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Top papers from the ESOT Congress 2023

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EDITORIAL
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Disruptive Innovation, Trusted Care

Gabriel C. Oniscu *

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Editorial on the Special Issue

ESOT Congress 2023 - Selected Papers

As we emerge from one of the greatest healthcare challenges in human history, we are meeting in Athens for the ESOT Congress 2023 for an opportunity to reconnect and discuss the future directions of travel in organ transplantation and organ replacement.

Despite a significant impact on the delivery of transplant care and a *de facto* research stand still during the last 3 years, we rebounded with renewed energy and it is reassuring to see the extraordinary progress of recent months with a leap in xenotransplantation [1], machine perfusion [2], telemedicine and redefinition of end points in clinical practice and research (Naesens et al.).

The pandemic broke boundaries and brought scientific communities closer in a quest to speed up the discovery of solutions for the challenges we faced. However, it did more than that. It made us reconsider the interaction with our patients and expedited the implementation of novel ways to undertake clinical activity and ensure that we continue to deliver a high quality and trusted care to all patients waiting for or having received a transplant.

The buzz of creativity and collaborative effervescence that defines the ESOT community is demonstrated once again by the innovations presented at the Congress and illustrated by this selection of the top papers submitted.

We live in a world on the brink of radical changes, fueled by an explosion of disruptive innovations that could redesign not only every aspect of our field but our very own way of living. These technologies can bring us closer to a personalized transplant care whilst ensuring a wider reach of transplantation and further improvements in clinical and patient relevant outcomes.

One such technology is *ex situ* machine perfusion. As it gathers clinical momentum, we start to gain a deeper understanding of its effects. Gilbo et al. demonstrated that *ex situ* liver machine perfusion is associated with an unexpected high level of injury to the bile duct, without a clinical translation into a higher incidence of ischaemic biliary strictures. This questions the validity of current assessment criteria and makes an important point that perfusion technologies will completely rehaul the existing concepts of organ assessment and definitions of viability.

Molecular diagnostic technology is another technology that has reached prime time and many of the papers presented at the Congress discuss the benefits and the hurdles of translation into routine care. Giarraputo et al. investigated the molecular refinement of the diagnosis of heart allograft rejection based on whole transcriptome analyses and suggested that a targeted gene panel can be used for detection of antibody mediated rejection and as such can mitigate against some of the challenges that have limited the widespread clinical application of molecular diagnostic technologies to date.

Despite the many advances, there remain persistent challenges in the delivery of transplant care in many parts of the world, of which the lack of organs to meet the growing demand for transplantation and the consequent inequity in access are the top priority. And yet, there is evidence that we can do better. Williment et al. report on a UK initiative that examined the transplant pathways and identified ways to reduce inequity of access, make the best use of available resources and drive innovation in organ transplantation. The authors highlight that a cultural change supported by adequate resources and implementation of technology and decision-making aids is likely to increase

Editorial

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organ utilization whilst improving patient experience and outcomes and empowering the transplant community.

One such potential decision making aid is a better understanding of the quality of organ on offer. With an increased proportion of extended criteria donors (ECD), clinicians and patients are sometimes reluctant to take additional risks. Patel et al. demonstrate that ECD kidneys are a valuable resource that provide better outcomes compared to remaining on dialysis and suggest that there is a need for a better definition of extended criteria donors since the current two classifications yield comparable results.

Post pandemic, there remains an acute awareness of other virological challenges. Ushiro-Lamb et al. report on the impact of a strategy for hepatitis E virus screening in the UK. Universal donor screening has ensured that patients at risk are identified and managed early to minimize the risks to the transplant and ensure a judicious use of available organs. Whilst minimizing the risk of viral transmission. Along the same lines, Böhler et al. provide a 6 year report on the risk of donor viral and malignancy transmission in Germany highlighting the importance of a reliable evaluation and alert system to assess the risks, assess the decision making and improved the safety of transplantation.

Whilst transplant is the desired treatment option for all patients with end organ failure, this may not be attainable for many reasons. As such, part of the shared decision making process, alternative treatment options, with their pros and cons should be fully discussed, in order to create and maintain a trusted care environment. Francica et al. illustrate the importance of discussing alternative treatment options for heart failure in the context of changes in technology and integration with the overall transplant strategy.

Disruptive innovation and trusted care are core values for the ESOT community and it is incumbent on us to ensure that all these innovations and efforts to increase organ utilization supported by evidence based decisions are integrated in clinical care across Europe and that we share this knowledge to widen access to transplantation.

This collection of manuscripts demonstrates yet again the high standard of science and research presented at the ESOT Congress 2023 and provides the reassurance that we are in a very strong position to continue innovating and deliver the high quality care expected by our patients.

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BRIEF RESEARCH REPORT
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Banff Human Organ Transplant Consensus Gene Panel for the Detection of Antibody Mediated Rejection in Heart Allograft Biopsies

*Alessia Giarraputo[1,2], Guillaume Coutance[1,3], Olivier Aubert[1,4], Marny Fedrigo[2], Fariza Mezine[1], Dina Zielinski[1], Michael Mengel[5], Patrick Bruneval[1], Jean-Paul Duong van Huyen[1,6], Annalisa Angelini[2] and Alexandre Loupy[1,4]**

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The molecular refinement of the diagnosis of heart allograft rejection based on whole-transcriptome analyses faces several hurdles that greatly limit its widespread clinical application. The targeted Banff Human Organ Transplant gene panel (B-HOT, including 770 genes of interest) has been developed to facilitate reproducible and cost-effective gene expression analysis of solid organ allografts. We aimed to determine *in silico* the ability of this targeted panel to capture the antibody-mediated rejection (AMR) molecular profile using whole-transcriptome data from 137 heart allograft biopsies (71 biopsies reflecting the entire landscape of histologic AMR, 66 non-AMR control biopsies including cellular rejection and non-rejection cases). Differential gene expression, pathway and network analyses demonstrated that the B-HOT panel captured biologically and clinically relevant genes (IFNG-inducible, NK-cells, injury, monocytes-macrophage, B-cell-related genes), pathways (interleukin and interferon signaling, neutrophil degranulation, immunoregulatory interactions, endothelial activation) and networks reflecting the pathophysiological mechanisms underlying the AMR process previously identified in whole-transcriptome analysis. Our findings support the potential clinical use of the B-HOT-gene panel as a reliable proxy to whole-transcriptome analysis for the gene expression profiling of cardiac allograft rejection.

Keywords: antibody-mediated rejection, heart transplantation, gene expression, transcriptome, heart rejection, molecular profiling

TOP 5% CONGRESS ABSTRACT

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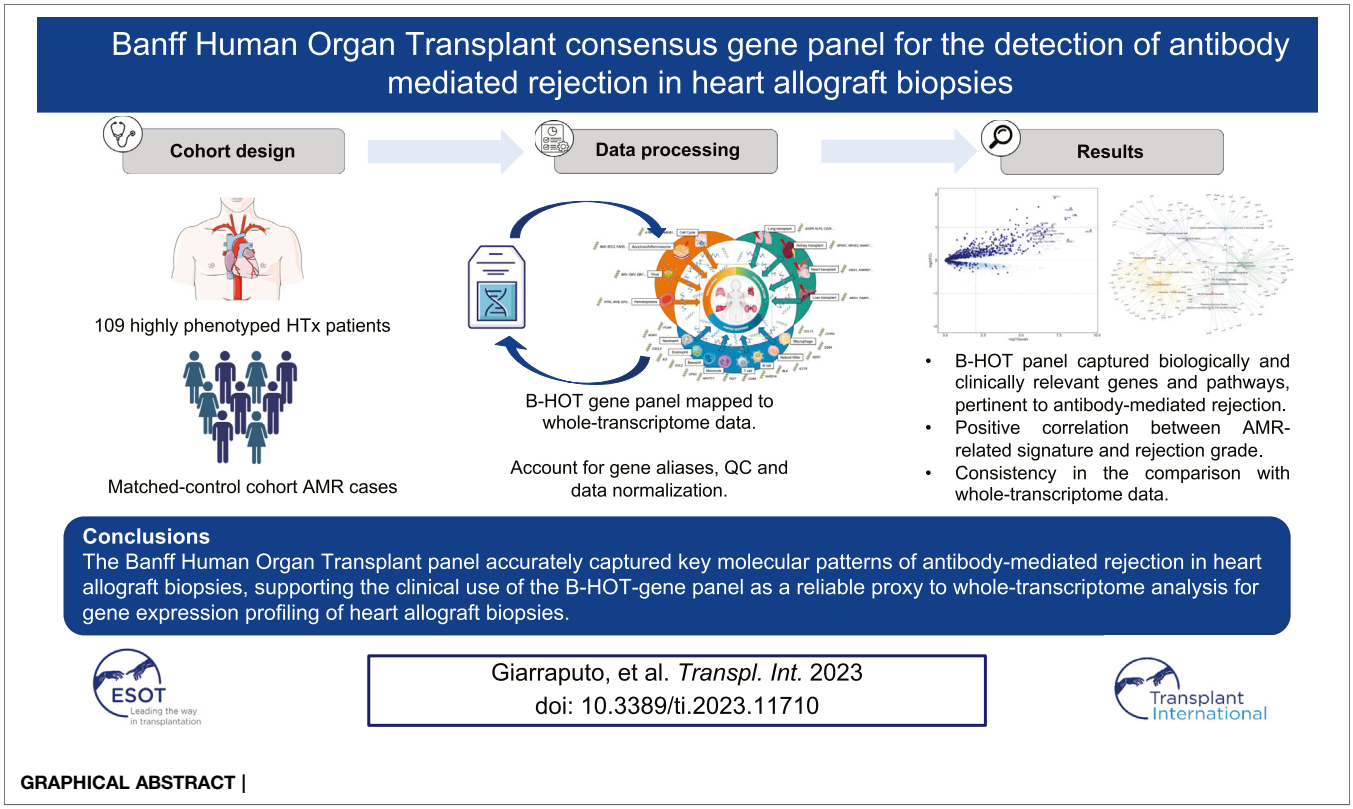
Abbreviations: ACR, Acute Cellular Rejection; AMR, Antibody-mediated rejection; B-HOT, Banff Human Organ Transplant Panel; EMB, Endomyocardial Biopsies; FDR, False Discovery Rate; FFPE, Formalin-Fixed and Paraffin-Embedded; HTx, Heart transplantation; INFG, Interferon-gamma; WT, Whole-transcriptome.



GRAPHICAL ABSTRACT |

INTRODUCTION

Allograft rejection remains an important complication after heart transplantation associated with poor outcomes. While the incidence and clinical importance of acute cellular rejection has declined over time, antibody-mediated rejection (AMR) is now recognized as a major risk factor for patient death, graft loss and various allograft injuries [1]. Even if important advances have been made in the standardization of its pathology diagnosis, disease severity, degree of myocardial injury and progression stage are crucial pieces of information which are poorly captured by the current working formulation [1]. Whole-transcriptome (WT) gene expression analysis of myocardial tissue has been shown to be a relevant companion tool to refine the pathology diagnosis of AMR after heart transplantation [2, 3]. However, important drawbacks have limited its widespread clinical application (extra-core sampling and inherent procedural risks, low reproducibility, technical and analytical burden) [4]. Targeted molecular profiling applicable to formalin-fixed paraffin-embedded (FFPE) endomyocardial biopsies (EMB) may allow the implementation of molecular diagnosis into the clinical routine [5]. Recently, the Banff Human Organ Transplant Panel (B-HOT), a consensual targeted panel comprising 770 genes, has been designed to capture molecular expression related to tissue injury, innate and adaptive immunity and rejection in solid organ transplants in order to facilitate cost-effective and reproducible expression analysis of solid organ allografts [5]. The combination of a FFPE-based tissue assessment together with pathological phenotyping of heart allograft biopsies had the potential of enlightening novel pathological mechanisms involved in antibody-mediated rejection correlating with pathological assessment. Whether this targeted panel provides enough granularity to capture the complexity and heterogeneity of AMR compared to whole-transcriptome analysis still remains unknown. We aimed to analyze *in silico* the ability of the B-HOT panel to capture relevant genes, pathways and networks associated with AMR compared to the whole-transcriptome analysis.

METHODS

Study Design and Participants

The study cohort consisted of 137 heart transplant biopsies from 109 patients performed between 2006 and 2011 at four French referral institutions (Hôpital Georges Pompidou and Pitié Salpétrière in Paris, Hôpital Laennec in Nantes, and Hôpital Charles Nicolle in Rouen), that have been previously studied and published [6]. This study is a non pre-specified ancillary analysis of a prospective study. This cohort comprised patients with AMR, ACR and non-rejection related cases. This study was conducted in compliance with the Declaration of Helsinki and approved by the institutional review board (CPP Île de France II - protocol 2014-12-26, registration number: 00001072).

Definition of Antibody-Mediated Rejection of Heart Allografts

Histology of EMBs was assessed by 2 expert pathologists (PB and JPVDH). Biopsies were graded according to the most recent international working formulations of Society for Heart and Lung Transplantation [1, 7]. As recommended, immunohistochemistry based on C4d capillary deposition (positive if >50% of the capillaries were labeled) and/or CD68-positive staining (positive if intravascular $CD68^+$ macrophages were present in >10% of the capillaries) were evaluated.

