of aortic occlusion balloons
3 Consent	*3.1 Informed consent to the use of OPTs*		Whether consent to OPTs is covered under general consent to donation Whether OPTs can be commenced prior to family consent
	3.2 The approach to the discussion of organ donation with next of kin	Families can be approached early, with sensitivity and respect and by trained staff	
4 Best interests			Whether best interests can be read widely at the population level to include wishes to donate
5 Societal responsibilities	*5.1 Societal benefits of uDCD*	uDCD will increase the organ pool and has other psychosocial benefits	
	5.2 Distributive justice	uDCD organs must be recovered and distributed in an equitable way	Ensuring equity of recovery and distribution
	5.3 Resource cost		Short and long term financial and opportunity costs of uDCD.
6 Public and professional knowledge, opinion, engagement and trust	*6.1 Public understanding, education, and transparency*	Public knowledge about uDCD is poor and must be improved via unbiased education	
	6.2 Public opinion and concerns about the uDCD process		Public opinion on uDCD in different intersections of society Impact of uDCD on trust
	6.3 Involvement and engagement	Public education and stakeholder engagement is imperative Debate should be facilitated	
7 Informed consent to the receipt of organs from uDCD donors		Transparency and informed consent are essential	

consideration of donation (or directing a patient towards a center that delivered this). ECPR is not yet widely available and evidence of its efficacy in the out-of-hospital cardiac arrest setting is still being gathered [55, 59, 61, 63]. Authors questioned whether the inclusion criteria for ECMO/E-CPR and uDCD are sufficiently similar for there to be a conflict [8, 55, 64], whether allowing uDCD without ECMO/E-CPR may disincentivize development of the latter [59, 60] and erode public trust [64] and whether insisting that all uDCD centers participate in ECMO/E-CPR practice or research will hinder donation, frustrate donor wishes [59] and create significant numbers of vegetative patients [65]. One of the included papers offered quantitative data; Goudet et al in their survey of 1057 hospital staff found that 20% of respondents thought that donation after circulatory death protocols should be suspended until precise indications for ECMO/E-CPR in refractory cardiac arrest have been defined [58].

There was consensus that TOR should be prohibited out of hospital while excluding reversible causes, i.e., if a shockable rhythm is present [8]. Ave et al went further, cautioning against TOR in non-shockable rhythms too as in the out-of-hospital cardiac arrest setting fine ventricular fibrillation and pulseless electrical activity could be missed; they considered the use of echocardiography at the hospital to rule this out [8]. Some protocols make TOR decisions upon arrival in the hospital [60], but some make them in the out of hospital setting, and then provide organ-preserving CPR during transit to the hospital [8, 66] whereupon death will be declared. In these latter cases there are concerns that the quality of CPR might be "subconsciously" compromised during transport [61].

Declaration of Death

In the circulatory determination of death, it is said that death is being declared at the permanent stage and that irreversibility will rapidly and inevitably ensue as no methods aiming at resuscitation will be performed [8, 59, 63, 65, 67–72]. Debate in terminology about declaration of death centers on these concepts of permanence (that circulation *will* not be restored) and irreversibility (that circulation *cannot* be restored); see **Supplementary Table SB** for further details. Some authors suggested that declaration of death in possible donation circumstances may require a higher standard of evidence of circulatory cessation than in non-donation circumstances

because the consequences are greater for the patient [68]. For example, rather than relying on mechanical asystole it may be necessary to prove absence of circulation via arterial line, arterial doppler or echocardiogram [8]. The approach varies considerably in different countries [8, 71].

Conversely, some authors argued that declaration of death in the uDCD setting is less complex as by definition the patient will have undergone rigorous resuscitative efforts known to have failed [65, 66, 69]. Survey data is inconclusive, with some studies associating donation after circulatory death with greater perceived certainty of death than Donation after Brainstem Death (DBD) [71] and others finding the opposite [70].

A common theme in the papers was to comment on logical and semantic inconsistencies that have emerged over the years as new definitions of death were introduced to facilitate new donation practices [65, 71] (in one case referred to as "gerrymandering" [65]); death was historically defined by cardiac, or circulatory, criteria and the concept of brain death was introduced in the 1960s to allow DBD. See **Supplementary Table SB** for a summary of the changing definitions of death.

Hands-Off Time

Debate about the length of hands-off time – the period between termination of resuscitation, declaration of death, and initiation of insertion of cannulae for organ preservation – focused on a tension between concerns about case reports of autoresuscitation (also known as Lazarus phenomenon) [8, 59, 61, 68] and maximizing organ viability [59]; too short a period risks not giving opportunity for autoresuscitation and too long a period risks reduced organ viability.

Ave et al referenced Hornby's systematic review of case reports of autoresuscitation: they are small in number, and most have occurred at under 5 min; those that occurred after that did so in the absence of continuous monitoring [8]. In view of this, Parent et al concluded that risks of autoresuscitation after 10 min are extremely low, and continuous monitoring would pick up those that occurred [59].

France and Spain have a hands-off period of 5 min [8]; Goudet et al, based on a survey of healthcare professionals, suggested a minimum of 2–5 min no touch time is necessary [58].

The Use of Organ Preserving Techniques

Once death has been declared, and a hands-off period observed, organ preserving techniques (OPTs) are instigated. Broad ethical issues include risk of resuming brain circulation [8, 63, 65, 69, 73] and retroactively negating declaration of death [8, 68, 70], violation of bodily integrity [8, 58, 62, 72, 74], resource cost [8, 72] and stress for the treating physicians [8].

Violation of bodily integrity was the most cited with a common theme: there was consensus that the least invasive methods possible should be used to preserve the opportunity to donate [59, 62, 74–76]. Bruce et al's study of emergency department (ED) patients and relatives found that a majority felt that insertion of groin tubes, CPR and ventilation were acceptable as OPTs, if there was as little invasion of the body as possible [75] and Goudet et al's survey found that majority of respondents did not consider cannulation as a "bodily integrity alteration" [58]. Volk et al also found support for OPTs; 80% of their participants expressed support for a rapid organ recovery where they live [57].

Many authors commented on the ethical issues raised by specific techniques. Use of NRP (ECMO to perfuse the organs only) is defended by some [65, 72] as an essential means of preserving donation opportunity with good outcomes for kidneys [65] but specifically opposed by others [8, 63, 68, 69]. Use of an aortic occlusion balloon was described by some as a responsible method of facilitating organ preservation whilst preventing perfusion of the brain [60, 65, 67, 77] while others were concerned that it might render a physician complicit in a patient's death [8, 63, 68, 70]. Use of cold preservation solution was opposed by two authors for reasons of poorer outcomes [65] and interference with determination of death [8] but supported by others as it carries less risk of brain reanimation [68]. Dubois et al in their survey of 70 members of the public found that 72% expressed support of a law permitting organ cooling in order to preserve organs [78].

Consent and Involvement of Next of Kin

Given the time pressures of instigating OPTs, several authors explored the issues with consent, and attempted to determine the optimal timing, place, and content for conversations with relatives of the deceased which are both respectful of autonomy and compassionate. Volk et al found that hypothetical family consent to donation in uDCD settings was high [69% (95% CI 65%–73%)] when compared with cDCD [70% (95% CI 66%–75%)] and DBD [66% (95% CI 62–71)], however that participants were less confident in making donation decisions about a relative when compared with themselves (71% and 75% respectively) [57].

Informed Consent to the Use of OPTs

While some authors argued that consent for OPTs is covered under general consent for donation [58, 60, 62, 69, 79], most felt it was not: authors argued most frequently that the public are not well enough informed about what OPTs involve [8, 73, 80] and, to a lesser extent, that OPTs are not done strictly for the patient's direct benefit [63, 80] and that people's views on OPTs may be too nuanced to be summarized in one binary decision [81]. Several authors therefore proposed that specific consent was needed for OPTs given that they damage bodily integrity [8, 58] and could potentially violate patient autonomy [58].

Four papers provided survey data on the need for and optimal timing of family consent for OPTs (see **Table 5**) [57, 58, 75, 78]; a slim majority in three papers felt it was acceptable to proceed with OPT prior to family consent, but only 17% of participants in Volk's 2010 study thought it was acceptable to proceed "in the absence of family consent or a known donor card" [57]; this study took place in the setting of an "opt in" system.

In support of commencing OPTs prior to family consent were arguments that OPTs in uDCD are no more invasive than interventions done in the DBD setting [74], that it is the only way to preserve the family's opportunity to make their own decision [79] and that to do otherwise renders protocols logistically impossible [21, 22, 67, 73]. Light et al and Wall

TABLE 5 | Survey results on the acceptability of commencement of OPTs prior to gaining family consent.

	Commencement of OPTs while family consent is being sought IS acceptable	Commencement of OPTs while family consent is being sought is NOT acceptable	Unsure
Dubois et al [78]	49%	39%	12%
Goudet et al [58]	46.8%	42.5%	10/7%
Volk et al [57]	17% (95% CI 13%–20%)	Not available	Not available
Bruce et al [75]	48% (groin tube), 51% (CPR), 57% (ventilator)	28% (groin tube), 24% (CPR), 21% (ventilator)	24% (groin tube), 25% (CPR), 22% (ventilator)

et al reflected on their experiences in Washington, D.C. and New York respectively in which the requirement for family consent was the main barrier to success [21, 22, 67]. Other authors supported use of OPTs prior to family consent but only if the techniques are minimally invasive [59, 82]. Some argued strongly for the opposite: that OPTs should only be applied once both donor consent *and* family consent have been confirmed [57, 69]. Arguments for this approach included reducing mistrust [78], respect for autonomy [63, 83], reduction of resource cost [83] and reduction of family distress [60].

Two alternative systems were suggested: Moorlock et al proposed a detailed anticipatory consent form with which people can learn about and communicate their nuanced views on the complexities of OPTs [81] and Verheijde et al questioned whether a system of mandated informed decision making would be best [63]. These models for anticipatory specific consent would overcome concerns that specific consent for OPTs would render uDCD protocols logistically unworkable in an emergency setting [8, 21, 67, 76] thus reducing the number of available donors.

The Approach to the Discussion of Organ Donation With Next of Kin

Most papers found an acceptance for conversations about donation with next of kin to happen early in the acute setting. Wall et al described that, in the New York protocol, families were not offended by being asked soon after witnessing their loved one's unexpected death [67]. Bruce et al, in their study of 200 members of the public, found that most people (54%) were willing to discuss donation soon after death in the ED [75], and that there is no difference in the number willing to discuss donation after circulatory death in ED (as is the case in uDCD) compared with brain death in ITU (72% in both cases, $p = 0.146$) [75]. Consistent with this, Wind et al found that consent rates were higher in patients who had an unexpected death than in those who had an expected death (61% and 45% respectively, $P = 0.007$) [82]. These empirical studies go some way to addressing Light's concerns that it may be hard for families to cope with a sudden loss and the question of donation at the same time [22], although time constraints in contacting families may present a logistical barrier [22].

There was consensus that families should be approached with sensitivity and respect, by staff with specialist training [75, 80].

Best Interests, and Whether This Can Extend Beyond Strict Medical Benefit

In uDCD protocols the patient will lack capacity and decisions must be made in their best interest [84, 85]. Best interests decisions must be made on a case-by-case basis [80, 81], but often little is known about the individual's desires in the emergency situation: best interests decisions are therefore based in the first instance on population level knowledge.

If the concept of best interests is taken in its narrow, medical sense, uDCD becomes ethically challenging because OPTs are invasive and done beyond the point at which there will be medical benefit to the patient. Potential harms to the patient are physical [72, 73, 80], and non-physical e.g., treating the patient as a means to an end [73], violation of a deep desire to not donate [73], distress to the family [80], and impact on the dignity of a person [62]. Moorlock et al and De Lora et al questioned whether any harm can be inflicted on a nearly dead patient [80, 81] but concluded that there is a duty to treat cadavers with respect [80], and that respect for dead persons and posthumous wishes is an established ethical concept [81].

Several authors suggested that best interests should be interpreted more broadly than considering physical integrity [72]. Arguments included that best interests are now accepted as extending beyond the strictly clinical [80] and include fulfillment of wishes to donate [73, 80], promotion of dignity for example by "favoring the accomplishment of their life project" to donate [62] and permitting altruism in end of life planning [73]. OPT may preserve the family's opportunity to make their own informed decision about donation [80] and preserve the autonomy of those patients who turn out to have expressed wishes to donate [72]. Without OPTs, the opportunity to donate is lost [72, 74, 78].

Societal Responsibilities

Several papers considered the ethical duty to consider responsibilities to society as well as to the individual.

Societal Benefits of uDCD

The most frequently raised benefit was the increased number of organs [21, 22, 55, 57–60, 63, 65–69, 71, 72, 74–79, 82, 83] and therefore reduced morbidity and mortality, which is widely seen as a "societal good" [74] with only one of the included papers disagreeing [63]. Several papers give data on the organ pool, providing international evidence of the potential benefit of introducing a uDCD program [57, 63, 65, 67, 69, 78].

Other societal benefits may include psychosocial benefits [73], comfort to grieving families [73], reduction in coercive or illegal organ practices if more legitimate organs are available [66], and economic benefits through taking patients off costly dialysis [72, 73] and returning them to economic activity [73].