Histological, Immunohistochemical and Transcriptomic Phenotyping of Biopsies

C4d staining was performed by immunohistochemistry on paraffin sections using an immunoperoxidase method and an anti-C4d antibody, additional staining were performed for characterization of macrophages capillary infiltration (anti-CD68) [8, 9]. All biopsies were processed for whole-transcriptome analysis. RNA extraction, labeling, and hybridization were performed to the HG-U219 GeneChip arrays (Affymetrix, CA, USA) following manufacturer's protocols (www.affymetrix.com). Microarrays were scanned using the Affymetrix Gene Array Scanner, generating.cel files with the GeneChip Operating Software Version 1.4.0 (Affymetrix) as previously described [10].

Mapping Banff Human Organ Transplant (B-HOT) Genes to Array Probesets

B-HOT gene annotations were defined according to the Banff 2019 meeting report [5]. The B-HOT panel consists of 770 genes, including 12 housekeeping genes only used for quality control and data normalization, and 758 endogenous genes to which microarray gene symbols were assigned. We excluded 4 viral-related genes (BK VP1, BK large T Ag, CMV UL83, EBV LMP2) due to lack of microarray correspondence. We corrected and accounted for gene alias discrepancies, noticing 4 endogenous genes that could not be mapped to the array: IGHG4, MIR155HG, OR2I1P, TRDC. Microarray gene annotations were retrieved from Bioconductor (hgu219.db) and mapped to probeset IDs, with multiple gene annotations being mapped to the same probeset ID. We finally excluded control array probeset AFFX and ERCC, resulting in unique annotated probesets mapping to relative genes.

Differential Expression Analysis

Raw gene expression data were normalized using the Robust Multichip Average (RMA) expression measure algorithm. Low variance probesets were excluded using IQR<0.5 filtering, with a total of 24697 probesets left. Differential expression analysis was conducted by fitting a linear model to the normalized expression values for each probeset. Fold changes and t-statistics were computed for the contrast of interest AMR versus non-AMR biopsies. Standard errors were moderated using an empirical Bayes model to compute a moderated t-statistic and a log-odds of differential expression for each contrast and each probeset [11]. Probesets were collapsed by gene identifiers for a total of 12170 unique genes, 662 of which were in the B-HOT panel, then by lowest *p*-value and highest fold changes (in the event of a *p*-value tie), adjusting nominal *p*-values for multiple comparisons using the Benjamini-Hochberg method.

We then compared differential expression analysis results derived from the whole-transcriptome or the targeted genes panel. Significant genes associated with AMR were filtered according to a false discovery rate *p*-value lower than 0.05 and annotated according to Uniprot as well as GeneCards databases [12, 13].

Analysis of AMR-Associated Pathways and Networks Based on B-HOT Genes

The enrichment pathways were generated based on the differentially expressed genes (FDR <0.05) for the contrast of interest derived from whole-transcriptome genes or restricted to B-HOT genes using ReactomePA [14]. Pathophysiological categories were then combined to investigate gene-to-gene interconnection by cnet plots (*enrichplot package*). Hierarchical clustering of enriched terms was implemented to account for pairwise similarities using Jaccard similarity index [15]. Statistical analyses were performed using R software (version 4.0.5).

RESULTS

Characteristics of Patients and Biopsies

Patients' characteristics (137 biopsies included from 109 patients from 4 French referral centers) are shown in **Supplementary Table S1**. The patients were mostly man (68.8%), their mean age at transplant was 43.2 years. A vast majority of biopsies were protocol biopsies (85%). The median biopsy time relative from transplant time is 10.67 months (IQR = 34.7). Among 137 heart allograft biopsies included, histology-based diagnosis identified 71 biopsies reflecting the entire spectrum of AMR as defined by international working formulations (pAMR1(I+): n = 20, pAMR1(H+): n = 24; pAMR2/3: n = 27) and 66 biopsies without AMR (comprising 24 with acute cellular rejection (ACR) and 42 with non-rejection diagnoses).

B-HOT Panel Gene Expression Appraisal to Detect AMR

B-HOT panel reliability in detecting gene expression pattern associated with AMR was evaluated through the comparison of the global gene expression changes in biopsies diagnosed with antibody-mediated rejection (n = 71) compared to all biopsies without AMR (n = 66), considering whole transcriptome genes or only those included in the targeted panel. The differential expression analysis showed a high enrichment of B-HOT

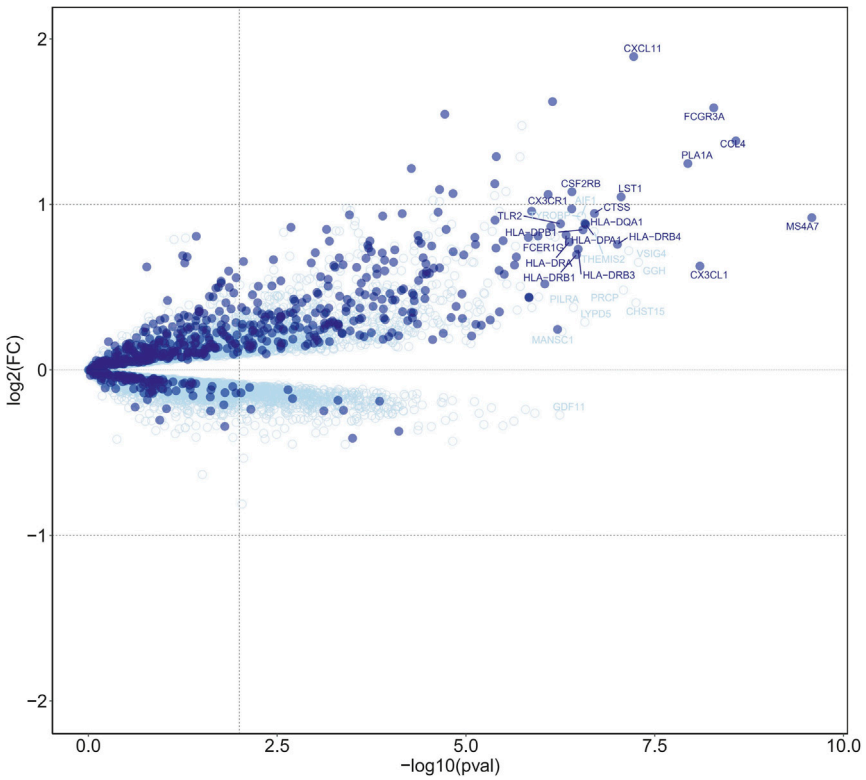


FIGURE 1 | Differential expression analysis of antibody-mediated rejection, highlighting B-HOT panel genes. Volcano plot of differentially expressed genes associated with AMR in heart allografts. Each dot represents an individual transcript. Dark blue points indicate genes targeted in the B-HOT panel and light blue points represent whole-transcriptome genes included on the microarray. The top 30 ranked differentially expressed gene symbols are shown according to 0.05 threshold (false discovery rate adjusted *p*-values). Differentially expressed B-HOT-related genes are associated to: IFNG-inducible genes (CX3CL1, CXCL11, HLA-DRB4, HLA-DRB1, HLA-DRB3, HLA-DPA1, HLA-DRA, HLA-DQA1, HLA-DPB1); NK-cell (CCL4, FCGR3A, CX3CR1); Injury (PLA1A, CTSS); Monocytes-macrophage (MS4A7, LST1, CSF2RB, TLR2); B-cell associated (FCER1G).

related genes (**Figure 1**). Of the top 30 genes identified in the whole transcriptome analysis, 19 were included in B-HOT panel and covered major immune response functions and cell specific types related to AMR: IFNG-inducible genes and adaptive immune response (CX3CL1, CXCL11, HLA-DRB4, HLA-DRB1, HLA-DRB3, HLA-DPA1, HLA-DRA, HLA-DQA1, HLA-DPB1); NK-cell related (CCL4, FCGR3A, CX3CR1); Injury related genes (PLA1A, CTSS); Monocytes-macrophage genes (MS4A7, LST1, CSF2RB, TLR2); B-cell associated gene (FCER1G) [12, 13]. We found a strong positive correlation between AMR-related gene expression and increasing AMR rejection grade (**Supplementary Figure S1**). The remaining 11 genes were related to functions and cell components associated with an unspecific immune response (**Supplementary Table S2**),: GGH (metabolism, hydrolysis); CHST12 (protein transport); VSIG4 (phagocytic receptor, negative regulator for T-cell receptor signaling and IL-2); PRCP (lysosomal peptidases); THEMIS2 (T-cell receptor signaling); LYPD5 (extracellular region protein); AIF1 (actin-binding protein, induced by cytokine and interferon); TYROBP (adapter protein); PILRA (cellular inhibitory receptor); MANSC1 (membrane protein); GDF11 (mediate cell differentiation, secrete ligand of TGF-beta).

Pathway and Gene-Concept Network Analysis of B-HOT AMR-Associated Genes

We then analyzed the ability of the B-HOT panel to capture clinically relevant biological pathways involved in AMR using functional enrichment analysis of all significant differentially expressed genes (FDR<0.05). Major pathophysiological mechanisms related to antibody-mediated response and injury (**Figures 2A, B**) identified in the whole-transcriptome analysis were also identified in the B-HOT derived analysis: interleukin (q = 1.00E-29) and interferon-gamma (INFG, q = 1.18E-21) signaling, antigen processing cross-presentation (q = 2.86E-15) and neutrophil degranulation (q = 9.03E-09). The whole-transcriptome analysis identified additional categories related to non-specific immune responses including caspase activation and regulated necrosis (**Supplementary Tables S3, S4**). Finally, we elucidated gene-to-gene interconnections by building functional networks (**Figures 3A, B**). Targeted- and

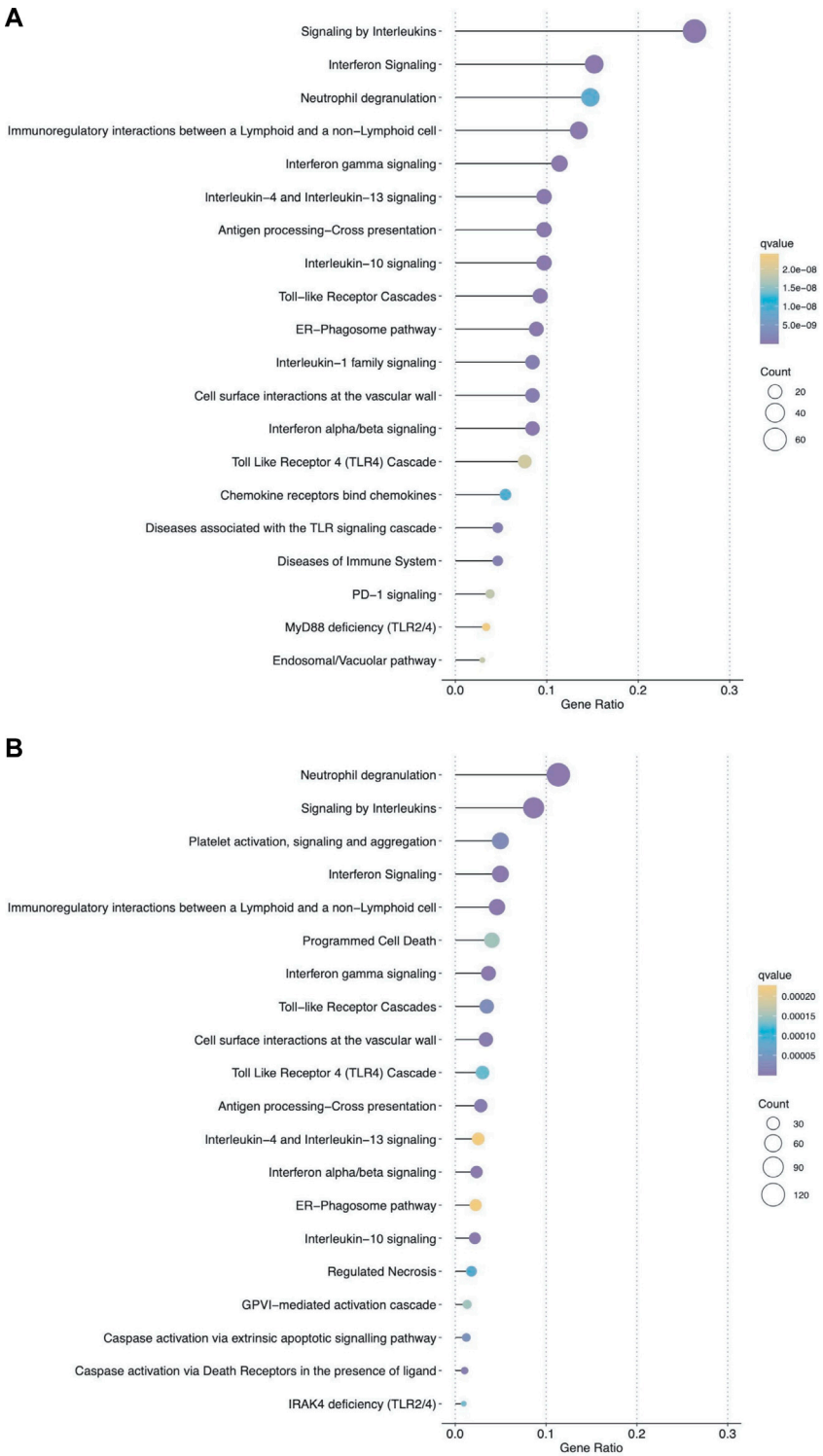


FIGURE 2 | Top ranked pathways associated with significant genes for antibody-mediated rejection using either the targeted panel only or all microarray genes. Dot plots show the top 20 enriched pathways based on significant differentially expressed genes (false discovery rate <0.05) associated with AMR in heart allografts (Panel **(A)**: B-HOT genes; Panel **(B)**: WT genes). The *x*-axis represents different gene categories, each enrichment result is plotted in accordance with the gene ratio (number of genes associated with the given pathway divided by the total number of genes analyzed). The size of the dots represents the number of genes in the significant differentially expressed gene list associated with the pathway and the color intensity of the dots represents the false discovery rate adjusted *p*-value.

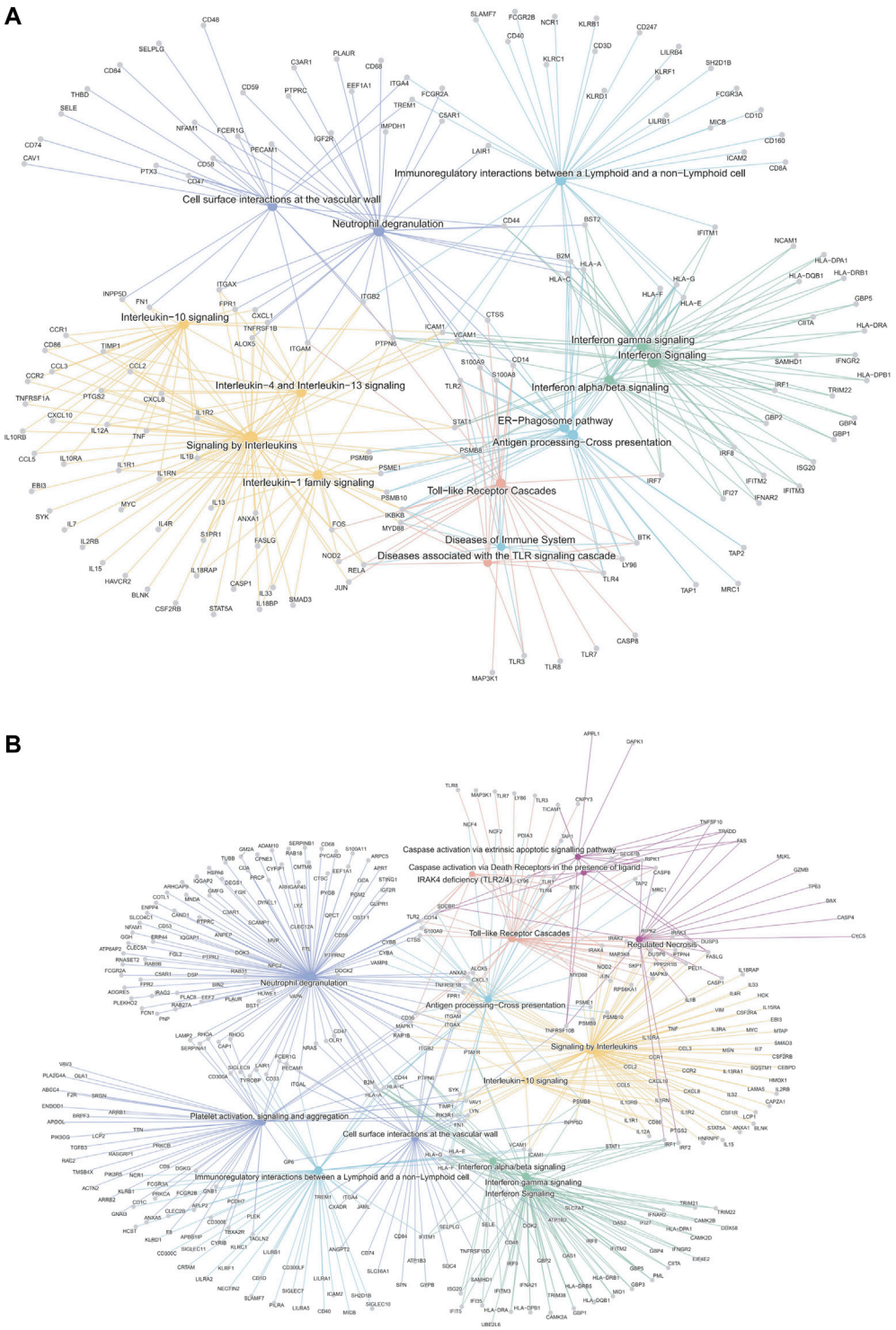


FIGURE 3 | Gene-Concept network analysis of significant differentially expressed genes associated with antibody-mediated rejection using the targeted panel or whole-transcriptome genes. The interaction networks depict the gene-to-gene interconnection in the enriched terms of biological categories from the Reactome repository. The top-ranked 15 signaling pathways are shown according to the general class of associated pathophysiological events involved in AMR (derived from B-HOT only and WT genes). Node size refers to the number of differentially-expressed genes in the enriched pathway. Genes shared between edges refer to terms belonging to multiple pathophysiological categories. Network plots of AMR associated genes (Panel **(A)**: B-HOT genes; Panel **(B)**: WT genes). Several pathways were shared between the two gene sets, especially related to: Toll-like receptor cascade, Interleukin and Interferon signaling. The network derived from B-HOT genes included pathways more specific to AMR pathophysiology associated with activation of specific Interleukin (IL-1, IL-4 and IL-13) and antigen processing cross-presentation mechanisms (ER-mediated). Networks based on WT genes showed categories with less specificity for antibody-mediated response, including Caspase activation and Apoptotic signals.

whole-transcriptome-derived networks showed high interconnections with a large overlap of pathophysiological categories: interleukin signaling, interferon signaling, adaptive immune system, Toll-like receptor cascade and cell surface interactions. Whole-transcriptome-based networks identified additional categories related to homeostasis, apoptosis regulation and caspase activation. Hierarchical clustering of enriched terms highlighted the importance of major immune-related classes in both approaches, displaying organization and relationships between the enriched pathways terms, ranking biological processes and pathways that are relevant to AMR condition (**Supplementary Figures S2A, B**). Overall, the analysis of pathophysiological mechanisms, gene-to-gene interactions within and between pathophysiological categories, as well as hierarchical clustering demonstrated that the B-HOT panel conserved similar functional information, thus showing less redundancy compared to the whole-transcriptome ones (**Figure 3**).

DISCUSSION

In this study, we evaluate the B-HOT panel ability to capture the key features of the molecular signature of AMR through comparative analysis with the whole-transcriptome approach. Using differential expression, pathway, and network analysis, we demonstrate that the B-HOT panel captured clinically-relevant AMR associated genes in heart allografts, and that the derived enriched pathways and functional networks were highly comparable to the whole-transcriptome derived ones. Our results suggest that the targeted panel may be sufficient and sensitive enough to serve as a surrogate to whole-transcriptome analysis.

In the last decade, whole-transcriptome based expression profiling has described the signature of allograft rejection in solid organ transplantation, and allowed the development of predicting models with good performance metrics [6, 16, 17]. However, this approach still relies on extra-biopsy cores, thus limiting the direct correlation of the molecular findings with the histology assessment.

While the molecular refinement of the diagnosis of rejection based on whole-transcriptome approaches faces several hurdles that limit its clinical application (e.g., variation due to cDNA conversion, amplification, labeling, probe redundancy), FFPE-based technology combined with a targeted panel has the potential to reduce experimental complexity, cost and turn-around time, thus refining rejection diagnosis and therapeutic decision-making in the framework of histo-molecular data contextualization. A first attempt to assess the B-HOT panel utility as a proxy for whole-transcriptome profiling on publicly available renal allograft expression data has been reported recently [18]. Our study extends this concept by contextualizing the clinical relevance of the targeted panel in the field of heart transplantation and appraising the gene expression molecular signature with the pathophysiological mechanisms associated with AMR. This advancement offers a more practical and cost-effective method to refine the pathology diagnosis of antibody-mediated rejection, paving the way for its potential implementation into clinical routine and aiding in the understanding of the complex mechanisms underlying heart allograft rejection. Some limitations of the study should be noted. First, additional studies investigating cellular rejection are required to validate the B-HOT panel as a relevant surrogate of whole-transcriptome analysis across the full spectrum of heart transplant pathology. Second, the interest of B-HOT-based molecular diagnostics in clinical practice remains to be evaluated by deriving and validating a specific targeted molecular signature of cardiac allograft rejection in multicenter cohorts. Novel precision diagnostic systems such as the B-HOT panel FFPE-tissue based had the potential to improve diagnostic accuracy, while reducing complexity and turn-around time. Additional studies are needed not only to precise the clinical value of the targeted gene expression analysis but also to combine invasive and non-invasive testing in the clinical field [19]. A synergistic approach that integrates multimodal assessment with multi-disciplinary expertise has never been more important for the global management of heart transplant recipients to optimize therapeutic decision-making and improve patients outcomes [5, 19, 20].

The Banff Human Organ Transplant panel accurately captured key molecular patterns of antibody-mediated rejection in heart allograft biopsies. Our study suggests that this specific targeted panel could be used as a proxy to whole-transcriptome profiling -based analysis after heart transplantation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Requests to access these datasets should be directed to AL, alexandre.loupy@inserm.fr.

ETHICS STATEMENT

The studies involving humans were approved by Ethics Committee CPP Île de France II. 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

Conception and design of the study, AG, GC, and AL; Data analysis and interpretation, AG, GC, OA, and AL. Writing, original draft preparation, AG, GC, and AL. Data acquisition OA and AL; Data interpretation and critically reviewed the manuscript AG, GC, OA, MF, FM, DZ, MM, PB, J-PD, AA, and AL. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

MM is the chairman of the Board of Trustees of the Banff Foundation for Allograft Pathology and receives consultancy honoraria from CSL Behring and Novartis as a central review pathologist for clinical trials.

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

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2023.11710/full#supplementary-material

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ORIGINAL RESEARCH
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Five-Year Outcome After Continuous Flow LVAD With Full-Magnetic (HeartMate 3) Versus Hybrid Levitation System (HeartWare): A Propensity-Score Matched Study From an All-Comers Multicentre Registry

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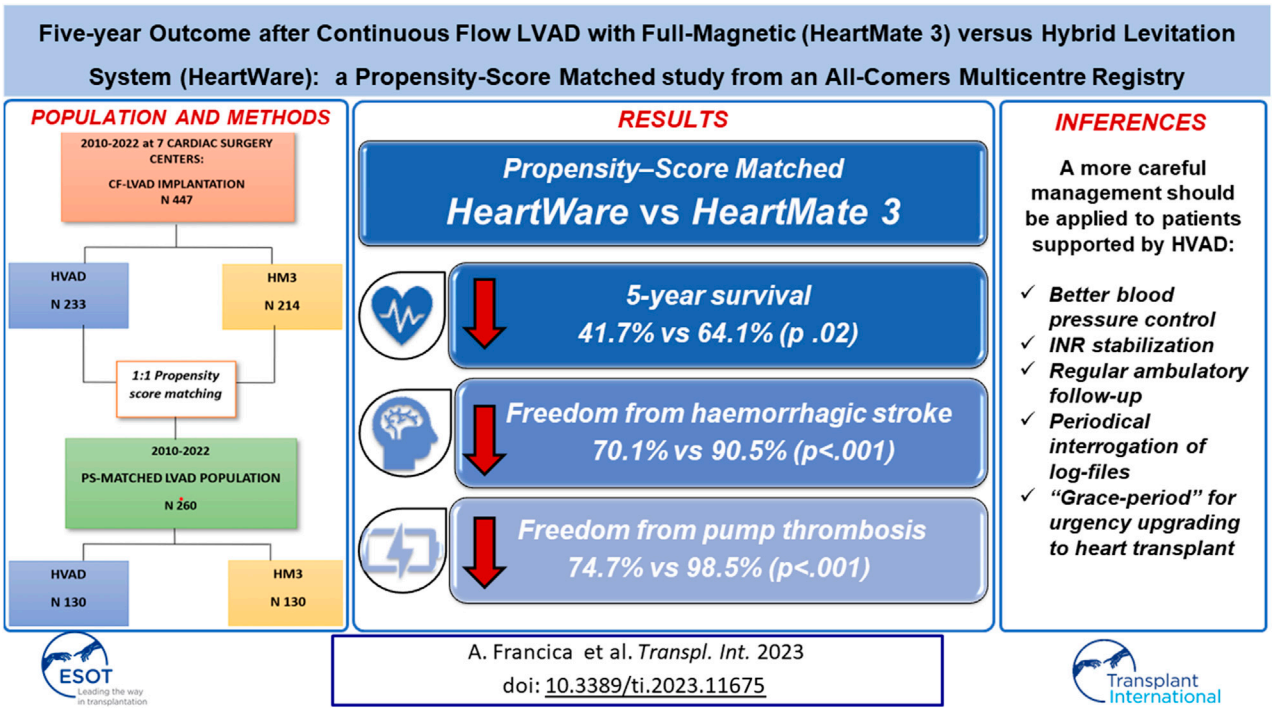
Despite the withdrawal of the HeartWare Ventricular Assist Device (HVAD), hundreds of patients are still supported with this continuous-flow pump, and the long-term management of these patients is still under debate. This study aims to analyse 5 years survival and freedom from major adverse events in patients supported by HVAD and HeartMate3 (HM3). From 2010 to 2022, the MIRAMACS Italian Registry enrolled all-comer patients receiving a LVAD support at seven Cardiac Surgery Centres. Out of 447 LVAD implantation, 214 (47.9%) received HM3 and 233 (52.1%) received HVAD. Cox-regression analysis adjusted for major confounders showed an increased risk for mortality (HR 1.5 [1.2–1.9]; p = 0.031), for both ischemic stroke (HR 2.08 [1.06–4.08]; p = 0.033) and haemorrhagic stroke (HR 2.6 [1.3–4.9]; p = 0.005), and for pump thrombosis (HR 25.7 [3.5–188.9]; p < 0.001) in HVAD patients. The propensity-score matching analysis (130 pairs of HVAD vs. HM3) confirmed a significantly lower 5 years survival (41.7% vs. 64.1%; p 0.02), freedom from haemorrhagic stroke (90.5% vs. 70.1%; p < 0.001) and from pump thrombosis (98.5% vs. 74.7%; p < 0.001) in HVAD cohort. Although similar perioperative outcome, patients implanted with HVAD developed a higher risk for mortality, haemorrhagic stroke and thrombosis during 5 years of follow-up compared to HM3 patients.