Distributive Justice

Several papers addressed concerns that organs may be recovered and distributed in an inequitable way on the uDCD pathway. It was noted that uDCD is likely to be disproportionately available in large inner-city hospitals [64] and that these usually serve socioeconomically disadvantaged populations [55, 61, 64] in which cardiac arrest [61] and violent or traumatic injury [22, 55, 61, 64] is more common. Authors commented on the disproportionate representation of ethnic minorities in donor populations [55, 64], resulting in complaints that the system is biased [55], and on minority group members expressing significant mistrust and suspicion toward organ donation [64]. Moorlock et al noted that uptake of advance care planning has been found to be lower among older people from ethnic minorities [81] and questioned whether their own proposal to introduce a comprehensive consent form would exacerbate existing inequalities in organ donation.

Ave et al argued that socioeconomically advantaged patients who have better access to health resources may be more likely to receive a uDCD transplant [61], and a case of perceived unjust allocation of organs to a wealthy, prominent figure was noted [64]. In contrast, Wall et al discussed data showing that underserved communities are disproportionately affected by conditions leading to renal failure and therefore receive more organs [66]. Allocation by age of recipient was raised by Light et al; they noted that recent moves to use expanded criteria donors have not benefitted younger, healthier recipients, only older ones, but that uDCD programs may.

Resource Cost

uDCD protocols are highly resource intensive [8, 22, 60, 66, 67, 69, 72, 73, 83, 86] in view of the equipment, personnel [60], transport [8] and training costs. The opportunity costs (for example in ambulances being unavailable for other sick patients because they are being used to transport patients into ED who might otherwise have been declared dead out of hospital [69]) associated with a uDCD program are significant although not universal and would vary depending on individual center capacities [73]. Some papers discussed ideas for mitigating opportunity costs, for example having separate ambulances for potential donors [83] or limiting uDCD to in-hospital settings only [69]. Several authors postulated that the overall uDCD costs would be mitigated in the long term with fewer patients on dialysis [69, 73] and with the development of economies of scale as projects expand [66].

Public and Professional Knowledge, Opinion, Engagement and Trust

Public and clinician trust in organ donation and in the wider medical system is imperative and links to our societal responsibilities [64]. If people do not trust the system they are less likely to donate and support transplantation as a whole [69].

Public Understanding, Education and Transparency

Several authors reported that current public understanding of uDCD is poor [8, 58, 86] and that uDCD protocols can differ substantially from common ideas of what donation involves [8]. In France and Spain no program of public information was conducted; the opt-out system was introduced without data on public opinion [8]. Bednecko et al found that 60% of their participants in Brazil didn't know about donation legislation [86], and Goudet et al found that a majority of their survey participants in France considered the paucity of public information to be unacceptable and possibly reflective of concerns the medical community itself has about uDCD [59].

Most authors agreed that more substantial public information is needed [58]. Understanding allows people to make informed autonomous decisions [8, 80], helps to avoid mistrust in the system [8, 64], ensures that policies are ethically acceptable [80], improves enrollment rates [66] and may even reduce illegal organ trade [66]. Education must be transparent and accurate [8, 56, 69, 72], comprehensive [59], be directed toward the local community [64], include information on how to opt-out [8, 80, 81], and be deliverable through diverse media [22].

Rady et al emphasized the difference between education (providing information) and propaganda (communicating with a view to influence) and suggested separation of the governmental agency responsible for organ transplantation practice from the agency responsible for organ donation campaigns [56]. They based this proposal on concerns about bias, inaccuracy, misinformation, and undeclared conflicts of interests perceived in other campaigns [56] and a noted discrepancy between controversies happening in the scientific communities, and public messages which suggest no such controversies exist [70]. Moorlock et al's proposal involves integrating education materials and specific elements of consent [81].

Public Opinion and Concerns About the uDCD Process

Several papers provided empirical data on opinions toward uDCD, with four finding equal support [57, 58, 71, 75], and two finding less support for uDCD than other types of donation [70, 86].

uDCD protocols have potential to engender mistrust due to the use of OPTs without consent [78], concerns that the patient may not actually be dead [56, 70, 72] and that there is violation of the prohibition against interfering with a dead body [66, 69, 83]. Several authors raised that mistrust is disproportionately felt by ethnic minorities [55, 64, 78]. Perceived conflict of interest between treatment and donation can cause mistrust toward, and between, healthcare professionals [63, 64] owing to the perception that organ donors may receive less aggressive life-saving care [59, 73], although Volk et al's study reported that "the idea of a rapid organ recovery program did not significantly increase fears that signing an organ donor card would make doctors not try as hard to save their life" [57].

Involvement and Engagement

Most authors agreed that, in order to achieve transparency, accountability [64], and sustainable program success [67] numerous stakeholders must be consulted, including the government, the transplant network, public health, medical and ethical communities, the public [60, 65], secular and

religious community organizations [59, 67, 71], community boards representing multi-ethnic populations [66], emergency practitioners [49] and specific local stakeholders [73]. Several authors also suggested that open and clear debate among both healthcare professionals and the public should be facilitated [62, 83], and Dubois et al raised the importance of monitoring uDCD protocols, suggesting that review boards be set up to assess adherence to policy and ensure accountability [78].

Delora et al explored how the mandate for uDCD protocols is established. They delineate the difference between allowing the initiation of OPTs on the basis of presumed consent via parliament legislation, as was the case in the Netherlands [80], and via governmental decree, as was the case in Spain [80]. The former involves democratic, accountable debate whereas the latter does not [80].

Informed Consent to the Receipt of Organs From uDCD Donors

Finally, two of the included papers raised the issue of how recipients of organs procured via uDCD should be consented for a transplant [8, 76] and how much information they should be given on the source of the organ. Data suggests that the long-term outcomes of organs transplanted in uDCD protocols are as good as those transplanted in DBD protocols [62] and in cDCD protocols [22, 59] however there is evidence to suggest that there is a higher rate of shorter term complication, i.e., delayed graft function in uDCD [8]. Transparency and informed consent are essential, particularly in areas where uDCD is in development.

DISCUSSION

We have reviewed the literature on uDCD and identified areas of broad consensus and areas of ongoing ethical tension. Teams proceeding in piloting uDCD protocols, should do so with concurrent outcome and ethical evaluation. Several issues require further analysis; we will focus on four with reference to wider empirical, philosophical, and ethical literature.

Optimizing Outcomes for the Individual and for the Organs

In attempting CPR, the primary intention is to regain spontaneous circulation and neurological recovery for the patient [87]; a secondary effect is optimal perfusion of the organs for transplantation should CPR be stopped. In transferring a patient to hospital, the primary intention is to ensure a comprehensive assessment of the irreversibility of the condition; a secondary effect is ensuring efficient organ recovery should CPR be stopped. Therefore, by optimizing CPR and transferring an arrest patient to hospital, the treating team is both optimizing patient outcomes and organ viability; they are not choosing one over the other [88].

Further, once CPR is stopped, 5 min of hands-off time followed by 5 min of continuous monitoring while cannulating results in a total of 10 min before the aortic occlusion balloon is inflated and NRP started. While case studies of autoresuscitation have been reported after termination after CPR, most are associated with confounders and a recent systematic reviews showed that it is extremely rare for them to take place after 10 min; none have occurred in the situation being proposed, with continuous monitoring for 5 min [89–91].

Some caveats do remain. First, we found consensus that decisions about TOR and entry into a uDCD protocol should be made by different teams; research into the logistics and outcomes of this is needed. Second, we found disagreement over whether the level of resuscitation should extend beyond advanced life support to ECMO/E-CPR; more research is needed into the benefits of these techniques in the out-of-hospital cardiac arrest setting and the impact that having uDCD without ECMO/ E-CPR may have on outcomes and on community trust.

Best Interests Can Extend Beyond an Individual's Lifetime

Authors of the included papers disagreed whether best interests in the uDCD context extend beyond the strictly clinical and beyond the individual's lifetime. UK law supports a broad reading of best interests, and in the cDCD debate it has been argued that "where a patient would wish to donate, measures [that] are necessary for organ donation to proceed . . . serve, rather than deny, the best interests of a patient" [92] and are therefore autonomy respecting. The difficulty is that within an opt out system (and without Moorlock and Draper's ambitious proposal of mandated anticipatory consent) [81], the specific wishes of most individuals are not known.

Although best interest decisions are, by definition, person specific, they are often initially made on population level knowledge. For example, a person found in cardiac arrest will be subject to CPR while further information on their wishes is sought [93]. This logic can reasonably be applied in the donation setting given that a majority of the population – with the information currently available to them – would like to donate [2]; while information is being sought about a person's wishes, it may be in their best interests to cannulate and start NRP to preserve opportunity for donation.

The Role of the Aortic Occlusion Balloon

There has been significant discussion about the role of the aortic occlusion balloon in All forms of DCD [8, 60, 63, 65, 67, 68, 70, 77, 94, 95]; this discussion is intimately associated with the definition of death [47, 96], and the philosophical debate around the ethical relationship between acts and omissions [97].

The device is required because a secondary effect of starting NRP is to resupply blood and oxygen to the brain to the same level of the attempted CPR. There is no evidence that this level of recirculation is likely to facilitate awareness or pain, but it is impossible to say for certain that there is no perception. Therefore, to avoid an unintended harm, the aortic occlusion

balloon is inserted to prevent all circulation to the brain and maintain a peaceful death.

A recent prospective study by Royo-Villanova et al showed that when the thoracic aorta was blocked with an aortic occlusion balloon the mean intracranial arterial blood pressure at the circle of Willis was the same during circulatory arrest as it was following NRP being started, confirming that this technique works to stop brain perfusion [98]; this study should provide reassurances to those to those who were concerned about the efficacy of the aortic occlusion balloon.

Some have expressed concern that insertion of an aortic occlusion balloon in order to block circulation to the brain is itself an act which hastens death [8, 59, 63, 68]. In the cases we are considering, however, the patient has already died; their heart has stopped, there has been no responsiveness with CPR, and a multidisciplinary team has recognized the futility of further efforts. We agree with Schiff et al who say: "this is similar to *ex vivo* perfusion, in which perfusion is restored to the recovered organ to increase transplant viability, while the process towards loss of brain function in the donor body is allowed to continue." [47] On this view, the aortic occlusion balloon is acting to minimize harm, while maximizing the individuals' potential to donate.

Transparency and Public Engagement

The above conclusions - namely that the interests of both resuscitation and donation can be simultaneously respected; that best interests apply posthumously and can be read broadly; and that an aortic occlusion balloon is in a patient's best interests – are contingent on transparency and public engagement [8, 47, 56, 58, 59, 63, 64, 69, 72, 80, 83, 99]. If population level data is to be used to inform initial presumptions about what is in a patient's best interests, public attitudes must be regularly surveyed and assumptions cannot be made [8, 56, 62, 80, 83].

There is some nervousness surrounding public discussion of the details of uDCD. While public attitudes toward donation are predominantly positive, there is an awareness that one bad media story can change views and potentially cost lives if it results in people opting out [21, 22]. The risks are increased when - as needs to be done - relatives are being asked to consent not only for transplant but for research into a new way of undertaking transplant. This nervousness is justified given the stakes, but it is a reason for ensuring that information about transplantation is understandable and widely available; hiding information is much more likely to erode trust in the long term. We should borrow from the World Health Organization's advice on transparency in public health emergencies: information must be *"factually accurate, easily understood by the intended audience and presented in a manner that promotes adoption of the desired behaviors"* and we *must "promote trust by being forthcoming and open …, including the evidence and assumptions used by authorities in making decisions, the manner in which those decisions are being made and by whom."* [100]

Finally, if public engagement and trust are to be sought, an alternative name to "Uncontrolled Donation after Cardiac Death" should be considered. The name derives from differentiating it from the controlled setting of an intensive care unit with planned withdrawal of treatment, but to those who don't know this history, the term "uncontrolled" implies chaos and lack of regulation. As O'Rourke et al state, "who would wish to be involved in an "uncontrolled process"?" [101] A name that clearly describes the practice could be considered: Organ Donation After Sudden Irreversible Cardiac Arrest (ODASICA), or some other clearly descriptive explanation, may go some way towards engaging the public.

STRENGTHS AND LIMITATIONS

We conducted a scoping review of the literature: the selection of papers was systematic, and blinded. Data was extracted on a standardized template and more than two authors read each paper to ensure agreement on the relevant themes.

Our study has limitations. There is some subjectivity in determining the difference between a review article and one which provides "original ethical analysis" of uDCD; we chose not to include review, opinion or comment articles as many of these were summarizing the articles which were already included. We may have missed some potentially relevant literature that did not fit the search terms, although this was minimized by snowballing the references which were identified. The review is based on published research literature and excluded operational or programmatic reports and book chapters which may have added valuable insights. The heterogeneous nature of the papers identified meant that it was not possible for us to evaluate quality of publications or provide many quantitative findings. The papers identified, however, provided rich material for a comprehensive review of the ethical issues associated with uDCD.