Keywords: continuous-flow LVAD, HeartMate3, HeartWare, full-magnetic levitation pump, hybrid levitation system pump



GRAPHICAL ABSTRACT |

INTRODUCTION

Improved outcomes and increased durability and applicability of long-term mechanical circulatory support have settled this treatment as an effective option for patients with advanced heart failure not suitable for heart transplant. Moreover, donor organ shortage caused a growing interest in Left Ventricle Assist Devices (LVAD) not only as a Bridge-To-Transplant (BTT), but also as destination therapy (DT). In this scenario, continuous-flow pumps have become a standard of care for end-stage heart failure and are currently regarded as the gold standard in LVAD therapy [1]. The HeartWare Ventricular Assist Device (HVAD) by Medtronic and the HeartMate 3 (HM3) by Abbott represents the third-generation centrifugal-flow LVADs (CF-LVADs) implanted worldwide during the last years. The ENDURANCE trial [2] showed the non-inferiority of HVAD versus previous axial-flow pumps, whereas the MOMENTUM-3 trial [3] demonstrated the superiority of the HM3 to the axial-flow Heartmate-II (HMII) in terms of survival and device-related complications. However, on June 2021, HVAD global production and distribution was withdrawn, due to an increased incidence of all-cause mortality and stroke; moreover, several pump failures without an identified cause were reported worldwide [4–6]. Despite its discontinuation, hundreds of patients are still on HVAD. Very limited data exist comparing outcomes with both devices, and previous studies mainly focused on short-term results. Therefore, it is the aim of this study to analyse 5 year survival and freedom from major complications in our Italian all-comer population supported with HVAD or HM3.

PATIENTS AND METHODS

Study Population

From June 2010 to December 2022, the Multicenter Italian Study on Radial Mechanically Assisted Circulatory Support (MIRAMACS) Registry [7] enrolled all-comer adult patients (>18 years of age) requiring LVAD support for end-stage heart failure at seven experienced Cardiac Surgery Centres. Only patients receiving HM3 (Abbott, Chicago, IL, United States) or HVAD (Medtronic, Minneapolis, MN, United States) devices were included in the analysis. All patients with biventricular VADs, isolated right ventricular assist device (RVAD), or axial -flow pumps were excluded. Pre-, intra- and post-operative data were collected. Five-years follow-up was prospectively conducted for all participants, through outpatient visits or direct phone contact to the patient or the referring cardiologist. All data were collected in a dedicated datasheet with predefined variables shared among the Participating Centres. All patient's data were anonymized with a code of serial numbers. Each Centres had a Principal Investigator and a Collaborator who checked and granted for the anonymization and for the completeness of data. The datasheets from each Centre were then merged in a single database.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the "Area Vasta Emilia Centro della Regione Emilia-Romagna" Ethical Committee, "Azienda Ospedaliero—Universitaria di Bologna, Policlinico S. Orsola-Malpighi" (n° 990/2020/Oss/AOUBo; date of approval: 19/11/2020).

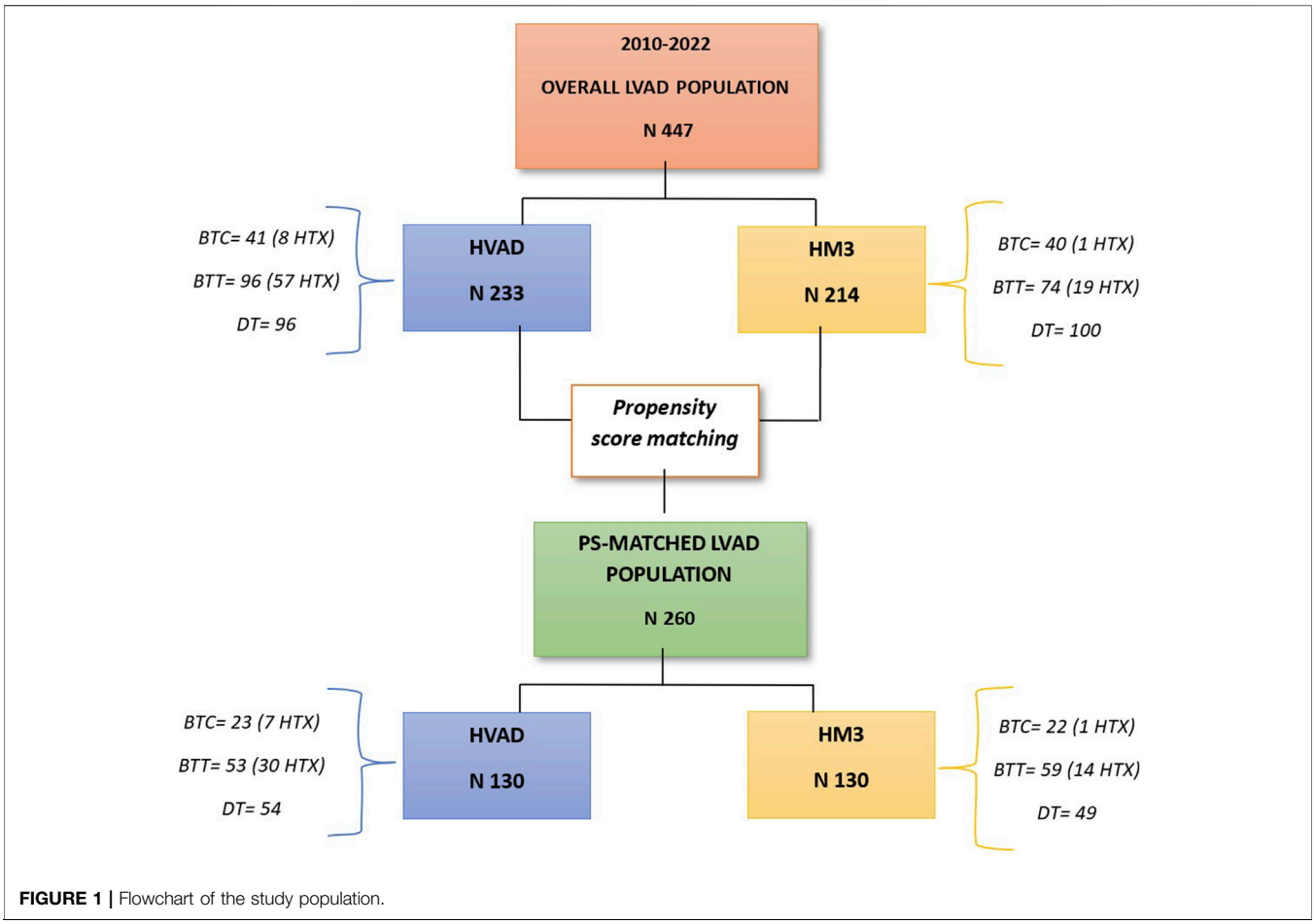


FIGURE 1 | Flowchart of the study population.

Endpoints

Five-year survival in patients supported by HM3 and HVAD was the primary endpoint of the study. Predictors of survival and 5 years freedom from major adverse events (ischaemic and haemorrhagic stroke, thrombosis, right ventricular failure, gastrointestinal bleeding, and driveline infection) were secondary endpoints. Perioperative outcomes were also assessed. A sub analysis between the first 50 patients implanted with HVAD and the first 50 patients implanted with HM3 was performed in order to investigate a potential learning curve effect. Finally, two sub-analyses were also conducted in patients requiring LVAD as a Destination Therapy (DT) or as a Bridge-To-Transplant (BTT).

Early and late adverse events were defined according to the latest ISHLT definition of adverse events for trials and registries of mechanical circulatory support [8].

Statistical Analysis

The STROBE checklist was used for reporting observational studies [9]. Descriptive statistics were used to analyse data. Continuous variables are reported as mean ± standard deviation or median (interquartile range), and categorical variables are reported as counts and percentages. Differences between groups were assessed using one-way ANOVA for continuous variables. Categorical data were compared between groups using Pearson's χ^2 tests or Fisher's exact tests, as appropriate. Time-to-event analysis was performed. Kaplan–Meier curves were estimated for mortality and each late adverse event. Differences between groups were assessed by the Log-Rank test. A Cox-regression analysis adjusted for major confounders was used to derive the hazard ratios (HR) and 95% confidence intervals (CI). A multivariate Cox-logistic regression was performed to assess predictors of survival among preoperative and post-operative factors in both HVAD and HM3 population. To account for imbalances between the two cohorts, a propensity score was calculated by logistic regression considering the statistically significant differences among preoperative variables. The Propensity-Score Matching (PSM) was conducted using greedy nearest neighbour matching with a 0.01 caliper and a 1:1 match ratio. The Standardized Mean Differences (SMD) were calculated to assess balance after PSM. The statistical analysis was performed using SPSS Version 27.0 (Armonk, NY, IBM Corp.). A p-value of <0.05 was considered statistically significant.

TABLE 1 | Independent determinants of survival in HVAD patients.

Independent determinants of survival in HVAD patients			
Preoperative and postoperative factors	**HR**	**95% confidence interval**	***p-value***
Age	1.03	1.003–1.06	*0.028*
Post-operative dyalisis	2.7	1.53–4.79	*<0.001*
Post-operative ischaemic stroke	2.87	1.16–7.1	*0.023*

**Statistically significant.*

TABLE 2 | Independent determinants of survival in HM3 patients.

Independent determinants of survival in HM3 patients			
Preoperative and postoperative factors	**HR**	**95% confidence interval**	***p-value***
Preoperative creatinin level	1.46	1.03–2.07	*0.032*
Post-operative dyalisis	1.99	1.08–3.67	*0.03*
Post-operative ischaemic stroke	7.24	3.35–15.6	*<0.001*
Post-operative right ventricular failure	2.96	1.62–5.43	*<0.001*

**Statistically significant.*

RESULTS

Overall Population

Between June 2010 and December 2022, a total of 447 patients were implanted with CF-LVADs at seven Italian Cardiac Surgery Centres: 214 patients (47.9%) received the HM3 and 233 patients (52.1%) received the HVAD (See **Figure 1**). The two populations differed in several preoperative characteristics. Patients receiving HVAD were younger, with a smaller body surface area and greater preoperative hepatic injury, when compared with HM3 recipients. On the other hand, HM3 patients presented a higher systolic pulmonary arterial pressure, and a more advanced renal impairment than HVAD patients (**Supplementary Table S1**). Fifty per cent of both populations was in INTERMACS 3, while 10% in INTERMACS 1. Ischemic heart disease and idiopathic cardiomyopathy represented the main indications in both groups, while hypertrophic cardiomyopathy was more observed in HM3 patients (**Supplementary Table S1**). Periprocedural mortality (14% vs. 9% for HM3 vs. HW; $p = 0.1$) was comparable between the two populations. Detailed hospital outcomes data were reported in **Supplementary Table S2**.

The mean follow-up time was 65.7 ± 3.1 months. The overall survival at 5 years was higher in HM3 patients (64.1% vs. 42.6%, $p = 0.004$) (**Figure 2A**). In HVAD cohort, age (HR 1.03 [1.003–1.057]; $p = 0.028$), post-operatively dialysis (HR 2.7 [1.53–4.79]; $p < 0.001$) and ischaemic stroke (HR 2.87 [1.16–7.1]; $p = 0.023$) resulted risk factors for mortality at follow-up (**Table 1**). In HM3 cohort, preoperative creatinine level (HR 1.46 [1.03–1.2.07]; $p = 0.032$), post-operatively dialysis (HR 1.99 [1.077–3.67]; $p < 0.03$), ischaemic stroke (HR 7.24 [3.4–15.6]; $p < 0.001$) and right ventricular failure (HR 2.96 [1.62–5.43]: $p < 0.001$) resulted risk factors for mortality at follow-up (**Table 2**).

HVAD patients reported a significantly lower freedom from both haemorrhagic (88.6% vs. 69.8%; $p < 0.001$) and ischaemic stroke (91.7% vs. 75.1%; $p = 0.054$), and from pump thrombosis (99.1% vs. 76.8%; $p < 0.001$) (**Supplementary Figures S1, S2**). No statistical differences in 5 years freedom from right ventricular failure and from driveline infection were reported between groups (**Supplementary Figure S2**). The Cox-regression analysis adjusted for major confounders showed that HVAD patients had a significantly increased risk for mortality (HR 1.5 [1.2–1.9]; $p = 0.031$), for pump thrombosis (HR 25.7 [3.4–188.9]; $p < 0.001$), and for both haemorrhagic stroke (HR 2.6 [1.3–4.9]; $p = 0.005$) and ischemic stroke (HR 2.08 [1.06–4.08]; $p = 0.033$) (**Table 1**). Five-year freedom from gastrointestinal bleeding was significantly higher in HM3 patients (90.5% vs. 80.2%; $p = 0.008$) (**Supplementary Figure S2**), though this difference was lost after adjusting for major confounders at Cox-regression analysis (**Table 3**).

Heart Transplant, LVAD Explant or Exchange

A total of 65 HVAD (57 BTT and 8 BTC) and 20 HM3 (19 BTT and 1 BTC) patients underwent to heart transplant. Among HVAD patients, 22 (33.8%) underwent to heart transplant because of LVAD complications (14 because of pump thrombosis, 4 because of LVAD infection), eight of whom in urgency tier. Only four patients (one in urgency) in HM3 cohort were transplanted because of LVAD infection. Only two patients underwent to HVAD explant for recovery, while one patient underwent HVAD exchange for pump thrombosis, but died postoperatively. All other patients who experienced thrombosis were pharmacologically treated and 14 of them transplanted.

Sub-Analysis of the First 50 Cases of HVAD and HM3 Implantation

The sub analysis on the first 50 cases of implantation of HVAD and HM3 confirmed a worse outcome in HVAD patients. Perioperative

TABLE 3 | HVAD vs. HM3: Non-adjust and adjusted Cox-regression analysis for major adverse events at follow-up.

Adverse event	Non-Adjusted Cox-regression		Adjusted[a] Cox-regression	
	HVAD vs. HM3 HR (95% CI)	*p*	HVAD vs. HM3 HR (95% CI)	*p*
Mortality	1.6 [1.16–2.17]	0.004	1.5 [1.2–1.9]	*0.031*
Haemorrhagic stroke	3.04 [1.6–5.8]	<0.001	2.6 [1.3–4.9]	*0.005*
Ischaemic stroke	1.8 [0.97–3.5]	0.058	2.08 [1.06–4.08]	*0.033*
Pump Thrombosis	27.7 [3.8–203.8]	0.001	25.7 [3.4–188.9]	*<0.001*
GI bleeding	2.4 [1.2–4.5]	0.01	1.6 [0.81–3.2]	*0.17*
RV failure	1.14 [0.77–1.7]	0.51	0.96 [0.62–1.4]	*0.83*
DL infection	1.3 [0.88–1.89]	0.2	1.3 [0.85–2.04]	*0.21*

[a]*Adjusted for age, BSA, ALT, creatinine, primary heart disease, sPAP.*

DL, driveline; GI, gastrointestinal; RV, right ventricle.

**Statistically significant.*

TABLE 4 | PS-matched population: Preoperative characteristics.

Preoperative characteristics *n* (%), m (SD)	HM3 (n 130)	HVAD (n 130)	*p*	SMD
Age, years	60.2 (8.7)	59.8 (10.5)	*0.71*	*0.04*
Sex, males	118 (90.8)	116 (89.2)	*0.68*	*0.03*
BSA, cm/m^2	1.9 (0.19)	1.9 (0.17)	*0.56*	*0*
Creatinine, mg/dL	1.4 (0.63)	1.4 (0.49)	*0.86*	*0*
AST, U/L	37.6 (37.9)	32.4 (31.3)	*0.24*	*0.1*
ALT, U/L	34.9 (35.3)	32.6 (26.3)	*0.55*	*0.07*
Atrial fibrillation	52 (24.3)	35 (15)	0.013	
EF, %	20.4 (5.9)	21.1 (7.1)	*0.41*	*0.1*
LVEDV, mL	263.4 (78.5)	261.3 (111.1)	0.9	0.002
TAPSE, mm	16.8 (4.3)	16.7 (4.5)	0.88	0.002
PVR (Fick), wood	3.3 (1.9)	3.5 (2.07)	*0.23*	*0.07*
Cardiac index (Fick)	1.9 (0.54)	1.9 (0.55)	*0.38*	*0*
Heart disease			0.73	*0.07*
Idiopathic	54 (41.5)	60 (46.2)		
Hypertrophic	3 (2.3)	5 (3.8)		
Ischemic	67 (51.5)	60 (46.2)		
Other	6 (2.3)	5 (1.9)		
Intermacs			*0.23*	*0.1*
1	21 (9.2)	7 (5.4)		
2	21 (16.1)	33 (25.4)		
3	68 (52.3)	65 (50)		
4	29 (22.3)	25 (19.2)		
IABP	44 (33.8)	33 (25.8)	*0.14*	*0.1*
VA-ECMO	7 (5.4)	8 (6.2)	*0.8*	*0.03*
REDO	8 (6.2)	10 (7.7)	*0.9*	*0.05*
Indication			*0.74*	*0.06*
BTT	59 (45.4)	53 (40.8)		
DT	49 (37.6)	54 (41.5)		
BTC	22 (16.9)	23 (17.7)		

BSA, body surface area; EF, ejection fraction; IABP, intra-aortic balloon pump; INTERMACS, interagency registry for mechanically assisted circulatory support; LVEDV; left ventricular end diastolic volume; PAP, systolic pulmonary arterial pressure; PVR, pulmonary vascular resistance; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

**Statistically significant.*

mortality was higher in HVAD patients compared to HM3, though not statistically significant (10% vs. 4%; $p = 0.43$). Long-term outcome analysis confirmed worse 5 years survival (24.8% vs. 68.1%; $p < 0.001$), lower freedom from haemorrhagic (54.5% vs. 80.8%; $p = 0.04$) and ischaemic stroke (71.2% vs. 95.8; $p = 0.007$) and from pump thrombosis (62.6% vs. 100%; $p < 0.001$). Five-year freedom from gastrointestinal bleeding (79.4% vs. 90.2%; $p = 0.12$), from right ventricular failure (66.4% vs. 77.9%; $p = 0.29$) and from drive-line infection (54.6% vs. 63.4%; $p = 0.83$) were similar between the two cohorts.

Propensity Matched Population

After PSM-analysis, 130 pairs of patients with similar preoperative profiles receiving HM or HVAD were selected. Preoperative characteristics are reported in **Table 4**. Post-operative complications remained similar between the groups, with the exception for prolonged ventilation and sepsis which were more frequent in HM3 patients (**Table 5**). HVAD patients confirmed a significantly lower 5 years survival (64.1% vs. 41.7%; p 0.02) (**Figure 2B**), freedom from haemorrhagic stroke (90.5% vs. 70.1%; $p < 0.001$) and from pump thrombosis (98.5% vs. 74.7%; $p < 0.001$)

TABLE 5 | PS-matched population: In-hospital outcomes.

In-hospital outcome n (%), m (SD)	HM3 (n 130)	HVAD (n 130)	*p*
In-hospital mortality	15 (11.5)	11 (8.5)	*0.41*
CPB time, min	106.3 (37.9)	98.4 (44.4)	*0.16*
Total Implantation time, min	317.72 (85.19)	329 (262.5)	*0.7*
Bleeding requiring surgical revision	16 (12.3)	18 (13.8)	*0.71*
Prolonged ventilation (>72 h)	37 (28.5)	11 (8.5)	*<0.001*
Dialysis	22 (16.9)	13 (10)	*0.1*
Sepsis	46 (35.4)	21 (16.2)	*<0.001*
Ischaemic stroke	7 (5.4)	5 (3.8)	*0.55*
Haemorrhagic stroke	0	0	
Right ventricular failure	27 (20.8)	15 (11.5)	*0.043*
Temporary RVAD	6 (4.6)	4 (3)	*0.8*
ICU days	17.8 (22.1)	15.2 (22.9)	*0.37*
In-hospital days	44.14 (50.1)	39.4 (46.7)	*0.45*

CPB, cardiopulmonary bypass; ICU, intensive care unit; RVAD, right ventricular assist device.
**Statistically significant.*

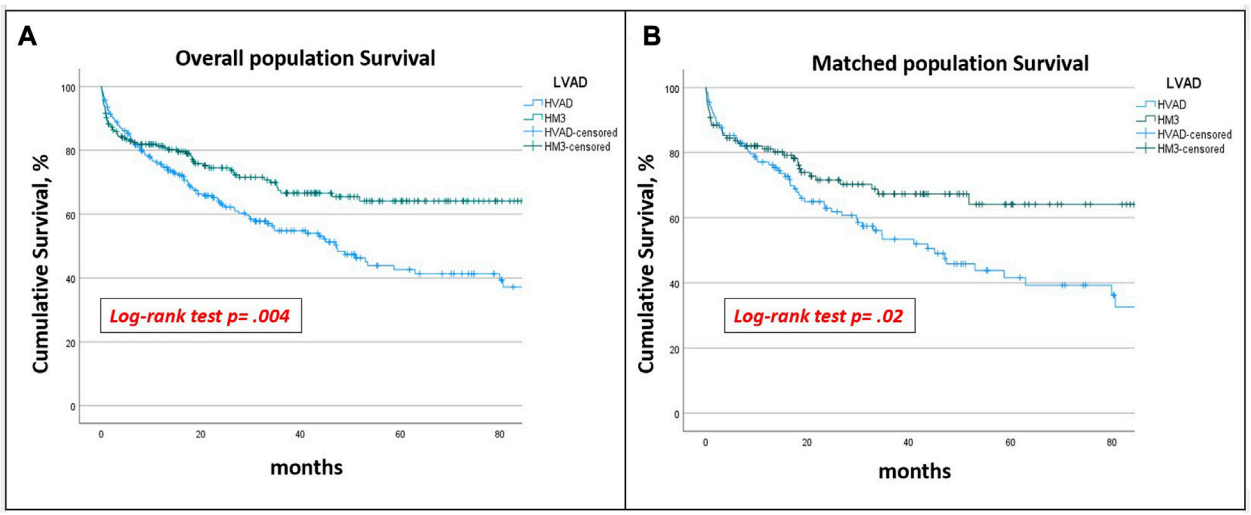


FIGURE 2 | Overall **(A)** and PS-matched survival **(B)**: HVAD patients had a significantly lower 5 years survival than HM3 patients in both unmatched and matched populations.

(**Figure 3**). Freedom from ischaemic stroke remained lower in HVAD compared to HM3, but non-statistically significant (**Figure 4**). Freedom from gastrointestinal bleeding, driveline infection and right heart failure were comparable between HM3 and HVAD (**Figure 4**).

Out of 103 DT patients, 49 received HM3 and 54 received HVAD. More than 80% were male in both groups, with a mean age of 66.2 ± 5.6 in HM3 vs. 67.5 ± 5.02 in HVAD (p = 0.18) (**Table 6**). Post-operative mortality was comparable (8.2% vs. 5.6% in HM3 and HVAD respectively; p = 0.7), as well as all post-operative complications, except for right ventricular failure that was more common in HM3 patients (**Table 7**). The HVAD cohort had lower 5 years cumulative survival (59.9% vs. 37% p = 0.03) (**Supplementary Figure S3A**) and freedom from haemorrhagic stroke (76.7% vs. 65.4%; p = 0.01) (**Supplementary Figure S3B**). In this sub-population, freedom from thrombosis resulted lower in HVAD, though not statistically significant (**Supplementary Figure S4**). No statistical differences were reported for the other adverse events (**Supplementary Figure S5**).

Out of 116 BTT patients, 59 were supported by HM3 and 53 by HVAD. Time to transplant was shorter in HVAD (36.7 vs. 49.9 months; p = 0.019) (**Supplementary Figure S6B**). The cumulative 5 years survival was comparable between the two cohorts (**Supplementary Figure S6A**), as well as the freedom from adverse events (**Supplementary Figures S7, S8**), except freedom from pump thrombosis which was lower in HVAD patients (**Supplementary Figure S7B**). Preoperative and post-operative data of BTT are displayed in **Supplementary Tables S3, S4**.

DISCUSSION

In this Italian multicentre observational study, we compared 5 years survival and freedom from major adverse events in patients

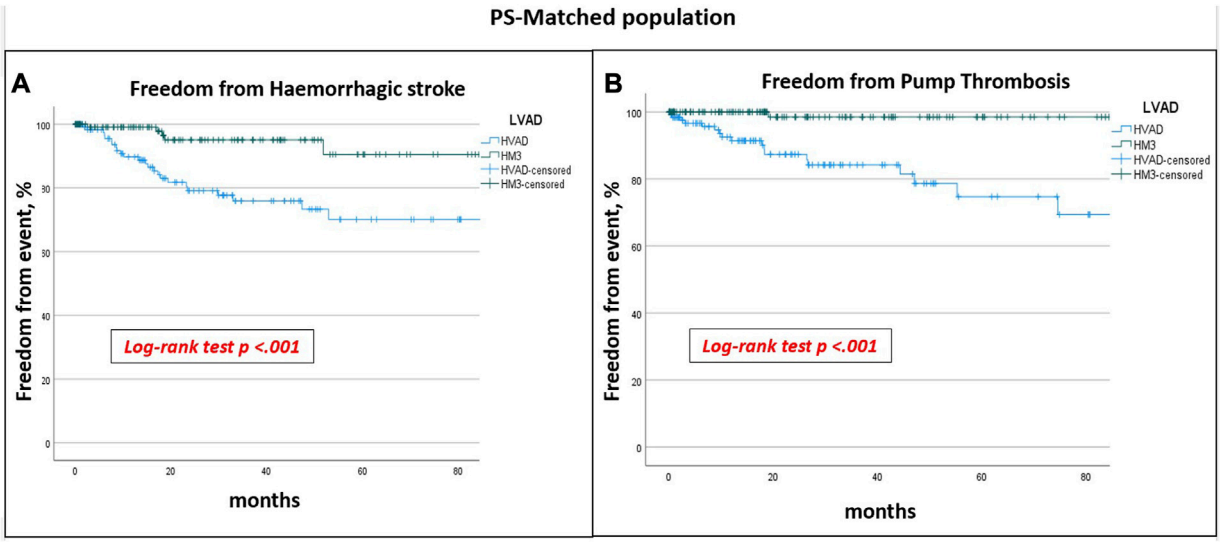


FIGURE 3 | PS-matched population freedom from haemorrhagic stroke **(A)** and from pump thrombosis **(B)**: HVAD patients had a significantly lower freedom from haemorrhagic stroke and from pump thrombosis.