CONCLUSION

uDCD – or Organ Donation after Sudden Irreversible Cardiac Arrest (ODASICA) – is a complex process which is unfamiliar to many; carefully considering the ethical issues involved at each stage is therefore critical. This review provides evidence of broad ethical consensus in many areas. Future protocols should acknowledge remaining areas of potential conflict and prospectively collect empirical evidence from relatives and clinicians to ensure greater understanding and transparency.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

ZF conceived the study, and wrote the protocol with AG and IK. IK designed the search strategy and supported paper screening and retrieval. AG, ZF, and MI preformed the initial screening and analysis; WT contributed to the reruns of searches and analysis along with AG and MI. AG wrote the first draft of the methods and

results, ZF the first draft of the introduction and discussion; WT provided the figures and tables, IK the PRISMA diagram. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.13992/full#supplementary-material

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Monoclonal Antibodies in Prevention and Early Treatment of COVID-19 in Lung Transplant Recipients: A Systematic Review and Perspective on the Role of Monoclonal Antibodies in the Future

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Coronavirus disease 2019 (COVID-19) has significantly impacted lung transplant recipients (LTR), who remain vulnerable to severe COVID-19 despite vaccination, prompting the use of monoclonal antibodies (mAbs) as a treatment option. This systematic review summarizes the clinical efficacy of mAbs against COVID-19 in adult LTR and provides a perspective on the role of mAbs for infectious diseases in the future. A systematic search of PubMed/MEDLINE, Embase and Cochrane was conducted for studies reporting clinical outcomes of adult LTR or solid organ transplant recipients (SOTR) including LTR with drug-specific outcomes. Twelve studies were included. Pre-exposure prophylaxis with mAbs reduced COVID-19 breakthrough infection in LTR. Early treatment of COVID-19 with mAbs correlated with a reduced incidence of severe COVID-19 outcomes, although statistical significance varied among studies. Overall, observational studies have demonstrated a potential benefit of mAbs in the treatment of COVID-19 in LTR, both in prophylaxis and early treatment, as well as the importance of early administration. Moreover, mAb therapy appeared safe and could be a viable option against other pathogens, a route that warrants further investigation.

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Keywords: lung transplantation, COVID-19, Sars-CoV-2, monoclonal antibodies, tixagevimab/cilgavimab, sotrovimab, casirivimab/imdevimab, bamlanivimab

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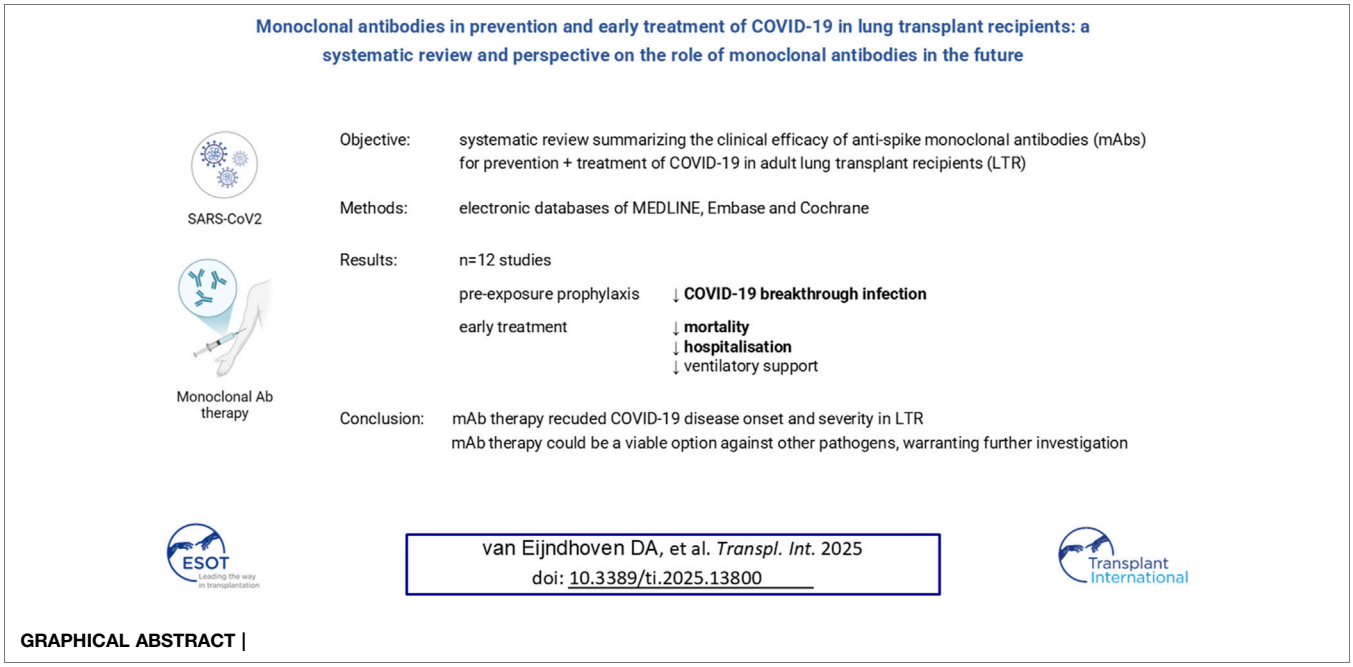
Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; LTR, lung transplant recipients; mAb, monoclonal antibody; PrEP, pre-exposure prophylaxis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOTR, solid organ transplant recipients.



GRAPHICAL ABSTRACT |

INTRODUCTION

Since its emergence in 2019, severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) significantly affected the field of organ transplantation. Solid organ transplant recipients (SOTR) are more susceptible to severe coronavirus disease 19 (COVID-19) outcomes compared to the general population, resulting in increased hospital admissions and mortality [1–3]. This is mainly due to a higher occurrence of underlying comorbidities and the use of immunosuppressive therapies in SOTR [3, 4]. Lung transplant recipients (LTR) in particular are at increased risk of severe COVID-19 compared to other SOTR [5–7]. Although mortality and hospitalization rates have decreased, LTR are still at elevated risk of severe COVID-19–related morbidity and mortality [8, 9].

Vaccination is a key element in the prevention of severe COVID-19. However, LTR have a lower antibody response compared to the general population, even after receiving multiple vaccinations [8–10]. The number of COVID-19 breakthrough infections after vaccination have been significantly higher in LTR compared to other SOTR [8, 10, 11]. Meanwhile, other prophylactic and therapeutic agents have been repurposed and developed to prevent and treat COVID-19.

Monoclonal antibody (mAb) therapy has been a promising treatment option for COVID-19. Multiple randomized controlled trials have reported reduced COVID-19-related hospitalization or death after administration of mAbs [12–16]. However, these studies were primarily focused on immunocompetent patients in an outpatient setting. Nevertheless, multiple mAbs received emergency use authorization for COVID-19 treatment in high-risk patients, including LTR. Subsequently, retrospective cohort studies reported decreased COVID-19-related hospitalization and mortality rates in SOTR after treatment with mAbs. Since then, mAbs have commonly been used for therapeutic management in SOTR [17, 18] However, the emergence of new SARS-CoV-2 variants has diminished the neutralizing efficacy of mAbs used early in the pandemic [17, 19]. Nevertheless, LTR and similar high-risk patients with weak post-vaccination antibody responses may still benefit from mAb therapy [4, 8, 10].

While multiple retrospective cohort studies reported use of mAbs in SOTR [20–22], data specifically about mAbs against COVID-19 in LTR remain scarce, even though LTR are identified as a high-risk group [6–10]. This systemic review aimed to describe the existing evidence pertaining the impact of anti-spike mAbs used for prevention and treatment of COVID-19 on clinical outcomes of adult LTR in two modalities: pre-exposure prophylaxis (PrEP) and early treatment in LTR with asymptomatic to moderate COVID-19.

METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [23]. A protocol for this review was registered on the PROSPERO International Prospective Register of systematic reviews (CRD42022382133).

Search Strategy and Eligibility Criteria

A systemic search on the databases of PubMed/MEDLINE, Embase and Cochrane Controlled Trials Register (CENTRAL/CCTR) was performed on 8th February 2023. The used search terms are listed in the **Supplementary Material**. Clinically commonly used COVID-19-specific, anti-spike mAbs were included. The following mAbs were included: tixagevimab/

cilgavimab, sotrovimab, casirivimab/imdevimab, bamlanivimab, bamlanivimab/etesevimab, regdanvimab, bebtelovimab, and sarilumab.

The articles were imported into Rayyan [24]. The abstracts and titles were independently screened by two reviewers (DV, SB) using predefined inclusion and exclusion criteria, followed by full-text review if potentially eligible for inclusion. Discrepancies were resolved by consensus.

Eligibility criteria were defined beforehand. The initial inclusion criteria were studies containing clinical outcomes on adult LTR after administration of mAbs, with drug-specific outcomes. Since only a limited number of studies reported LTR-specific data, we subsequently broadened the inclusion criteria to cohorts of SOTR that also included LTR [so only combined groups of SOTR, other organ transplant-specific outcomes (e.g., kidney transplant population) were not included]. Eligible studies included any randomized controlled trials, prospective and retrospective observational cohort studies, case series, and letters to the editor if they included clear data analysis. Conference abstracts, case reports, reviews, letters to the editor without separate data analysis, and non-English articles were excluded. No time restrictions were applied.

Data Collection Process and Items

One reviewer (DV) performed data extraction using a standardized data extraction form that was inspected by a second reviewer (SB). From each included study we extracted study properties, patient characteristics, therapeutic regimen, and outcomes. Main outcomes were overall mortality and COVID-19-related mortality. Additional outcomes were defined as incidence of hospital admission, intensive care unit (ICU) admission, necessity of respiratory support (defined as high-flow nasal oxygen, non- invasive ventilation or mechanical ventilation), secondary complications (bacterial and fungal secondary infection, renal insufficiency, and venous thromboembolism), and long-term lung function data.

Risk of Bias Assessment

One reviewer (SB) performed a risk of bias assessment using the revised Cochrane risk- of-bias tool for randomized trials [25] or the Newcastle-Ottowa Scale [26] for non- randomized trials (including case control and cohort studies).

Data Synthesis

Random-effects meta-analyses would be performed if the extracted outcomes were clinically and statistically feasible for pooled analysis. However, due to significant heterogeneity across the included studies, data could not be pooled for meta-analyses. Outcomes are reported per mAb in the evidence profiles (**Supplementary Material**).

RESULTS

Literature Search

The database searches yielded 798 articles. After removing 220 duplicates, 578 studies were screened by title and abstract. Sixty-three papers were assessed for full-text eligibility with 43 articles excluded. Reasons for exclusion are summarized in **Figure 1**. Subsequently, results for tocilizumab, a non-COVID-19-specific mAb, were excluded as well as to include only data on anti-spike mAbs. In total, three studies with LTR-specific outcomes [27–29] were included and nine articles with SOTR-specific outcomes that included LTR [30–38].

mAbs were given as PrEP in four studies [27, 28, 30, 31] and as early treatment in LTR with asymptomatic to moderate COVID-19 in nine studies [29, 31–38]. No data on bamlanivimab/etesevimab, regdanvimab and sarilumab were found in our specific population. In terms of risk of bias analyses, most outcomes had an intermediate risk of bias, meaning that there were some concerns in at least one domain in the risk-of-bias judgement for a specific outcome. Additional information can be found in the evidence profiles in the **Supplementary Material**.

Pre-Exposure Prophylaxis

Studies that included LTR who were not infected with COVID-19 at the time of mAb administration.

Tixagevimab and Cilgavimab

Four studies were included in which tixagevimab/cilgavimab was administered as PrEP against COVID-19 in an outpatient setting [27, 28, 30, 31]. Vaccination coverage among the studies was high (94%–100%) [27, 28, 30]. Most common SARS-CoV-2 variants were Omicron B.1.1.529 [27], BA.4, BA.5 [30, 31] and BA 2 [27, 30, 31].

LTR-Specific Outcomes

Tixagevimab/cilgavimab was used in one matched cohort study (n = 444, including 77 LTR who were treated with PrEP and compared with 70 matched LTR) [27], and a retrospective cohort study (n = 1,112, which included 36 LTR) [28].

Both studies reported a rate of breakthrough COVID-19 infection of 8% for LTR treated with tixagevimab/cilgavimab [27, 28], which was significantly lower than that for the control group (8% vs. 23%, p = 0.010) [27]. In the matched cohort study, a higher (300/300 mg) dose was associated with a lower rate of breakthrough infection compared to low-dose PrEP (150/150 mg) (log-rank p = 0.025). A stratified analysis, considering the number of vaccines, indicated a reduced rate of breakthrough infections after treatment with tixagevimab/cilgavimab compared to the control group. This reduction was observed in SOTR with 0–3 vaccines (log-rank p = 0.006) and among those who received 4–5 vaccines (log-rank p = 0.008) [27]. Overall mortality for LTR was 0% in both studies [27, 28] with one LTR (1%) hospitalized in the study of Jurdi et al. [27]. The other study reported no need of respiratory support [28].

Outcomes From SOTR Studies

Two prospective studies evaluated the use of tixagevimab/cilgavimab in SOTR, consisting of one nationwide study (n = 392, including 54 LTR) [30] and one single-center study (n = 350, with PrEP administered to 205 SOTR) [31].

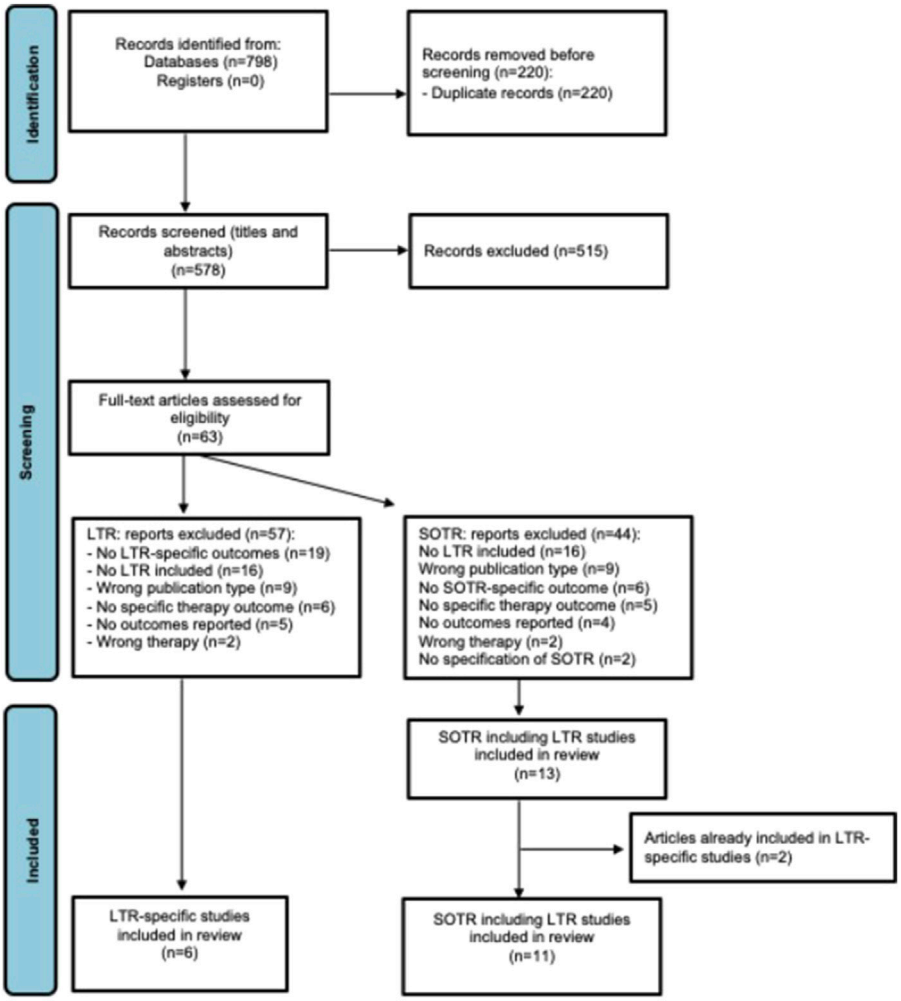


FIGURE 1 | PRISMA flow diagram of included studies. LTR, lung transplant recipients; SOTR, solid organ transplant recipients.

Breakthrough COVID-19 infections were low (8%–9%) [30, 31]. The nationwide study reported a higher infection rate for SOTR treated with a single dose of 150/150 mg of tixagevimab/cilgavimab (28%) compared to 300/300 mg (8%) or a double dose of 150/150 mg (0%) [30]. Incidences of mortality (0%–1%) and hospitalization (0.5%–1%) among SOTR were very low [30, 31], and no patients were admitted to the ICU or required respiratory support according to Alejo et al. [30].

Early Treatment of COVID-19

Studies that reported SARS-CoV-2 positive LTR with asymptomatic to moderate disease according to the WHO scale receiving mAbs [39]. mAbs in early treatment consisted out of sotrovimab, casirivimab/imdevimab, bamlanivimab, and bebtelovimab.

Sotrovimab

Six studies used sotrovimab as early outpatient treatment after SARS-CoV-2 infection [29, 32–36]. During the study period, the predominant SARS-CoV-2 strain was Omicron BA.1 [29, 32, 35, 36], along with Omicron B.1.1 [32, 34–36] and Omicron BA.2 [29, 32, 33]. Vaccination coverage was moderate (53%–96% of SOTR received ≥3 SARS-CoV-2 vaccines) [32–35].

LTR-Specific Outcomes

One prospective cohort study reported 114 SARS-CoV-2-positive immunocompromised patients, including 16 LTR. Sotrovimab was initially only given to hospitalized patients. Due to high hospitalization rates, sotrovimab was subsequently implemented as an outpatient treatment for 14 LTR. Before outpatient treatment, 69% of LTR were hospitalized, 36% required at least 15 L/min or high-flow nasal oxygen therapy and one LTR (6%) died due to COVID-19. Administration in outpatient setting resulted in a significant reduction of hospital admissions [7% (11/16) versus 69% (1/14), $p < 0.001$]. Additionally, no LTR died after the implementation of outpatient therapy [29].

Outcomes From SOTR Studies

Five studies were included. In a prospective single-center cohort study by Solera et al. (n = 300), 106 SOTR, including 34 LTR, received sotrovimab and were compared to 187 SOTR, including 26 LTR [32]. A nationwide population-based study (n = 2,933) reported 800 SOTR (with 49 LTR and 2 heart-lung transplants), with 88% of SOTR receiving sotrovimab in outpatient setting and 12% during hospitalization [33]. Additionally, there were three retrospective cohort studies by Yetmar et al. (n = 361, with 260 SOTR, including 17 LTR) [34], Hedvat et al. (n = 154, of whom 51 SOTR, including 4 LTR) [35] and Cochran et al. (n = 88, including 18 LTR) [36].

Hedvat et al. and Solera et al. reported a lower incidence of overall mortality in SOTR with sotrovimab compared to their controls [0/51 (0%) versus 3/75 (4%) and 0/106 (0%) versus 12/187 (6%), respectively] [32, 35]. The remaining studies also reported a low mortality incidence (0%–1%) after sotrovimab [33, 34, 36]. Mortality due to COVID-19 was lower in the intervention cohort than in the control group of Hedvat et al. (0% versus 4%) [35]. Delayed admission of sotrovimab (≤3 days versus >3 days after positive test) was significantly associated with increased mortality in the study of Rasmussen et al. [multivariate hazard ratio 4.88 (95% CI: 0.59–1.83)] [33].

Sotrovimab significantly reduced COVID-19-related hospitalization and mortality rates in SOTR [10% (5/51) versus 31% (23/75) in controls, p = 0.007)] with a similar trend in overall mortality and hospitalization [12% (6/51) versus 33% (25/75), p = 0.009]. After adjusting for organ transplant type, sotrovimab was associated with a lower risk of 30-day hospitalization or death [adjusted relative risk 0.15 (95% CI: 0.05–0.47)] [35]. Solera et al. also noted a lower incidence of hospital admission after sotrovimab compared to the control cohort, although this was not statistically significant [16% versus 28%, relative risk 0.58 (95% CI: 0.59–1.83)]. However, the median hospitalization duration was significantly shorter in the intervention group (4 versus 7 days) (p = 0.002) [32]. Hospital admission in the remaining studies varied between 3% and 23% [33, 34, 36].

In the studies with control groups, no SOTR treated with sotrovimab required mechanical ventilation versus 5%–8% of control SOTR [32, 35]. Similarly, Cochran et al. found no need for respiratory support in 88 SOTR after sotrovimab [36]. Secondary infections occurred in 8% of the sotrovimab group and 15% in the control group [32]. Acute kidney injury was less frequent in the intervention cohorts, but differences were not statistically significant [10% versus 28% (p = 0.17) and 13% versus 21% (p = 0.12)] [32, 35].

Casirivimab and Imdevimab

Two retrospective single-center cohort studies included casirivimab/imdevimab as early treatment against COVID-19 in an outpatient setting. Both studies described solely SOTR-specific outcomes. COVID variant B.1.1.7 was dominant, however, no systematic testing and prevalence were reported. The studies were performed before SARS-CoV-2 vaccination implementation [37, 38].

Outcomes From SOTR Studies

Yetmar et al. reported the use of casirivimab/imdevimab in 18 SOTR (n = 73, including 2 LTR) [37], while Sarrell et al. compared 22 SOTR treated with casirivimab-imdevimab to 72 SOTR who did not receive mAbs (n = 165, including 13 LTR) [38].

No deaths occurred in the SOTR after casirivimab-imdevimab administration [37, 38] in contrast to 3% (2/72) in the comparator cohort of Sarell et al., with 1% (1/72) attributed to COVID-19 [38]. Hospital admission for SOTR treated with casirivimab-imdevimab ranged from 0% to 6% [37, 38], which was lower compared to the control group [15% (11/72) of SOTR hospitalized for COVID-19-directed therapy] [38].

None of the treated SOTR were admitted to ICU, compared to 1% (1/72) in the control cohort [38]. In both studies, no SOTR required respiratory support [37, 38]. Fewer patients required renal replacement therapy in the intervention group than in the control group (0% versus 9% of the hospitalized patients) [38].

Bamlanivimab

In the aforementioned studies of Yetmar et al. and Sarell et al., bamlanivimab was also used as early treatment against COVID-19 in the outpatient setting [37, 38]. No LTR-specific data were available.

Outcomes From SOTR Studies

Fifty-two SOTR were treated with bamlanivimab in the study of Yetmar et al. (n = 73) [37]. In the other retrospective cohort study (n = 165), 71 SOTR received bamlanivimab and were compared to 72 control SOTR [38].

Among the in total 126 SOTR treated with bamlanivimab, mortality rate was 0% versus 3% (2/72) in the control cohort of Sarrell et al., of which 1% (1/72) attributed to COVID-19 [37, 38]. The need for hospitalization for COVID-19-directed therapy was higher in the control group (15%) compared to SOTR treated with bamlanivimab (11%–13%), but this difference was not significant after age adjustment in the study of Sarell et al. [(95% CI: 0.18–1.32), p = 0.161] [37, 38]. Average length of hospital stay ranged from four to 7 days for bamlanivimab-treated SOTR [37, 38] versus 7 days in the control cohort [38]. Delayed administration of mAbs after COVID-19 symptom onset was associated with a higher incidence of hospitalization (p = 0.03) [37].

ICU admission occurred in 0%–3% in the bamlanivimab group versus 1% in controls, and 1% of the treated SOTR needed mechanical ventilation compared to 0% in controls [37, 38]. While Yetmar et al. reported no SOTR requiring respiratory support [37]. Among hospitalized SOTR, 75% of bamlanivimab-treated SOTR developed acute kidney injury, compared to 36% in the control group. However, no-one in the intervention group required renal replacement therapy, whereas 1% in the control cohort [38].

Bebtelovimab

No LTR-specific data were available. Two SOTR studies were included where bebtelovimab was used as early treatment in an

TABLE 1 | Main findings.

Type of treatment	Type of studies	Main outcomes
Prophylaxis		
- Tixagevimab/cilgavimab	LTR (n=2) SOTR with LTR (n=2)	- Low rate of breakthrough infections [18, 27, 30, 31] - Reduced breakthrough infections versus controls [27] - Reduced breakthrough infections with high- or double-dose PrEP versus low-dose PrEP [27, 30]
Early treatment		
- Sotrovimab	LTR (n=1) SOTR with LTR (n=5)	- Low mortality rate [29, 32–36] - Lower incidence of death versus controls [32, 35] - Early mAb administration was associated with reduced mortality [33] - Reduction in hospitalization rate [29, 32, 35] - Low need for respiratory support [32, 35, 36]
- Casirivimab/imdevimab	SOTR with LTR (n=2)	- Low mortality rate [37, 38] - Lower incidence of death versus controls [38] - Low hospitalization rate [37, 38] - Reduced incidence of hospitalization versus controls [38] - Low need for respiratory support [37, 38]
- Bamlanivimab	SOTR with LTR (n=2)	- Low mortality rate [37, 38] - Lower incidence of death versus controls [38] - No difference in incidence of hospitalization for COVID-19-directed therapy [37, 38] - Early mAb administration was associated with reduced incidence of hospitalization [37]
- Bebtelovimab	SOTR with LTR (n=2)	- Low mortality rate [31, 34] - Low hospitalization rate [31, 34] - mAb administration did not affect hospitalization

LTR, lung transplant recipients; mAb, monoclonal antibody; PrEP, pre-exposure prophylaxis; SOTR, solid organ transplant recipients. Respiratory support defined as high-flow nasal canula, non-invasive ventilation or mechanical ventilation.

outpatient setting [31, 34]. Omicron BA.2 [31, 34] predominated, accompanied by Omicron BA.5 [31] and B.1.1.527 [34]. Of the SOTR, 73% were fully vaccinated while 14% were unvaccinated according to Yetmar et al. [34].

Outcomes From SOTR Studies

Bebtolivimab was administered to 145 SOTR in one prospective single-center study (n = 300, including 18 LTR) [31] and to 92 SOTR (with 4 LTR) in a multicenter retrospective study (n = 361) [34].

The studies of Yetmar et al. and Cochran et a. showed a low overall mortality (0.7% and 2.0%, respectively) and hospitalization rate in bebtelovimab-treated SOTR (3% and 12%, respectively) [31, 34]. In the retrospective study, bebtelovimab treatment was not significantly associated with hospitalization ($p > 0.99$), whereas inadequate vaccination status was ($p = 0.007$) [34]. Cochran et al. reported no ICU admissions [31], and Yetmar et al. noted one case (0.7%) of mechanical ventilation during hospitalization [34].

DISCUSSION

This systematic review aimed to assess the efficacy of mAbs against COVID-19 in LTR. Despite the higher risk of severe COVID-19 in this population [6–10], specific studies pertaining the use of mAbs for LTR remain scarce. A summary of main findings is provided in **Table 1**.