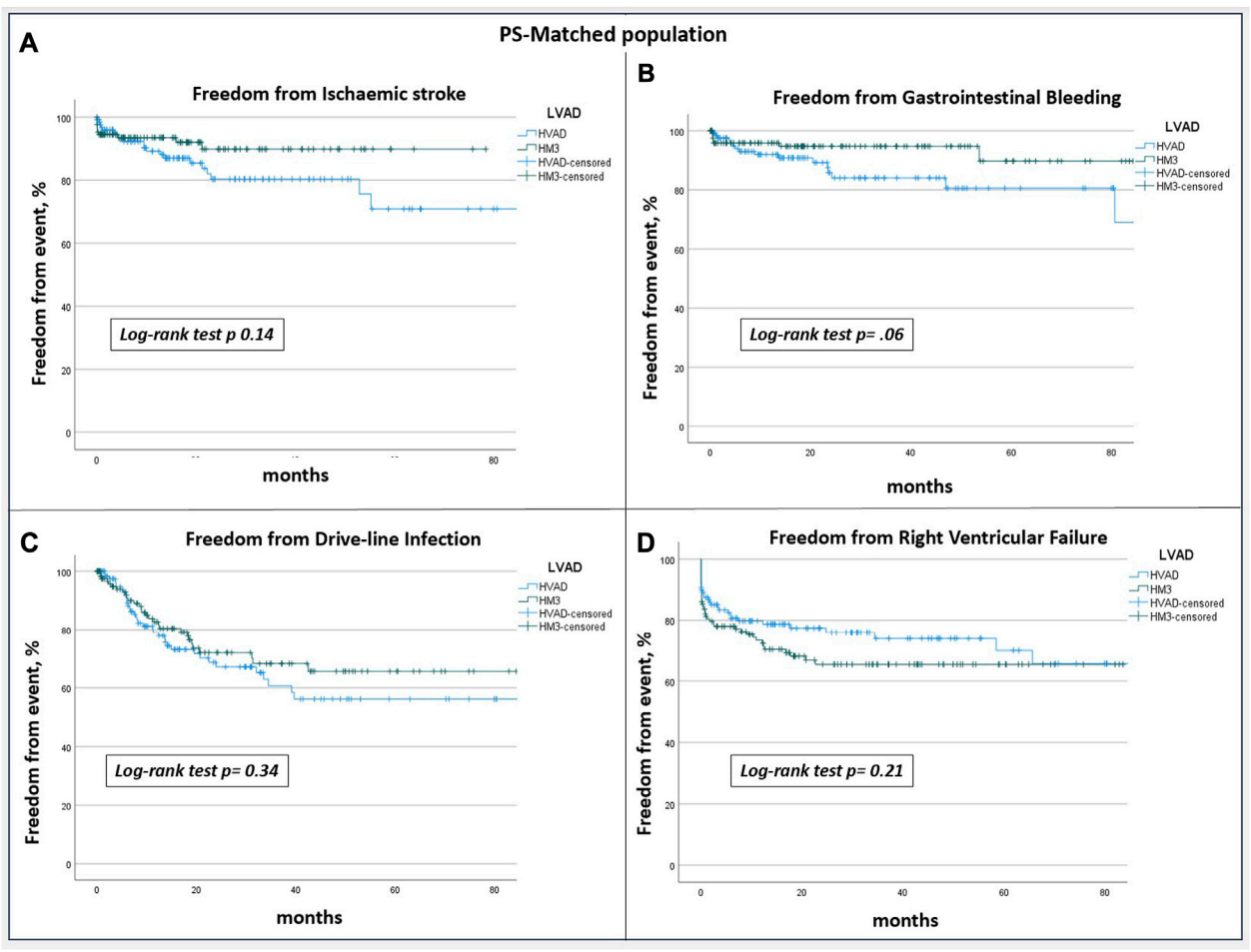


FIGURE 4 | PS-matched populations freedom from **(A)** ischaemic stroke, **(B)** gastrointestinal bleeding, **(C)** driveline infection, **(D)** right ventricular failure: no statistically significant differences at 5 years were found between HVAD and HM3 cohorts.

TABLE 6 | PS-matched DT population: Preoperative characteristics.

Preoperative characteristics n (%), m (SD)	HM3 (n 49)	HVAD (n 54)	*p*
Age, years	66.2 (5.6)	67.5 (5.02)	*0.18*
Sex, males	43 (87.8)	46 (85.2)	*0.7*
BSA, cm/m^2	1.9 (0.16)	1.8 (0.15)	*0.21*
Creatinine, mg/dL	1.6 (0.76)	1.5 (0.45)	*0.65*
AST, U/L	33.09 (34.4)	41.6 (59.4)	*0.39*
ALT, U/L	26.1 (14.9)	38.8 (37.9)	*0.03*
Atrial fibrillation	15(30.6)	12 (22.2)	*0.33*
EF, %	18.9 (6.4)	18.9 (5.7)	*0.98*
LVEDV, mL	247.12 (94.2)	272. 5 (94.2)	0.26
TAPSE, mm	16.9 (4.03)	17.5 (5.3)	0.55
PVR (Fick), wood	2.7 (1.3)	3.1 (2.1)	*0.19*
Cardiac index (Fick)	2.2 (0.65)	2.13 (0.57)	*0.5*
sPAP, mmHg	43.04 (15.5)	40.4 (15.2)	*0.38*
Heart disease			0.41
Idiopathic	16 (32.7)	25 (46.3)	
Hypertrophic	0	0	
Ischaemic	31 (63.3)	28 (51.9)	
Other	1 (2)	1 (1.9)	
Intermacs			*0.21*
1	3 (6.1)	1 (1.9)	
2	7 (14.3)	16 (29.6)	
3	29 (59.9)	29 (53.7)	
4	10 (20.4)	8 (7.8)	
IABP	20 (40.8)	22 (40.7)	*0.99*
VA-ECMO	2 (4.1)	5 (9.3)	*0.44*
REDO	5 (10.2)	4 (7.4)	*0.73*

BSA, body surface area; DT, destination therapy; EF, ejection fraction; IABP, intra-aortic balloon pump; LVEDV; center ventricular end diastolic volume; PAP, systolic pulmonary arterial pressure; PVR, pulmonary vascular resistance; VA-ECMO, veno-arterial extracorporeal membrane oxygenation
**Statistically significant.*

TABLE 7 | PS-matched DT population: In-hospital outcomes.

In-hospital outcome n (%), m (SD)	HM3 (n 49)	HVAD (n 54)	*p*
In-hospital mortality	4 (8.2)	3 (5.6)	*0.7*
CPB time, min	109.7 (35.)	107.03 (49.9)	0.08
Total Implantation time, min	318.6 (87.7)	392 (348.12)	*0.22*
Bleeding requiring surgical revision	4 (7.4)	4 (7.4)	*1*
Prolonged ventilation (>72 h)	13 (26.5)	6 (11.1)	*0.044*
Dialysis	8 (16.3)	4 (7.4)	*0.22*
Sepsis	15 (30.6)	7 (13)	*0.029*
Ischaemic stroke	2 (4.1)	1 (1.9)	*0.6*
Haemorrhagic stroke	0	0	—
Right ventricular failure	11 (22.4.6)	3 (5.5)	*0.019*
Temporary RVAD	3 (6.1)	2 (3.7)	*0.8*
ICU days	18.9 (24.4)	17.6 (21.3)	*0.79*
In-hospital days	38.3 (25.3)	33.3 (25.5)	*0.38*

DT, Destination therapy; CPB, cardiopulmonary bypass; ICU, intensive care unit; RVAD, right ventricular assist device.
**Statistically significant.*

supported either by HVAD or HM3. HVAD recipients showed a significantly lower 5 years survival with a higher risk of haemorrhagic stroke and pump thrombosis compared to the HM3 patients, before and after the PSM analysis. Freedom from ischaemic stroke, gastrointestinal bleeding, right heart failure, and driveline infections did not significantly differ between the two groups after PSM. To the best of our knowledge, scanty data exist comparing 5 years outcome of these two different CF-LVADs outside of the industry-driven trials. Furthermore, both devices have been preferentially compared to historical cohorts implanted with the second generation axial-flow pumps [2, 3]. More in detail, few retrospective single-centre studies and three registry-based studies compared HM3 and HVAD, and all reported a higher incidence of adverse events in HVAD patients [10–16]. In line with our results, Mueller et al. [10] and Numan et al. [12] reported a significantly higher incidence of haemorrhagic stroke and pump thrombosis in HVAD patients at 12 and 36 months, respectively, whereas Mihalj et al. [13] reported an increased risk of device malfunctions, though excluding pump thrombosis. However, none of these single-centre studies showed a significant difference in follow-up survival between HM3 and HVAD, but the median follow-up time never exceeded 3 years. Similarly, the EUROMACS analysis by Potapov et al. [14] reported a higher incidence of pump thrombosis and haemorrhagic stroke in HVAD recipients already at 2 years of follow-up, although survival was comparable. However, despite the reported survival of HVAD and HM3 of all the above-mentioned studies was always comparable, the slopes of the curves always addressed a higher survival in the HM3 cohorts, thus highlighting the potential for biases related to the small sample sizes and the short-term follow-up times of these analyses [10–16]. On the contrary, our data agree with the latest report from the STS Intermacs database published by Pagani et al. [16], which identified an important survival benefit at 2 years of follow-up after HM3 implantation compared to HVAD support. Analogous results were also observed by a recent large-scale

multicentre study by Numan et al. [17], which confirmed a significantly better survival and a lower occurrence of pump thrombosis for HM3 patients at 2 years of follow-up, in both un-adjusted and adjusted populations. All these results are in line with our findings and suggests that patients on HVAD support have a worse life-expectation than patients on HM3 support, an we also demonstrated that it did not depends by the learning curve time. Indeed, one large multicentre study reported the longest follow-up of HVAD-patients: this study was the only one able to achieve a 6 years freedom from any stroke of 82%, and a freedom from severely disabling stroke of 89% [18], possibly suggesting a better risk-profile and a better patient selection than our and all the above-mentioned studies.

Different from our findings, Numan et al. [17] found no differences in the occurrence of haemorrhagic stroke between HVAD and HM3. Conversely, an in-depth analysis of cerebrovascular adverse events from the INTERMACS registry [15] showed a higher occurrence of both ischaemic and haemorrhagic cerebrovascular adverse events in patients on HVAD support. Similarly, our study reported higher ischaemic and haemorrhagic strokes in the overall population of HVAD patients, although the incidence of ischaemic stroke loses statistical significance after the PSM analysis. The latter finding could be explained by the reduced number of events in the matched cohorts. On the other hand, we observed no differences for gastrointestinal bleeding, driveline infections, and right heart failure, as reported in previous studies [10–16].

When DT subgroup was considered, a higher survival rate and lower incidence of haemorrhagic stroke were still observed in the HM3 cohort when compared with HVAD, in line with a recent single-centre study by Wasilewski et al. [19] who reported a better survival and freedom from complications in HM3 compared to HVAD in DT patients at 2 years of follow-up. Finally, our sub analysis on BTT patients showed that HVAD recipients underwent heart transplant more commonly than HM3. This is explained by the different follow-up time between the two cohorts given that HM3 was launched in the market later than HVAD, as also highlighted in previous studies [14,17], and by the fact that patients on HVAD were transplanted more quickly because of the higher rate of pump thrombosis, thus qualifying for a high urgency tier. Finally, the occurrence of pump thrombosis confirmed to be higher in patients HVAD population. Preemptive replacement of the HVAD by HM3 has shown to reduce survival compared with continued HVAD support [20], resulting in the current recommendation to strict follow-up these patients and to optimize their clinical management. Blood pressure control, INR stabilization with an increased INR point-of-care testing, more regular ambulatory follow-up with periodical interrogation of log-files, echo-guided rump tests, have been all demonstrated to improve survival, reduce stroke, and early detect subclinical thrombosis [21–27]. A recent ISHLT consensus [28] on the management of patients still supported by HVAD better summarized all these key-points, highlighting how a successful long-term management of HVAD patients depends on comprehensive care by a multidisciplinary team. Based on our findings, reporting lower survival, higher stroke, and higher pump thrombosis in HVAD patients, as early as after the first year of follow up, we stigmatize the importance of all the above-mentioned recommendations for the care of these patients. Furthermore, a recently approved new Italian allocation system for heart transplants allows a yearly 1 month "grace-period" (i.e., upgrade to urgency status LVAD-patients with at least 18 months of follow-up who do not reach the standard criteria for urgency/emergency). We therefore suggest that patients on HVAD fulfilling "grace period criteria," especially if at low- or intermediate-risk for heart transplant, should be deeply considered for the transplant.

Limitations

The main limitation of the study stems for its non-randomized nature. However, the strength of the study is that confirms over 5 years of follow up findings already reported over shorter time frames. MIRAMACS is the first Italian nation-level observational multicentre registry, gathering all-comer adult patients undergoing third generation CF-LVAD. Therefore, it reports "real-world" data from a wide interinstitutional experience. Though it confirms the worse-life expectation of HVAD patients, it also highlights the good 5 years outcome of HM3 device outside from MOMENTUM-3 data [3].