Pre-exposure prophylaxis against COVID-19 was reported in four studies [27, 28, 30, 31] in which the use of tixagevimab/cilgavimab showed a reduction of COVID-19 breakthrough infection in LTR [27]. Other COVID-19-associated outcomes (e.g., ICU admission, mortality) were very low, with a not significantly lower incidence in the PrEP-treated cohorts [27, 28, 30, 31]. These findings align with recent studies showing lower morbidity and mortality in SOTR during the Omicron period with high vaccination rates [40–42]. Other reviews also reported reduced COVID-19 incidence and reduced COVID-19 complications (hospitalization, severe COVID-19 and mortality) in SOTR [9] and immunocompromised patients following the use of tixagevimab/cilgavimab [43]. Importantly, low-dose tixagevimab-cilgavimab was associated with a higher incidence of breakthrough infections [27, 30], supporting high-dose PrEP [44].

Early treatment of LTR with COVID-19 included sotrovimab, bebtelovimab, casirivimab- imdevimab, and bamlanivimab. Only one study reported LTR-specific outcomes in which sotrovimab was used for hospitalized and outpatient therapy with a significant reduction in hospitalization in case of outpatient therapy [29], emphasizing the importance of early treatment.

The remaining studies also suggested a positive trend in early mAbs treatment for SOTR, generally showing lower incidences of severe COVID-19 outcomes compared to SOTR not treated with mAbs. However, among the studies, these findings were inconsistent and not always statistically significant. Likewise, a recent meta-analysis reported a reduced likelihood in overall hospital admission and mortality after sotrovimab in SOTR with mild to moderate COVID-19 [45]. Similar benefits were observed in other retrospective studies, with decreased risks of severe respiratory illness [46] and hospitalization [47]. Importantly, two studies in our review showed that early administration of mAbs was associated with reduced

hospitalization [37] and mortality [33], while another study showed shorter hospital stays [32], again highlighting the beneficial effect of prompt treatment. This was also shown in another recent study that showed that administration of mAbs as early treatment was associated with a lower risk of hospitalization or death in lung transplant recipients [48].

Initial RCTs deemed mAbs to be safe with minimal risk of serious and mild adverse events [12–16]. Multiple studies in our review concurred with these findings, reporting no to very low incidences of moderate to severe adverse events [27, 30, 31, 35, 36, 38]. Despite increased cardiovascular risk in SOTR, cardiovascular events after mAbs were rare (0%–2%) [27, 30, 31]. Importantly, allograft rejection was also rare with few to no episodes of rejection reported [30, 35, 36, 38]. Concluding that mAbs are well tolerated without evidence of increased risk of severe adverse events or allograft dysfunction.

Perspective on the Role of Monoclonal Antibodies in LTR in the Future

The COVID-19 pandemic has shown that swift development of mAb therapy was possible for emerging viruses, resulting in efficacious treatments with acceptable safety profiles. This fosters exploration of near-future development of mAbs against other virulent pathogens for LTR and other immunocompromised patients.

mAbs are laboratory-made proteins, produced from a cell lineage created by cloning a unique white blood cell, that act like antibodies and attack specific epitopes on antigens.

Modern medicine is further revolutionizing towards personalized "tailored" therapy, adapted to individualized specific disease characteristics. In theory, mAb can be produced to bind to virtually any suitable target and current mAb production can produce human/humanized mAbs, minimizing the risks originally associated with their predecessors. Another advantage is that mAb therapy, in comparison with vaccines, relies less on the patient's immune response, which is crucial in patients receiving immunosuppressive treatment. Their mechanisms of action include direct cell toxicity, immune-mediated cell toxicity, vascular disruption, and modulation of the immune system. [49] Nevertheless, despite the advances made during the COVID-19 pandemic, current routine use of mAbs in infectious diseases remains limited, and these products are largely unavailable for the broader transplant community. The latter is crucial, since infections are very common among SOTR, especially LTR, and are difficult to prevent despite precautionary measures and sometimes with only limited treatment options available or with important risks of adverse events associated with systemic administration of antivirals (e.g., hemolytic anemia with ribavirin, skin reactions with oseltamivir, etc.). The COVID-19 pandemic has demonstrated that the field for mAb development is much wider and may be applicable to other viral infections for which there are currently no effective treatments, such as MERS, norovirus, Ebola virus, hantavirus, dengue virus, Zika virus, etc., or for which current therapies for prevention and treatment are suboptimal, such as cytomegalovirus and others. On a broader scope, lessons learned from the use of mAbs during the COVID-19 pandemic may therefore hopefully accelerate the development of novel, much-needed antibody drugs as therapeutic agents for transplant recipients, which should ideally be evaluated in well-designed randomized trials [50].

Our study encountered several limitations. First, scarcity of studies reporting outcomes specific to LTR, reflecting limited available data in this very specific patient population and underscoring the need for further research in this population. Moreover, all included studies were observational, with the majority being retrospective. Subgroup analyses in studies which included SOTR were not always present, necessitating caution when extrapolating these findings to LTR. Furthermore, follow-up periods were short (1–3 months), which could limit the incidence of long-term outcomes. Additionally, one outcome (long-term lung function data) was not reported in the included studies, although this might be of specific interest for the lung transplant population. Specific criteria (e.g., mAb administration, ICU admission) differed among nations and studies which could lead to distorted results. The heterogeneity of included studies, encompassing the stages of the COVID-19 pandemic with the emergence of different variants alongside the development of additional therapies and vaccinations, further complicated the independent assessment of efficacy of mAbs. Finally, the mAbs included in this study are currently not used due to limited efficacy against circulating variants [51–53]. Since March 2024, an emergency use authorization has been issued for pemivibart as PrEP in moderate to severely immunocompromised patients, including LTR [54, 55]. Further evaluation of the efficacy and safety of this biological in LTR has yet to be evaluated.

CONCLUSION

mAb therapy was shown to be safe and beneficial in LTR for PrEP and early treatment of COVID-19 disease. While these mAb may currently not be effective anymore due to evolving SARS-CoV-2 variants, it demonstrates the utility of mAb therapies. This type of prophylaxis and treatment may also be very valuable for other pathogens, especially for immunocompromised populations at increased risk of infections and related complications and mortality, demonstrating the need for further research and development.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

DV: Screened the studies, performed the data collection, wrote the manuscript. RV: Coordinated and designed

the study, critically revised the manuscript. SB: Coordinated and designed the study, screened the studies, checked the data extraction, critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.13800/full#supplementary-material

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Mono-HOPE Versus Dual-HOPE in Liver Transplantation: A Propensity Score-Matched Evaluation of Early Graft Outcome

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Hypothermic oxygenated machine perfusion (HOPE) has become an integral technique to enhance donor graft function in liver transplantation (LiTx). This study compares early posttransplant outcomes of mono-HOPE (portal vein perfusion only) versus dual- HOPE (both portal vein and hepatic artery perfusion). A retrospective analysis was conducted on 183 LiTx recipients, with 90 receiving mono-HOPE and 93 receiving dual-HOPE grafts. Propensity Score Matching (PSM) was applied, resulting in a matched cohort of 146 patients. Primary outcomes included one-year patient and graft survival, and non-anastomotic biliary strictures (NAS). Secondary outcomes included hospital length of stay (HLS). One-year patient survival was 81.7% in the mono-HOPE and 81.7% in the dual-HOPE group, and overall survival did not differ (p = 0.990). One-year death-censored graft survival was similarly comparable (91.2% vs. 93.3%, p = 0.893). NAS were observed in 10.96% in the mono-HOPE and 8.22% in the dual-HOPE group (p = 0.574). The median HLS was 29 days for both groups. Results suggest that dual-HOPE did not significantly improve patient or graft survival, nor did it reduce NAS or HLS compared to mono-HOPE. Assuming that larger cohorts and long-term follow-up data confirm this, additional cannulation of the hepatic artery during machine perfusion in hypothermic conditions may not be beneficial.

Keywords: liver transplantation, end-ischemic liver preservation, hypothermic oxygenated machine perfusion, mono-Hope, dual-HOPE

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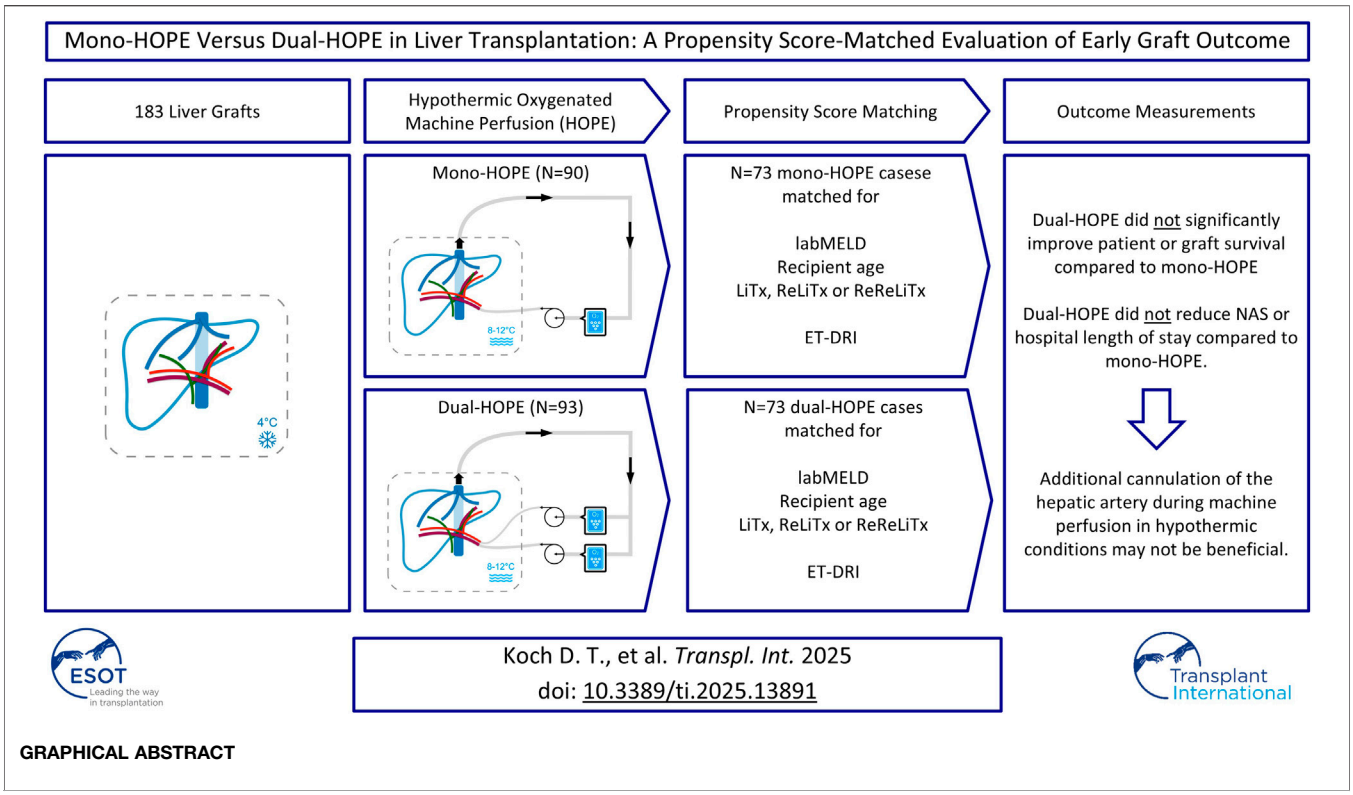
INTRODUCTION

Liver transplantation (LiTx) remains the definitive therapeutic option for patients suffering from end-stage liver diseases and for selected liver malignancies, significantly improving patient survival and quality of life. However, the scarcity of suitable donor grafts has driven the use of extended criteria donors (ECD) to expand the donor pool. These grafts, though increasing the availability of organs, are associated with a higher risk of complications, including delayed graft function (DGF) and biliary complications (BC).



GRAPHICAL ABSTRACT

Hypothermic oxygenated machine perfusion (HOPE) has emerged as a valuable technique in preserving ECD livers. By supplying oxygenated perfusate at low temperatures, HOPE minimizes ischemia-reperfusion injury (IRI) – a key factor contributing to graft dysfunction and failure – by providing oxygen and nutrients to the graft at low temperatures, thereby maintaining metabolic activity at a reduced rate and minimizing the accumulation of reactive oxygen species (ROS) [1–3]. Most notably, HOPE has been shown to improve early graft function and reduce BC, which are more prevalent in ECD grafts. HOPE improves electrolyte balance, enhances hemodynamic stability, lowers post-reperfusion syndrome (PRS) incidences, and shows overall improved outcomes [4–6]. It has gained considerable traction in recent years due to its relatively simple initiation process and its cost-effectiveness, reflected in shorter intensive care unit (ICU) and hospital length of stay [7]. As a result, HOPE is increasingly being used, not only in ECD livers.

HOPE can be administered in two configurations: Perfusion of the portal vein only (mono-HOPE) and perfusion of both the portal vein and the hepatic artery (dual-HOPE). The dual-HOPE approach is hypothesized to provide superior graft protection by delivering oxygenated perfusate through both vascular systems, thereby enhancing the preservation of the entire liver parenchyma and, crucially, the bile ducts. Dual vascular perfusion is believed to mitigate the risk of ischemic cholangiopathy, a severe and potentially life-threatening complication that can occur following transplantation.

Despite the hypothesized benefits, limited comparative studies exist regarding the efficacy of dual-HOPE versus mono-HOPE in liver graft preservation. This study aims to elucidate the impact of these two perfusion modalities on early post-transplant outcomes through a Propensity Score-matched analysis, focusing on metrics such as patient survival, graft survival, non-anastomotic biliary strictures (NAS), and hospital length of stay (HLS).

PATIENTS AND METHODS

Study Design

This is a single-center, retrospective cohort study conducted at the Department of General, Visceral, and Transplant Surgery, LMU University Hospital Munich, Germany. The study's primary objective was to compare the outcome of LiTx recipients who received grafts preserved using end-ischemic mono-HOPE versus dual-HOPE from October 2019 to May 2024.

Study Population

In this analysis, we included 183 patients who underwent orthotopic liver transplantation during the study period. Patients were included based on the following criteria:

Inclusion Criteria

- Adult patients (≥18 years old) who received liver grafts preserved with end-ischemic HOPE.
- Availability of complete clinical and follow-up data.
- The received grafts were preserved in Histidine-tryptophan-ketoglutarate solution (HTK) and transported on ice.

- Only DBD (Donation after brain death) organs were included, as there is no DCD (Donation after cardiac death) program in Germany.

Exclusion Criteria

- Patients who underwent combined organ transplantation, e.g., liver and kidney or liver and lung, were excluded to avoid confounding factors.
- Patients who received grafts that were preserved by static cold storage (SCS) only.

Regardless of surgeon preferences, all grafts fulfilling these criteria were allocated to end-ischemic HOPE. There was no distinction between extended criteria donor (ECD) and non-ECD grafts. Among the included patients, 90 received grafts preserved by end-ischemic mono-HOPE, and 93 received grafts preserved by end-ischemic dual-HOPE.

HOPE Protocol

All liver grafts were preserved and transported to our center using the standard protocol of SCS in HTK solution on ice. Upon arrival, grafts were prepared for implantation at the back table. This also included artery dissections and any necessary arterial reconstructions. Following back table preparation, the subsequent protocols for HOPE were conducted:

Mono-HOPE Protocol

- Only the portal vein was cannulated for machine perfusion.
- Machine perfusion was initiated using the LiverAssist® device (XVIVO, Groningen, Netherlands, and Göteborg, Sweden) with University of Wisconsin machine perfusion solution (UW-MPS) maintained at a temperature of 8°C–12°C.
- Portal vein pressure was adjusted to 3–5 mmHg, with continuous monitoring of flow rates, aiming for a flow rate of 100–150 mL/min [6].
- Machine perfusion was conducted until the recipient wasready for graft implantation.

Dual-HOPE Protocol

- Both the portal vein and the hepatic artery were cannulated for perfusion.
- Machine perfusion was initiated with the LiverAssist® device, and UW-MPS was maintained at a temperature of 8°C–12°C as for mono-HOPE.
- Perfusion of the portal vein followed the same protocol as for mono-HOPE.
- Hepatic artery pressure was adjusted to 20–25 mmHg, with continuous monitoring of flow rates.
- Machine perfusion was conducted until the recipient wasready for graft implantation.

In both protocols, perfusion was continued throughout the recipients' hepatectomy. Immediately before implantation, the grafts were flushed with HTK solution to remove residual UW-MPS.

Our approach to machine perfusion techniques evolved as we gained experience, resulting in two different eras regarding the criteria used to determine which perfusion technique was performed. Initially, we focused exclusively on mono-HOPE to develop confidence and refine our expertise with the method. As our proficiency increased, we transitioned to dual-HOPE whenever cannulation of the hepatic artery was feasible. This progression highlights the deliberate, stepwise approach we adopted to ensure safety and effectiveness. However, there was no randomization.

Liver Transplantation and Immunosuppression

LiTx was predominantly performed using the vena cava-preserving "piggyback" technique. Bile duct reconstruction was achieved through duct-to-duct anastomosis when feasible. Immunosuppression was initiated with a standard triple therapy regimen of tacrolimus, mycophenolate mofetil, and corticosteroids. Corticosteroids were tapered and discontinued by the third post-transplant month, with tacrolimus further reduced, except in cases requiring prolonged use due to clinical indications such as acute rejection or autoimmune hepatitis (AIH).

In patients transplanted for malignancy, immunosuppression was modified at 3 months by transitioning from mycophenolate to an mTOR inhibitor, such as Everolimus, in combination with low-dose tacrolimus. This strategy aims to reduce the risk of tumor recurrence while preserving effective graft protection [8, 9].

Additionally, patients received standard anti-infective prophylaxis for 6 months, including sulfamethoxazole-trimethoprim and valganciclovir.

Outcome Measures

Multiple parameters were analyzed. Primary outcomes included patient survival, graft survival, and incidence of non-anastomotic biliary strictures (NAS) within the first year. NAS were defined as one or more focal areas of narrowing of the bile ducts proximal to the biliary anastomosis [10–12]. Magnetic resonance cholangiopancreatography (MRCP) and direct cholangiography through endoscopic retrograde cholangiography (ERC) and percutaneous cholangiography (PTC) for diagnosis of NAS were obtained based on clinical indications.

Secondary outcomes included hospital length of stay (HLS) following LiTx.

Further data were collected to characterize the study population and to perform Propensity Score Matching (PSM).

All patient data were extracted from our institutional electronic medical records system, and relevant clinical information was reviewed by two independent investigators to ensure accuracy.

Propensity Score Matching

To reduce the impact of potential confounders and ensure comparability between the mono-HOPE and dual-HOPE group, Propensity Score Matching (PSM) was applied. The following recipient variables were used for matching: lab

Model for End-stage Liver Disease (labMELD) score, recipient age, and whether the LiTx was the first, second, or third for the patient. The Eurotransplant-Donor Risk Index (ET-DRI) was utilized as a representative donor variable. There were no missing data, and a Propensity Score match tolerance of 0.01 with a 1-to-1 matching method was applied, resulting in a matched cohort of 146 patients (73 patients in each group) for further analysis (**Figure 1**).

The ET-DRI includes donor age, cause of death (COD), donation after cardiac death (DCD) or donation after brain death (DBD), partial/split or whole liver, regional or national share, cold ischemia time, latest GGT and if it was a rescue offer:

ET-DRI = exp{0.960 × [(0.154 if 40≤age<50) + (0.274 If 50≤age<60) + (0.424 if 60≤age<70) + (0.501 if 70≤age) + (0.079 if COD = anoxia) + (0.145× if COD = cerebrovascular accident) + (0.184 if COD = other) + (0.411 if DCD) + (0.422 if partial/split) + (0.105 if regional share) + (0.244 if national share)] + [0.010 × (cold ischemia time−8 h)] + 0.06 × {[latest lab GGT (U/L) - 50]/100} + (0.180 if rescue offer)}.

PSM was performed using IBM SPSS Statistics 29 (IBM, Armonk, New York, United States).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 29 (IBM, Armonk, New York, United States).

The Propensity Score-matched data were treated as a regular dataset, and conventional statistical analyses were applied. Therefore, the matched data were regarded as pooled data, and the analyses were conducted under the independence assumption:

- Continuous variables were compared using unpaired t-tests for normally distributed data. Welch's correction was applied when variances were unequal (as determined by a Levene test with a $p < 0.05$).
- Cohen's d was used to calculate standardized mean differences (SMD).
- Categorical variables were compared using the Chi-square-test.
- Survival analyses and time-to-event analyses were performed using Kaplan-Meier curves, and comparisons between the two groups were made using the log-rank test.
- Graft survival was assessed by non-death-censored and death-censored graft survival. For non-death-censored graft survival, the graft was considered as non-functioning when the patient died. Therefore, an event was defined as Re-liver transplantation (ReLiTx) or death. For death-censored graft survival, an event was only defined as ReLiTx, and death was censored.
- A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics of the Propensity Score-Matched Study Population

The PSM resulted in a matched cohort of 146 patients, with 73 patients in both the mono- and the dual-HOPE group. The patient characteristics are shown in **Figure 2**.

There was no significant difference in the patient-associated variables used for PSM, confirming a successful matching process: Age ($p = 0.867$), labMELD ($p = 0.617$), and whether the liver transplantation was the first, second, or third for the patient ($p = 1.000$).

Except for the body mass index (BMI) with a p-value of 0.026, all other patient characteristics did not differ significantly between the two groups: Sex ($p = 0.603$), diagnosis ($p = 0.323$), blood group ($p = 0.793$) and ASA Score ($p = 0.384$).

Donor Characteristics and Machine Perfusion Times of the Propensity Score-Matched Study Population

The donor characteristics for the Propensity Score-matched cohort of 146 patients are shown in **Figure 3**. There was no significant difference in the donor-associated variable ET-DRI used for PSM, confirming a successful matching process ($p = 0.957$). Germany has no DCD program, so no DCD organs were included. Except for the number of partial or split liver grafts with a p-value of 0.016, all other donor characteristics did not differ significantly between the two groups: Donor age ($p = 0.280$), cause of death ($p = 0.552$), regional or national share ($p = 0.102$), cold ischemia time ($p = 0.307$), latest lab GGT ($p = 0.513$), and number of rescue offers ($p = 0.224$).

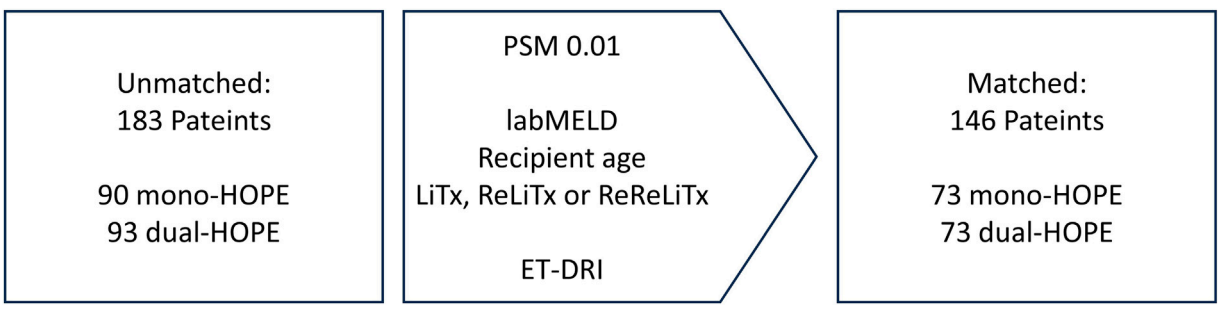


FIGURE 1 | Propensity score matching; labMELD, lab Model for End-stage Liver Disease; LiTx, liver transplantation; ReLiTx, Re-liver ransplantation; ReReLiTx, ReRe-liver Transplantation; ET-DRI, Eurotransplant-Donor Risk Index.

	Mono-HOPE (N = 73)	Dual-HOPE (N = 73)	Total (N = 146)	p-value t-test	p-value Chi-square-test	SMD Cohen's d
Age - Mean	54.57	54.82	54.70	**0.867**		-0.028
Sex - N (%)						
Femal	24 (32.9%)	27 (37.0%)	51 (34.9%)		0.603	
Male	49 (67.1%)	46 (63.0%)	95 (65.1)			
BMI - Mean	25.49	27.39	26.44	0.026		-0.373
Diagnosis - N (%)						
HCC	21 (28.8%)	17 (23.3%)	38 (26.0%)			
LC alcoholic	14 (19.2%)	22 (30.1%)	36 (24.7%)			
LC other	8 (11.0%)	12 (16.4%)	20 (13.7%)			
LF acute	8 (11.0%)	3 (4.1%)	11 (7.5%)			
PSC	7 (9.6%)	3 (4.1%)	10 (6.8%)		0.323	
Transplant failure	3 (4.1%)	4 (5.5%)	7 (4.8%)			
PBC	1 (1.4%)	3 (4.1%)	4 (2.7%)			
SSC	2 (2.7%)	2 (2.7%)	4 (2.7%)			
NAFLD	1 (1.4%)	3 (4.1%)	4 (2.7%)			
other	8 (11.0%)	4 (5.5%)	12 (8.2%)			
labMELD - Mean	22.40	23.27	22.84	**0.617**		-0.083
Blood Group - N (%)						
0	30 (41.1%)	28 (38.4%)	58 (39.7%)			
A	27 (37.0%)	30 (41.1%)	57 (39.0%)		0.793	
AB	5 (6.8%)	7 (9.6%)	12 (8.2%)			
B	11 (15.1%)	8 (11.0%)	19 (13.0%)			
ASA Score - N (%)						
III	25 (34.2%)	20 (27.4%)	45 (30.8%)		0.384	
IV	47 (64.4%)	53 (72.6%)	100 (68.5%)			
V	1 (1.4%)	0 (0.0%)	1 (0.7%)			
ReLiTx - N (%)						
First LiTx	69 (94.5%)	69 (94.5%)	138 (94.5%)		**1.000**	
ReLiTx	4 (5.5%)	4 (5.5%)	8 (5.5%)			
ReReLiTx	0 (0.0%)	0 (0.0%)	0 (0.0%)			

FIGURE 2 | Patient characteristics; SMD, standardized mean difference; BMI, body mass index; HCC, hepatocellular carcinoma; LC, liver cirrhosis; LF, liver failure; PSC, primary sclerosing cholangitis; PBC, primary biliary cholangitis; SCC, secondary sclerosing cholangitis; NAFLD, non-alcoholic fatty liver disease; labMELD, lab Model for End-stage Liver Disease; ASA Score, American Society of Anesthesiologists Score; LiTx, liver transplantation; ReLiTx, Re-liver transplantation; ReReLiTx, ReRe-liver transplantation.