Another limitation relates to the difference in mean follow-up time between HVAD and HM3, though this unavoidable bias stems from the different marketing time of the two devices. However, Cox regression analysis and PSM analysis were performed to account for possible confounders.

Finally, this study reports a national trend in LVAD policy and management, and unaddressed bias might limit its reproducibility in countries with other allocation systems and policies.

DATA AVAILABILITY STATEMENT

The dataset will be available on request. Requests to access the datasets should be directed to the last corresponding author.

ETHICS STATEMENT

The studies involving humans were approved by "Area Vasta Emilia Centro della Regione Emilia-Romagna" Ethical Committee, "Azienda Ospedaliero—Universitaria di Bologna, Policlinico S. Orsola-Malpighi" (n° 990/2020/Oss/AOUBo; date of approval: 19/11/2020). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization, FO, AF, and AL; Methodology, FO and AF; Software, AF; Validation, FO, AF, AL, AT, AI, MD, TN, MB, MC, MR, IV, FM, MA, GL, and DP; Investigation AF, MC, TN, MM,

and AT; Formal Analysis, AF and FO; In re-sources, FO, AF, AL, AT, AI, TN, MC, MR, IV, FM, and MM; Data curation, AF; Writing—original draft preparation, AF; Writing—review and editing, FO, AF, and AL; Visualization, FO, AF, AL, MD, AT, AI, TN, MC, MB, MR, VI, FM, GL, MR, and DP; Supervision, FO, GL, DP, FM, MR, and AL. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

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

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The study was accepted for presentation at ESOT Congress, Athens, 2023.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2023.11675/full#supplementary-material

Supplementary Figure S1 | Overall population freedom from haemorrhagic stroke **(A)** and from pump thrombosis **(B)**: HVAD patients had a significantly lower freedom from haemorrhagic stroke and from pump thrombosis.

Supplementary Figure S2 | Overall populations freedom from **(A)** ischaemic stroke, **(B)** gastrointestinal bleeding, **(C)** driveline infection, **(D)** right ventricular failure: HVAD showed lower freedom from ischaemic stroke and from gastrointestinal bleeding compared to HM3 patients. No differences were found in freedom from driveline infection and right ventricular failure.

Supplementary Figure S3 | PS-matched population: DT 5 years survival **(A)** and freedom from haemorrhagic stroke **(B)**: HVAD patients had a significantly lower survival and freedom from haemorrhagic stroke at 5 years compared to HM3 patients.

Supplementary Figure S4 | PS-matched population: DT 5 years and freedom from pump thrombosis **(B)**: no statistically significant differences were found in freedom from pump thrombosis between HM3 and HVAD cohorts.

Supplementary Figure S5 | PS-matched populations: DT freedom from **(A)** ischaemic stroke, **(B)** gastrointestinal bleeding, **(C)** driveline infection, **(D)** right ventricular failure: no statistically significant differences at 5 years were found between HVAD and HM3 cohorts.

Supplementary Figure S6 | PS-matched population: BTT 5 years survival **(A)** and time to heart transplant **(B)**: HM3 and HVAD patients had comparable survival, but time to transplant was lower for HVAD patients.

Supplementary Figure S7 | PS-matched population: BTT freedom from haemorrhagic stroke **(A)** and from pump thrombosis **(B)**: HVAD patients had a significantly lower freedom from pump thrombosis, but not from haemorrhagic stroke.

Supplementary Figure S8 | PS-matched populations: BTT freedom from **(A)** ischaemic stroke, **(B)** gastrointestinal bleeding, **(C)** driveline infection, **(D)** right ventricular failure: no statistically significant differences at 5 years were found between HVAD and HM3 cohorts.

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BRIEF RESEARCH REPORT
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Impact of Hepatitis E Virus Screening in the UK Deceased Organ Donor Population

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Universal Hepatitis E Virus (HEV) screening of deceased organ donors was implemented by the UK national organ procurement organisation in October 2017. Donor testing for HEV infection is done post-transplant; detection of HEV ribonucleic acid (RNA) in donor plasma is therefore not a contra-indication for organ donation, with the result being used to inform recipient management. Immediate post-transplant detection of donor HEV viraemia triggers notification to transplant centres. Follow up of liver and kidney recipients has shown that transmission through solid organs is very efficient, particularly through liver grafts, as expected; no other organ types were transplanted in this cohort. Although donors with higher plasma viral load (VL > 10^3 IU/mL) were invariably associated with recipient infection, transmission was also documented at lower VL levels. Knowledge of donor HEV status has led to identification of transmission of infection via solid organ grafts followed by close patient monitoring and informed clinical management decisions. The purpose of this strategy is to allow early detection of infection and recurrence and treatment to circumvent the risk of accelerated liver damage from chronic HEV infection due to undiagnosed, inadvertent donor-derived transmission of infection.

Keywords: donor screening, hepatitis E virus, donor-derived infection, transplant-related infection, donor-derived transmission

TOP 5% CONGRESS ABSTRACT

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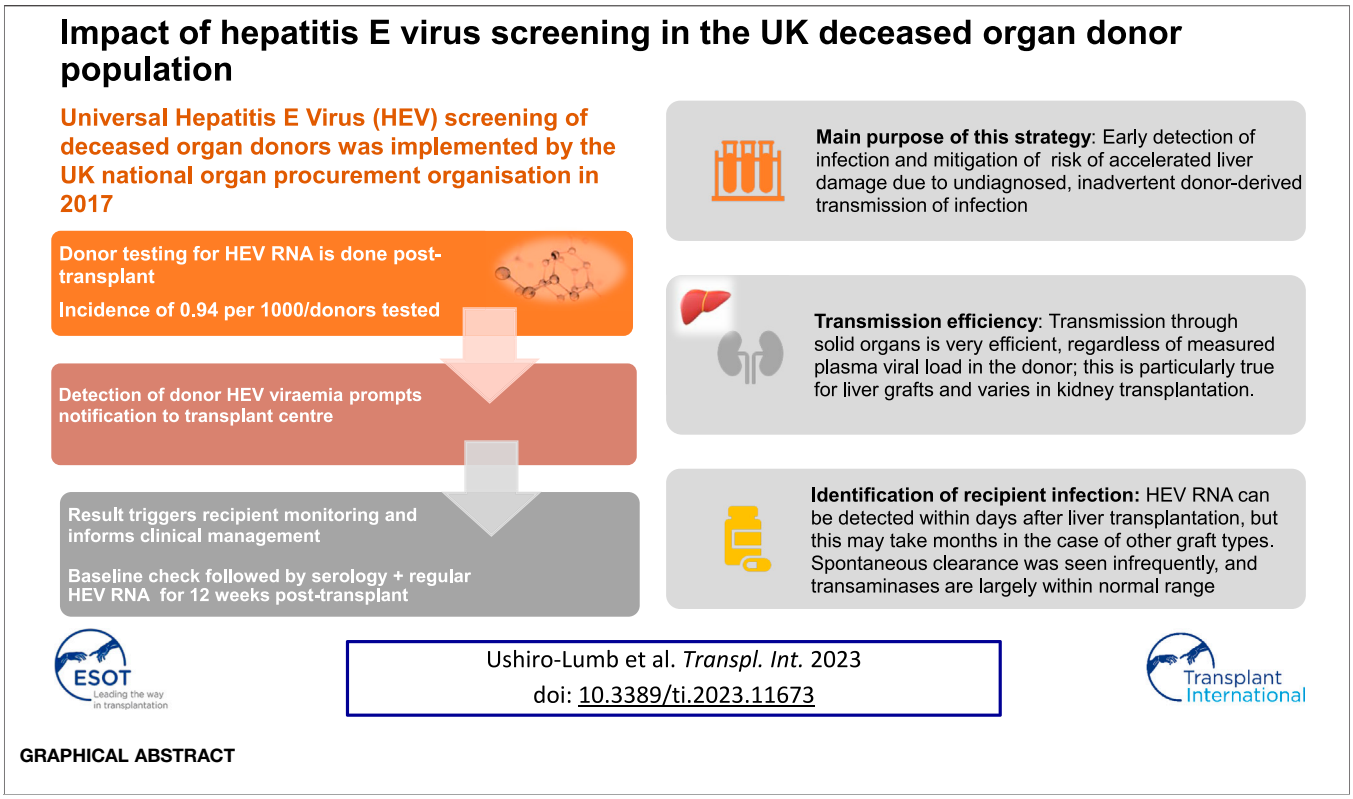
INTRODUCTION

Hepatitis E virus (HEV) is a very common cause of acute hepatitis worldwide [1]; the epidemiology, distribution and natural history of infection differs according to the viral genotypes 1–4. Infection is asymptomatic or mild and self-limiting in most people. However, individuals with a significantly impaired immune system are at higher risk of complications, including establishment of chronic infection and accelerated progression to cirrhosis, typically caused by genotype 3 viruses. Immunocompromised individuals are at much higher risk of acquiring HEV infection from diet than from transfusion of blood components and organ transplantation, hence advice and education on control of dietary exposure remains essential. In 2016, following guidance from the UK Standard Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), universal screening of blood donors for hepatitis E was introduced; the UK was the first country in the world to adopt this



GRAPHICAL ABSTRACT

strategy and the screening of organ donors commenced in October 2017 [2]. Following the principle of a balanced approach to improve outcomes for organ transplant recipients, screening is performed post-donation.

PATIENTS AND METHODS

All potential deceased organ donors undergo mandatory infection screening at the time of donor characterisation are tested post-donation for HEV Ribonucleic Acid (RNA). This testing is done in a single reference laboratory where plasma samples are tested individually by a transcription mediated assay (TMA) according to manufacturer's instructions (Procleix HEV assay, Grifols diagnostic solutions inc.; 95% lower limit of detection 7.89 IU/mL). Reactive samples are re-tested in an alternative molecular assay (ampliCube HEV 2.0 Quant, Mikrogen diagnostic, 95% lower limit of detection 36.13 IU/mL) and where possible, the viral load is quantified. Serology is also applied to all reactive samples (HEV-IgG Elisa, Fortress diagnostics). Transplant centres receive the screening results within an average of 5 days from the date of transplant; in addition, centres are promptly contacted in the event of positive donor results and advised to commence recipient testing, with hepatology referral. Pre-transplant recipient serum is retrospectively tested for HEV IgG to document baseline serostatus. Follow up plasma samples are taken on communication of the donor's result, and thereafter at regular intervals when the patient is reviewed in clinic for no less than 12 weeks. These are tested for HEV RNA and IgG and the HEV infection status of each recipient is recorded centrally.

Ethical Approval

NHSBT is reliant on the General Data Protection Regulation Article 6(1)(e)—Performance of a public task. Under Article 9(2)(h), (i), and (j), NHSBT is allowed to use patient identifiable information for service evaluation and safety monitoring without the consent of patients.

RESULTS

9,500 deceased potential organ donors were screened between October 2017 and October 2022, with nine confirmed viraemic cases identified; this incidence of 0.94 per 1,000 is approximately four times higher than that seen in our blood donor population. One potential donor who retrospectively tested positive for HEV RNA did not donate tissues or organs. The remaining eight proceeding donors, with plasma viral load (VL) ranging from 100 to 270,000 IU/mL, donated fourteen kidneys and six livers to twenty recipients (**Table 1**). All liver recipients had demonstrable HEV RNA in plasma, detected at various time points post-transplantation. which was commenced at different time points after diagnosis of HEV infection. Time of commencement, duration of treatment, ribavirin dose and dose adjustments, as well as changes in immunosuppression were determined by the teams caring for individual patients.

TABLE 1 | Donor and recipient demographics, with outcomes of donation from HEV viraemic deceased organ donors.

Donor characteristics						Recipient characteristcs							
Donor	**Age (years)**	**Gender**	**Cause of death**	**Donor type**	**HEV plasma load (IU/mL)**	**Recipient**	**Gender**	**Age (years)**	**Organ type**	**Pre-transplant HEV IgG**	**Transplant-related HEV infection**	**Post-transplant HEV RNA detection (days)[a]**	**Post ribavirin SVR**
1	60	M	ICH	DCD	100	1A	F	64	Liver	Negative	Yes	11	Yes
						1B	M	62	R Kidney	Negative	Yes	74	Spontaneous clearance
						1C	M	61	L Kidney	Negative	Yes	42–106	Yes
2	44	M	ICH	DBD	3,653	2A	M	60	Liver	Negative	Transient positivity	9	n/a
						2B	M	35	R Kidney	Negative	Yes	54	Yes
						2C	M	62	L Kidney	Negative	Yes	70	Yes
3	36	M	HBD	DBD	435	3A	M	53	Liver	Negative	Yes	<10[b]	Yes
						3B	F	25	R Kidney	Negative	No	—	n/a
						3C	F	32	L Kidney	Negative	Yes	84	on ribavirin
4	60	M	HBD	DBD	287,000	4A	M	64	Liver	Negative	Yes	<10	Yes
5	57	M	HBD	DBD	98,300	5A	M	58	Liver	Negative	Yes	7	Yes
						5B	M	68	R Kidney	Positive	Yes	13–80	Yes
						5C	M	36	L Kidney	Negative	Yes	115[c]	Yes
6	58	M	HBD	DCD	436	6A	M	37	R Kidney	Negative	No	—	n/a
						6B	F	61	L Kidney	Negative	No	—	n/a
7	58	M	ICH	DBD	3,340	7A	F	38	R Kidney	Negative	Yes	<18	Yes
						7B	M	62	L Kidney	Negative	Yes	<12	RIP
8	36	M	ICH	DBD	111	8A	M	38	Liver	Positive	Probable	<10	on ribavirin
						8B	F	39	R Kidney	Negative	No	—	n/a
						8C	F	44	L Kidney	Negative	No	—	n/a

ICH, intracerebral haemorrhage; HBD, hypoxic brain damage; DCD, donation after circulatory death; DBD, donation after brain death; SVR, sustained virological response.
[a]Time when first positive result available; does not indicate precise start of detectable viraemia in most cases. Date of last negative to first positive interval is given in some cases as first measured, viral load indicates viraemia would have been detectable between those dates.
[b]< Viral load indicates viraemia would have been detectable before that date.
[c]Ribavirin from day 5 to 35; regular surveillance revealed late viraemia.