The Propensity Score-matched mono-HOPE group's mean machine perfusion time was 154.15 min, ranging from 35.0 min to 370.0 min. The mean machine perfusion time in the dual-HOPE group was 178.94 min, ranging from 60.0 min to 480.0 min. With a p-value of 0.097 for the unpaired t-test, the difference was not significant.

Patient Survival

Patient survival was assessed by Kaplan-Meier analysis. There was no difference in the survival curves of the mono- and dual-HOPE group (log-rank: p = 0.990). The median follow-up time assessed with reverse Kaplan-Meier was 872 days for the mono-HOPE group and 367 days for the dual-HOPE group. The overall one-year patient survival was 81.7% (SD 4.8%) in the mono-HOPE group and 81.7% (SD 5.0%) in the dual-HOPE group. The Kaplan-Meier curves for patient survival are shown in **Figure 4**.

Graft Survival

ReLiTx had to be performed in 6 out of 73 (8.22%) cases in the mono-HOPE group and 5 out of 73 (6.85%) cases in the dual-HOPE group. The Chi-square-test revealed no significant difference between the two groups (p = 0.754).

The graft survival was assessed by Kaplan-Meier analysis. We assessed non-death-censored and death-censored graft survival.

For non-death-censored graft survival, the graft was considered as non-functioning when the patient died. There was no difference in the non-death-censored graft survival curves of the mono- and dual-HOPE group (log-rank: p = 0.899). The one-year non-death-censored graft survival was 77.9% (SD 5.1%) in the mono-HOPE group and 79.6% (SD 5.1%) in the dual-HOPE group. The Kaplan-Meier curves for non-death censored graft survival are shown in **Figure 5**.

There was no difference in the death-censored graft survival curves of the mono- and dual-HOPE group (log-rank: p = 0.893). The one-year death-censored graft survival was 91.2% (SD 3.4%) in the mono-HOPE group and 93.3% (SD 3.3%) in the dual-HOPE group. The Kaplan-Meier curves for death-censored graft survival are shown in **Figure 6**.

	Mono-HOPE (N = 73)	Dual-HOPE (N = 73)	Total (N = 146)	p-value t-test	p-value Chi-square-test	SMD Cohen's d
ET-DRI - Mean	2.12	2.12	2.12		**0.957**	-0.009
Donor age - Mean	53.48	57.01	55.25	0.280		-0.180
Cause of death - N (%)						
Anoxia	17 (23.3%)	22 (30.1%)	39 (26.7%)			
Cerebrovascular accident	39 (53.4%)	38 (52.1%)	77 (52.7%)		0.552	
Other	17 (23.3%)	13 (17.8%)	30 (20.5%)			
DCD - N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1.000	
Partial or split	10 (13.7%)	2 (2.7%)	12 (8.2%)		0.016	
Regional or national share - N (%)						
Regional share	26 (35.6%)	17 (23.3%)	43 (29.5%)		0.102	
National share	47 (64.4%)	56 (76.7%)	103 (70.5%)			
Cold ischemia time [h] - Mean	9.99	9.63	9.81	0.307		0.170
Latest lab GGT [U/l] - Mean	76.78	89.29	83.03	0.513		-0.109
Rescue offer - N (%)	29 (39.7%)	22 (30.1%)	51 (34.9%)		0.224	

FIGURE 3 | Donor characteristics; SMD, standardized mean difference; ET-DRI, Eurotransplant-Donor Risk Index; DCD, Donation after cardiac death; lab GGT, lab Gamma-Glutamyl-Transferase.

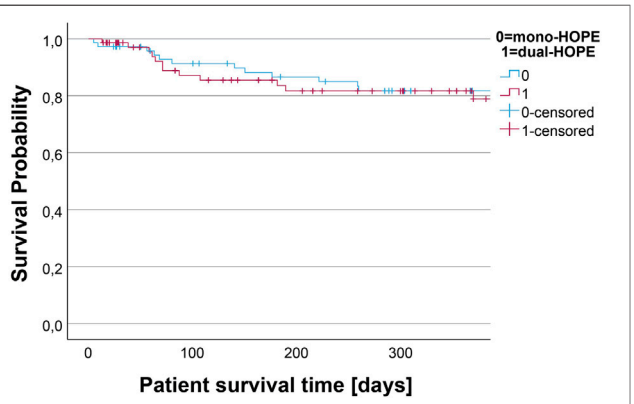


FIGURE 4 | Kaplan-Meier curve for patient survival.

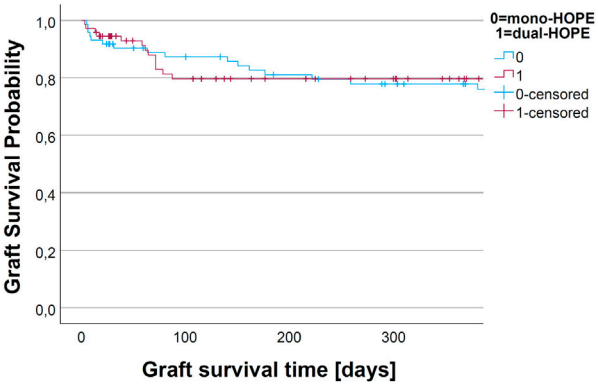


FIGURE 5 | Kaplan-Meier curve for non-death-censored graft survival.

Non-Anastomotic Biliary Strictures

All NAS detected with MRI, ERC, or PTC within 1 year were recorded. There were no protocol MRI scans conducted.

NAS occurred in 8 out of 73 (10.96%) cases in the mono-HOPE group and 6 out of 73 (8.22%) cases in the dual-HOPE group within the first year following LiTx. This difference did not reach statistical significance (Chi-square-test: p = 0.574). With an inclusion time from October 2019 to May 2024, not all patients reached a full follow-up of 1 year.

Hospital Length of Stay

Cumulative ICU days were assessed for all patients, including patients who died during the hospital stay. Patients in the mono-HOPE group had a median of 6 cumulative ICU days (mean 22.41 days), and patients in the dual-HOPE group had a median of 7 cumulative ICU days (mean 14.84 days). The t-test with Welch's correction was used as the Levene test was significant (Leven test: p = 0.001). The t-test with Welch's correction did not show a difference between the two groups (p = 0.110).

Hospital length of stay (HLS) was analyzed by a time-to-event analysis. Patients who died were censored. The median HLS in both groups was 29 days and there was no significant difference in the two time-to-event curves of the two groups (log-rank: p = 0.331).

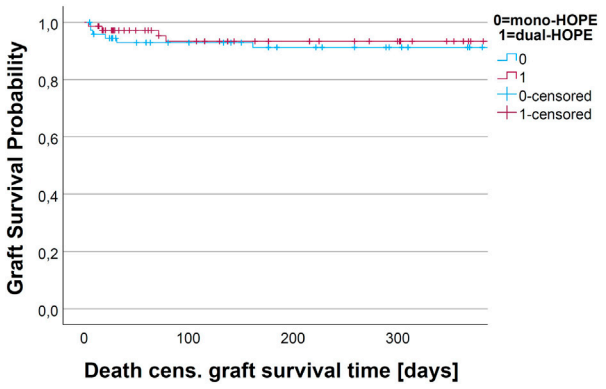


FIGURE 6 | Kaplan-Meier curve for death-censored graft survival.

Sensitivity Analysis Excluding Recipients of Partial and Re-Liver Transplantations

Recipients of ReLiTx, ReReLiTx, and partial or split LiTx were excluded from the Propensity Score-matched cohort to perform a sensitivity analysis. The sensitivity analysis showed comparable results to the original Propensity Score-matched cohort. There were still no significant differences regarding one-year patient survival, one-year graft survival, NAS, and HLS between the mono- and dual-HOPE group (**Figure 7**).

DISCUSSION

End-ischemic hypothermic oxygenated machine perfusion (HOPE) has become an increasingly valuable technique for graft preconditioning prior to liver transplantation (LiTx), particularly for extended criteria donor (ECD) grafts, which are more susceptible to ischemia-reperfusion injury (IRI) [13–15]. Previous studies have demonstrated that HOPE can effectively mitigate this injury, resulting in improved early graft function and reduced incidence of cholangiopathy, notably non-anastomotic biliary strictures (NAS) within the first year post-transplantation – a significant complication associated with ECD liver grafts [1–3].

Our study evaluated the impact of dual-HOPE, which perfuses both the portal vein and the hepatic artery, compared to the standard mono-HOPE, which only perfuses the portal vein.

Our findings did not show a statistically significant improvement in patient or graft survival with dual-HOPE compared to mono-HOPE. These results suggest that adding hepatic artery perfusion may not confer additional protection to the graft. This finding contrasts with the initial hypothesis that dual vascular perfusion would offer enhanced preservation of the entire hepatic parenchyma and, by extension, improve early graft function and survival.

While the dual-HOPE group exhibited a lower incidence of NAS compared to the mono-HOPE group, this difference did not reach statistical significance. In addition, the shorter follow-up time of the dual-HOPE group could be an explanation for falsely reduced NAS incidence in this group. The original hypothesis – that dual-HOPE would provide superior graft protection by delivering oxygenated perfusate through both vascular systems, thereby enhancing the preservation of the entire liver parenchyma and, crucially, the bile ducts – must, therefore, be reconsidered. The lack of significant impact on NAS incidence indicates that the theoretical advantages of dual vascular perfusion do not translate into measurable clinical benefits, at least in the context of our study population.

After Propensity Score Matching, the mono-HOPE and dual-HOPE group were well-balanced, with the only significant difference in donor characteristics being BMI and the amount of partial or split organs. While partial or split liver transplantation is associated with higher risks, outcomes in experienced centers can be comparable to those of full graft transplantation for carefully selected recipients [16]. Thus, the imbalance in the number of partial or split grafts in our cohort

	Prepensity Score-matched cohort			ReLiTx, ReReLiTx, and partial/split LiTx excluded		
	Mono-HOPE *(N = 73)*	***Dual-HOPE*** *(N = 73)*	***p-value***	***Mono-HOPE*** *(N = 60)*	***Dual-HOPE*** *(N = 67)*	***p-value***
One-year patient survival	81.7% (SD 4.8%)	81.7% (SD 5.0%)	0.990 (Log-rank)	83.2% (SD 5.1%)	81.4% (SD 5.3%)	0.740 (Log-rank)
One-year graft survival						
non-death-censored	77.9% (SD 5.1%)	79.6% (SD 5.1%)	0.899 (Log-rank)	80.2% (SD 5.4%)	82.4% (SD 5.1%)	0.848 (Log-rank)
death-censored	91.2% (SD 3.4%)	93.3% (SD 3.3%)	0.893 (Log-rank)	91.0% (SD 3.9%)	95.8% (SD 2.9%)	0.504 (Log-rank)
NAS *- N (%)*	8 (10.96%)	6 (8.22%)	0.574 (Chi-square)	7 (11.67%)	6 (8.96%)	0.615 (Chi-square)
HLS *- Median*	29 days	29 days	0.331 (Log-rank)	27 days	29 days	0.672 (Log-rank)

FIGURE 7 | Sensitivity analysis excluding recipients of partial and Re-liver transplantations; Original Propensity Score-matched cohort (left) and subgroup with recipients of ReLiTx, ReReLiTx, and partial or split LiTx excluded (right); LiTx, liver transplantation; ReLiTx, Re-liver transplantation; ReReLiTx, ReRe-liver transplantation; SD, standard deviation; NAS, non-anastomotic biliary strictures; HLS, hospital length of stay.

needs to be mentioned but is unlikely to have influenced the results and, if anything, might have favored better outcomes in the dual-HOPE group. In addition, we performed a sensitivity analysis by excluding recipients of partial and Re-liver transplantations from the original Propensity Score-matched cohort, and there were still no significant differences regarding one-year patient survival, one-year graft survival, NAS, and HLS between the mono- and dual-HOPE group.

The absence of significant differences in survival outcomes or NAS rates may also be attributed to the heterogeneity of the study population, which included both ECD and non-ECD donors. The complex interplay of additional risk factors, such as donor comorbidities and graft steatosis, in ECD grafts likely overshadows the potential benefits of dual-HOPE. These findings suggest that dual-HOPE might have a more pronounced impact in specific subgroups of particularly vulnerable grafts. Future studies with larger cohorts are warranted to explore these subgroup effects, especially for marginal donor organs, which may benefit more substantially from advanced perfusion strategies. However, for this indication, normothermic machine perfusion could also play a complementary role, particularly for high-risk organs [15]. Normothermic perfusion enables functional graft assessment prior to transplantation, which is critical for determining organ viability. While liver viability can be assessed by mitochondria-derived flavin mononucleotide values in perfusate during hypothermic perfusion [17], normothermic perfusion allows viability assessment with physiological biomarkers like lactate clearance, pH maintenance, or bile production [18–20]. Under normothermic conditions, dual vascular perfusion may be more important, as oxygen consumption is significantly higher, and inadequate hepatic artery flow could exacerbate the risk of complications like cholangiopathy. Additionally, the multifactorial nature of post-transplant complications necessitates a comprehensive approach beyond perfusion strategies alone.

One limitation of our study is the absence of donation after circulatory death (DCD) grafts, as no DCD program exists in Germany. DCD organs are a primary target for dynamic preservation techniques in other countries [21, 22]. Thus, the lack of DCD grafts limits the generalizability of our findings, particularly in settings where DCD transplantation is more common. Expanding future studies to include DCD organs would provide a broader understanding of dual-HOPE's potential utility.

In conclusion, dual-HOPE did not demonstrate a significant advantage over mono-HOPE regarding patient survival rates, graft survival rates, or post-transplant NAS for DBD liver grafts. Expanding the study population and incorporating long-term follow-up could better elucidate the potential benefit of dual vascular perfusion, especially in ECD liver transplantation. Such insights would be pivotal in refining machine perfusion strategies to optimize graft preservation and patient 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 Institute of Ethics, History and Theory of Medicine, Faculty of Medicine, LMU Munich, Germany. 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

DoK, MG, and DiK contributed to the design and implementation of the research; DoK, CL, MI, HN, BR, JW, MG, and DiK supervised the research process; DoK, MT, and DiK contributed to the data acquisition; DoK, HN, MG, and DiK contributed to the statistical analysis of the data; DoK, MG, and DiK contributed to the writing of the original manuscript; DoK., MT, MS, MD, SJ, CL, MI, HN, BR, JW, MG, and DiK contributed to the validation and the editing 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.

GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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GLOSSARY

AIH Autoimmune hepatitis
BC Biliary complications
COD Cause of death
DBD Donation after brain death
DCD Donation after cardiac death
DRI Donor risk index
DGF Delayed graft function
ECD Extended criteria donor
ERC Endoscopic retrograde cholangiography
ET-DRI Eurotransplant-Donor Risk Index
GGT Gamma-Glutamyl-Transferase
HCC Hepatocellular Carcinoma
HLS Hospital length of stay
HOPE Hypothermic oxygenated machine perfusion
HTK Histidine-tryptophan-ketoglutarate solution
ICU Intensive Care Unit
IRI Ischemia-reperfusion injury
labMELD lab Model for End-stage Liver Disease
LC Liver cirrhosis
LF Liver Failure
LiTx Liver transplantation
MELD Model for End-stage Liver Disease
MRCP Magnetic resonance cholangiopancreatography
MRI Magnetic resonance imaging
NAFLD Non-alcoholic fatty liver disease
NAS Non-anastomotic biliary strictures
PBC Primary biliary cholangitis
PRS Post-reperfusion syndrome
PSC Primary sclerosing cholangitis
PSM Propensity Score Matching
PTC Percutaneous cholangiography
ReLiTx Re-liver transplantation
ReReLiTx Re-Re-liver transplantation
ROS Reactive oxygen species
SCC Secondary sclerosing cholangitis
SCS Static cold storage
SMD Standardized mean differences
UW-MPS University of Wisconsin machine perfusion solution

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Proteomic Analysis of Transbronchial Biopsy Tissue Reveals a Distinct Proteome and Mechanistic Pathways in High-Grade Eosinophilic Inflammation After Lung Transplantation

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Dear Editors,

Eosinophilic (EOS) allograft inflammation is detected after lung transplant (LTx) in ~10% recipients. A retrospective study showed that it is an independent risk factor for both chronic lung allograft dysfunction (CLAD) and allograft rejection [1, 2]. The presence of EOS is associated with higher grades of acute cellular rejection (ACR), however, EOS is also observed in the absence of histologic ACR [3, 4]. The mechanisms by which the presence of EOS inflammation is associated with poor long-term outcomes remains unclear. EOS inflammation may contribute to ongoing tissue injury, or may reflect tolerogenic and tissue repair pathways. Therefore there is a need to clarify signalling pathways and proteins which contribute to EOS inflammation and identify diagnostic biomarkers for early CLAD and subsequent graft loss after LTx. Proteomic, which studies the structure of proteins and their cellular activities, has increased our understanding of biological processes in transplantation. Coupled with advanced bioinformatics, proteomics enables the clarification of key molecular pathways and supports biomarker discovery and identification of therapeutic targets [5, 6]. The aim of this pilot study is to identify the proteomic signature in the transbronchial biopsy (TBBx) after LTx. In this study we compare histologic high-grade EOS with a group of TBBx demonstrating ACR without eosinophils. A control group included TBBx with stable allograft function without EOS inflammation.

This single-centre and cross-sectional cohort study was approved by the St Vincent's ethics office. A consort flow diagram describing the sample collection and study procedure is depicted in

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Abbreviations: ACR, Acute cellular rejection; BALF, Bronchoalveolar lavage fluid; CLAD, Chronic lung allograft dysfunction; DEPs, Differentially expressed proteins; EOS, Eosinophilic inflammation; ISHLT, International Society for Heart and Lung Transplantation; LTx, Lung transplantation; TBBx, Transbronchial biopsy; UEPs, Uniquely expressed proteins.

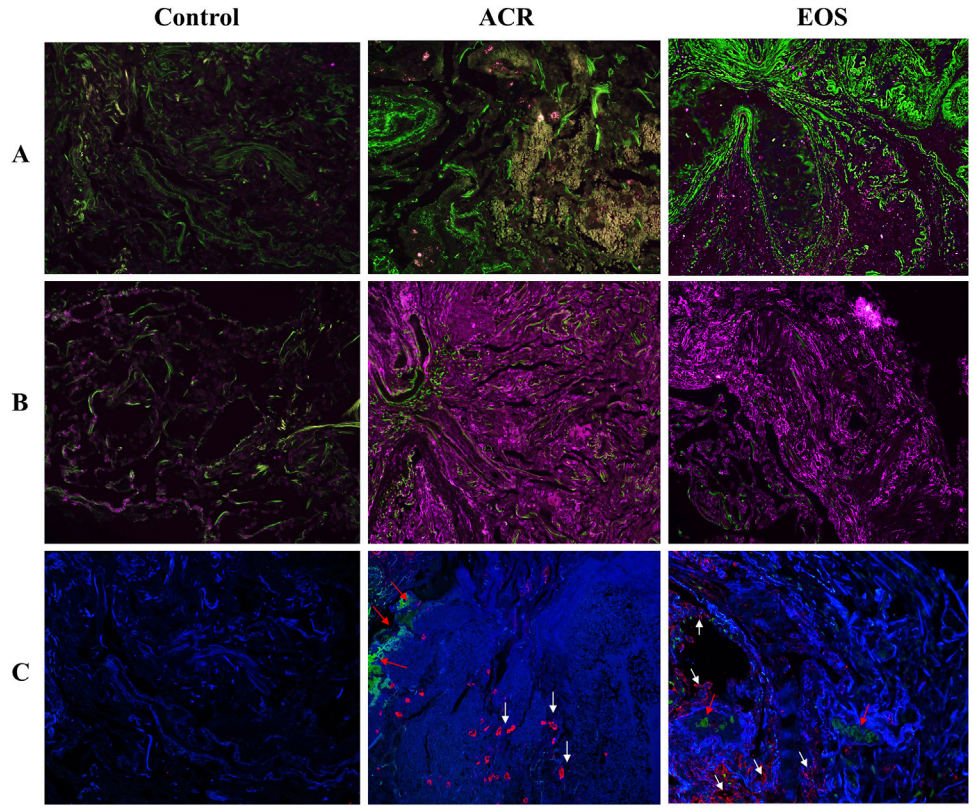

FIGURE 1 | Representative immunohistochemistry staining of target proteins in TBBx of LTx patients. IHC staining confirmed the presence and upregulation of **(A)** Cofilin 1 (green) and **(B)** Serpin H1 (purple) in TBBx of EOS and ACR groups compared to stable control. **(C)** IHC staining detected the presence and upregulation of Galectin-3 (red, white arrow), Serpin B1 (red arrow) and Coronin A (blue) in TBBx of EOS and ACR groups compared to stable control. Original magnification ×63. ACR, Acute cellular rejection; EOS, Eosinophilia; IHC, Immunohistochemistry; LTx, Lung transplantation; TBBx. transbronchial biopsies.

Supplementary Figure S1. TBBx specimens were prospectively collected by bronchoscopy for routine surveillance or to diagnose acute lung allograft dysfunction. Each TBBx was systematically reported for the presence of eosinophils and quantification was performed as the numbers of cell per high-power field [7]. High-grade EOS was defined in this study as >10 eosinophil/high power field. ACR was diagnosed using the International Society for Heart and Lung Transplantation (ISHLT) guidelines [8] for A- and B-grade components by expert transplant pathologists. Only high grade ACR cases (A2) without concurrent mixed rejections or other histologic findings were included. Patients with positive bronchoalveolar lavage fluid (BALF) microbiology test and positive donor specific antibodies were excluded from the study. A total of 18 TBBx from 18 patients were selected based on inclusion criteria, comprised of: (i) EOS TBBx group (n = 6) (ii) ACR TBBx group (n = 6), and (iii) stable control TBBx (n = 6) were selected from the 3 months surveillance time-point in LTx recipients with improving allograft function, without ACR or EOS inflammation and negative BAL microbiology. Whole proteomics analysis was performed on collected TBBx as described in **Supplementary Material**. Differentially expressed proteins (DEPs) were identified and quantified using advanced bioinformatic tools and then validated by immunohistochemistry (IHC) staining (**Supplementary Material**).

The main basic and clinical characteristics of the patients are detailed in **Supplementary Table S1**. The main indications for transplantation were COPD (44.4%) and idiopathic pulmonary fibrosis (22.2%). We noted the development of CLAD in 83.3% recipients after EOS inflammation, compared with only 16.67% and 33.33% in recipients with normal TBBx and with ACR. A total of 502 proteins (44.62%) were overlapped between all three groups (**Supplementary Figure S2**). The proteomics analysis revealed a high protein overlap (74.84%) between ACR and EOS groups, which may indicate proteomic overlap between these distinct histologic phenotypes (**Supplementary Figure S2**). Volcano plots revealed that there were small differences in expression pattern of DEPs between EOS and ACR groups (**Supplementary Figure S2**). Only 13 proteins displayed significant changes in ACR group. Patients with EOS and ACR tended to be more similar to each other compared to the stable controls (**Supplementary Figure S2**). Compared to the control group, a total of 61 and 124 DEPs were found in EOS and ACR patients, respectively. WARS1, SerpinG1, DDX3X, CCT8, CCT3, SerpinB1, Cofilin-1, Coronin1A, SET, and Galectin-3 were

among the most upregulated proteins in the TBBx of both EOS and ACR patients (**Supplementary Tables S2, S3**). Functional enrichment analysis of DEPs showed that DEPs in EOS and ACR groups were involved in 23 and 34 significant pathways, respectively. The proteome analysis coupled with bioinformatics tools discovered a set of proteins of interest, including SerpinB1, SerpinH1, Galectin-3, Cofilin-1, macrophage migration inhibitory factor, DDX3X, CCT8, Coronin1A, Collagens and Mucins, which were significantly upregulated in the TBBx of patients EOS inflammation. IHC staining of 5 DEPs, including Serpin B1, Galectin-3, Serpin H1, Cofilin-1 and Coronin1A was performed to confirm the results of proteome data. Staining intensity and expression pattern of Serpin B1, Galectin-3, Serpin H1, Cofilin-1 and Coronin1A was higher in ACR and EOS patients compared to controls (**Figure 1**), representing that protein expression findings are consistent with the proteomics data. Further functional enrichment analysis using bioinformatics platforms revealed that these proteins have collectively pivotal roles in different signalling pathways, including leukocytes migration and activation, inflammasome formation, free radicals production and oxidative stress, apoptosis, epithelial mesenchymal transition, myofibroblasts activation, and excessive deposition of extracellular matrix that are a major sign of CLAD development, fibrosis and graft rejection (**Supplementary Figure S3**). The identified signalling pathways may explain the enhanced CLAD risk and fibrosis after EOS inflammation which may be independent of ACR. The discovered proteins are interesting biomarker validation for CLAD. These proteins may represent therapeutic targets further for treatment of eosinophilic inflammation to prevent CLAD. Our study is limited by its cross-sectional, single-center study, limited sample size design. The post-transplant timing of sampling was significantly differs between groups, with EOS being obtained on average 5 years post-LTx vs. both other groups within 2 months post-LTx. The absence of TBBx eosinophils phenotyping (E1 and E2 types) should be a focus of future research.

In conclusion, our pilot study elucidates mechanistic insights that support the idea that high-grade EOS inflammation, even without the classic features of ACR, is linked with CLAD and allograft injury. We discovered a set of proteins of interest in EOS inflammation TBBx that not only offers important insights into its development and pathogenesis, but may also serve as potential biomarkers for the early identification of CLAD and graft loss that require future validation. Further studies with larger number of samples are needed to validate and measure the level of these target proteins in the blood and BALF to identify a cut-off for early protein diagnostics using minimally invasive tests.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/ **Supplementary Material**.

ETHICS STATEMENT

The human ethics committee of St Vincent's Hospital (Ethics number: 2020/ETH00023) reviewed and approved the study. 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

DD, and MP, designed this study; ET and AP performed experiments and analyzed data; TC, AR, MR, VS, and CT assisted with experiments and analysis of data. ET and DD wrote the manuscript and revised the paper. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

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

GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14080/full#supplementary-material

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