Time to achieve initial negative viral RNA measurement, followed by sustained virological response (SVR, i.e., negative viral RNA in plasma and stool beyond 6 months from completion of antiviral treatment) ranged significantly, from 4 weeks up to 24 months. Rapid viral clearance (undetectable viral RNA by the locally applied standard of care methodology), with a first negative result in plasma was observed in two liver recipients who were commenced on ribavirin immediately upon detection of viraemia. Significant intolerance to ribavirin was noted in three recipients, and prolonged treatment course was required in one liver recipient who suffered from side effects requiring interruption of the drug, with virus rebound on three occasions. A snapshot of recipient outcome is shown in **Figures 1**, **2**. Detailed recipient characteristics, their management and outcomes, as well as molecular analysis of the infecting strains, are the subject of a separate piece of work involving all the various teams and will be described elsewhere.

DISCUSSION

Yield From Universal HEV RNA Screening

The introduction of universal screening was considered in the context of the relevant UK epidemiology for this zoonotic infection and its clinical impact on immunocompromised patients. The incidence of asymptomatic acute HEV infection observed in the UK blood donor population was around 1 in 2,850 donors when a large study was conducted in 2012/13 [3] with no significant changes in the immediate subsequent years and a decline from 2017, mirroring the epidemiology in the UK general population [4]. A gradual drop in incidence has been observed over more recent years, with 1 in 4,347 being the approximate figure for blood donors in 2021 [5]. Interestingly, the yield from deceased organ donor screening has been showing a different pattern, with one case of acute HEV being identified per 536, 1,682 and 1,797 donors tested in 2020, 2021, and 2022, respectively. The reason for this is not entirely clear, and not only do we continue to detect HEV viraemia in deceased donors, but we have also seen an increase in incidence during the COVID-19 pandemic. The demographics of acutely infected donors reflects the epidemiology of the general UK population, with more cases seen in men in the >50 year old age group [4]. The numbers tested are low, on average 1,600 to 1,800 potential donors per year, hence the number of identified infected donors is small, but significant; the screening strategy introduced in the UK in late 2017 has led to the identification of 20 recipients who have

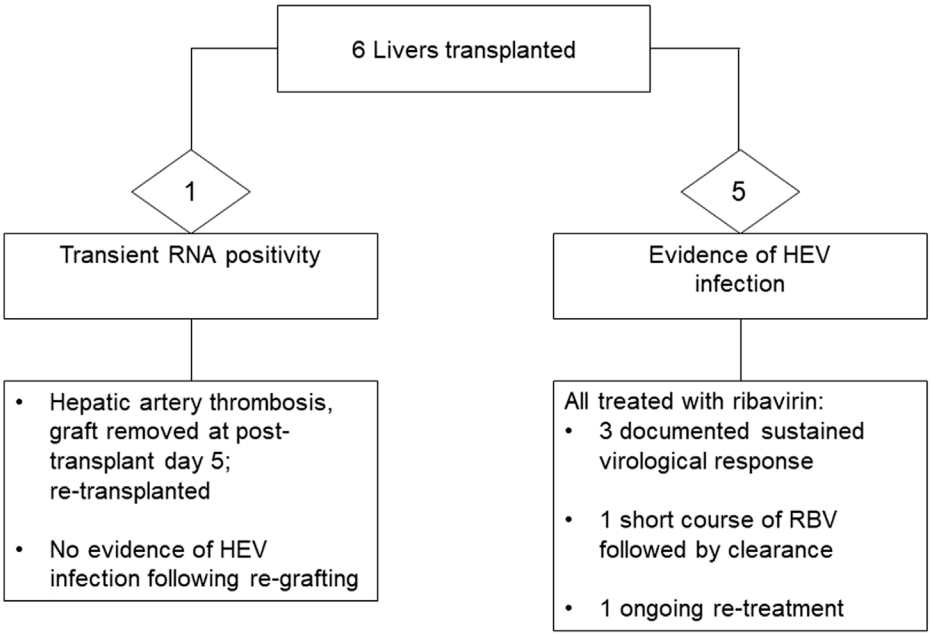


FIGURE 1 | Outcome of liver donation from donors with confirmed HEV viraemia.

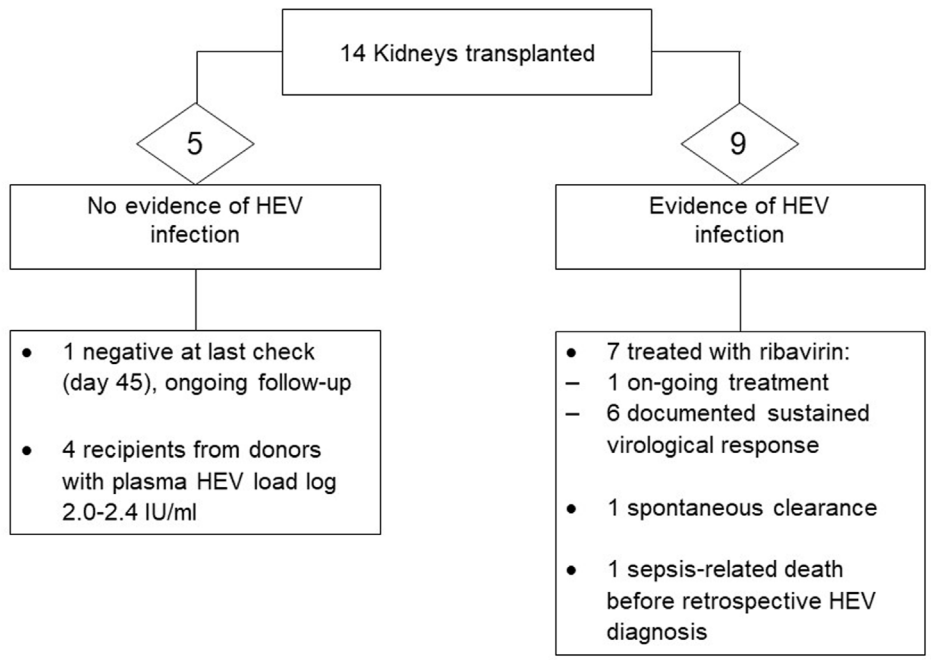


FIGURE 2 | Outcome of kidney donation from donors with confirmed HEV viraemia.

benefited from monitoring and tailored intervention to avoid ultimate liver damage due to late diagnosis. The approach hereby described ensured no transplant-related chronic infections were missed in the organ recipients since donor screening was initiated. Many more infections acquired through consumption of contaminated food are likely to be missed, so information and awareness amongst patients and healthcare professionals remains important.

Thresholds of Transmission and Course of Infection in Recipients

Donor-derived HEV infection has been infrequently described, with scarce publications available in the literature [6–8]. Without organ donor screening and post-transplant recipient surveillance for HEV RNA positivity, there is a real possibility of under recognition of infection of donor origin; diagnosis of chronic HEV infection many months or years after transplantation does not necessarily trigger look back investigations. It is acknowledged however, that apart from further contribution from transfusion-associated infections, the dietary route remains the main route of acquisition of zoonotic HEV genotypes. In the setting of significant immunocompromise, absence of significant inflammatory responses with normal or mildly abnormal liver enzymes may not trigger testing, particularly in the early post-transplant period. Familiarity with local epidemiology and need to include HEV in testing panels, where appropriate, can address some of the issues with under ascertainment and late diagnosis.

There is no definition of infectious dose in the context of an infected organ being used for transplantation, and presence of viable virus within the graft is theoretically sufficient to pose a transmission risk; no data exist to suggest thresholds of transmission based on measured plasma viral load in the donor and indeed, low plasma loads in our donor cohort were associated with transmission through not only liver, as would be expected, but also kidneys (**Table 1**). Risk of transmission is of course multifactorial, but some observations from this cohort are worthy of mention. As viable virus will be present in the liver, viral load in plasma during early acute and early resolving infection in the donor cannot be used to stratify risk of transmission through this organ; as seen in our cases, low level VL in the order of 10^2 IU/mL resulted in transmission through the liver but not through kidneys from the same donor. Transmission via an infected liver graft with undetectable viral RNA in plasma has been described [6]. Determinants of transmission and control of infection have not been defined but both viral and host factors are expected to play a role; this includes the net immune status of recipients as regards to control of viral infections. Previously described recipient characteristics that are linked to progression to HEV chronicity include lower lymphocyte count and exposure to tacrolimus [9]; detailed variables are also being collated for this cohort.

Where local epidemiology, risk-benefit and cost analysis justify testing of donors and/or recipients, it is important to note that recipient follow up needs to be extended and should not be shorter than 12 weeks, as late RNA detection in non-liver recipients does occur. Conversely, in liver recipients, with the graft being the main site of virus replication, viremia becomes detectable within days from transplant.

Understanding the Course of Infection Acquired via the Transplanted Graft

Guidance on the management of HEV in solid organ transplantation [1, 10], advise to monitor for 3 months from the point of diagnosis, unless otherwise clinically indicated, allowing time to assess the infection status and possible control without anti-viral treatment. Previous studies have indicated that approximately 33% of acutely infected solid organ transplant recipients clear HEV infection spontaneously within this time frame, with the remaining progressing to chronicity [9, 11]. Of note, subjects in the studied cohort had had their transplants years before acquiring HEV infection, a scenario that differs from when infection is acquired at the time of transplant, as the net state of immunosuppression and other parameters may differ between these time points. Whether a similar proportion of solid organ transplant patients undergoing acute donor-derived infection would have the same outcome, is unknown. In the UK cohort, only one out of the 15 individuals who tested positive for HEV RNA in plasma went on to become negative within 3 months from diagnosis of acute hepatitis. None of the patients who were either monitored beyond 3 months from the date of first positive result or who had a delayed diagnosis of HEV infection made beyond the first 3 months from transplantation, managed to control the infection and went on to receive ribavirin. This suggests that in the setting of donor-derived infection, and in contrast to infection acquired later in the post-transplant period, earlier treatment may be an approach that deserves consideration; further accrual of data from more cases may help clarifying this. Logically, this gap in knowledge and practice stems from the fact that risk of exposure through the transplanted graft can only be considered where donor screening is in place; given the variable incidence of HEV genotype 3 infection, this is a practice limited to certain regions where the epidemiology justifies such an approach. This puts countries where screening takes place, in an obligatory position to monitor the impact of the chosen strategy, follow up outcomes and use the data to inform policy and guidance.

CONCLUSION

The first 5 years of universal HEV RNA screening of deceased organ donors in the UK has revealed that just under 1 in every 1,000 potential donors have confirmed HEV RNA detected in plasma due to early acute HEV infection. Donor testing and recipient follow up beyond 12 weeks has led to identification of twenty transplant recipients who were at risk of infection from the organs they had received. The majority of recipients became infected and inability to clear the virus within 3 months from diagnosis of infection was the predominant trend, except when there was intervention at an earlier point. Identification of potential exposure to the virus allowed monitoring, diagnosis and treatment, which led to control of infection in those who have completed follow up. The route and point of exposure to the virus, together with the infection dynamics in donor and recipients are known; analysis of available parameters is underway, and this will help informing the course of infection acquired via solid organ grafts, leading to a clearer understanding on how best to manage donor-derived infection in solid organ transplant recipients.

Since its inception, donor screening and recipient surveillance has ensured no donor-derived infections were missed and has

allowed treatment of infections that had or would likely have evolved to chronicity. In the current UK setting, the observed yield of this screening strategy and positive impact on the outcome of organ transplant recipients indicate that the program is justified.

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

NHSBT is reliant on the General Data Protection Regulation Article 6 (1) (e)—Performance of a public task. Under Article 9 (2) (h), (i), and (j), NHSBT is allowed to use patient identifiable information for service evaluation and safety monitoring without the consent of patients.

AUTHOR CONTRIBUTIONS

IU-L lead the planning and writing of the manuscript. IU-L, CG, VM, BH, SI were involved in data generation or data acquisition. IU-L, DM, JF, DT critically reviewed the manuscript. All authors read, commented and approved the work before submission.

CONFLICT OF INTEREST

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

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ORIGINAL RESEARCH
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The Effect of Continuous Liver Normothermic Machine Perfusion on the Severity of Histological Bile Duct Injury

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Static Cold Storage (SCS) injures the bile duct, while the effect of Normothermic Machine Perfusion (NMP) is unknown. In a sub-study of the COPE trial on liver NMP, we investigated the impact of preservation type on histological bile duct injury score (BDIS). Transplants with at least one bile duct biopsy, either at end of preservation or 1 h post-reperfusion, were considered. BDIS was determined by assessing peribiliary glands injury, stromal and mural loss, haemorrhage, and thrombosis. A bivariate linear model compared BDIS (estimate, CI) between groups. Sixty-five transplants and 85 biopsies were analysed. Twenty-three grafts were preserved with SCS and 42 with NMP, with comparable baseline characteristics except for a shorter cold ischemic time in NMP. The BDIS increased over time regardless of preservation type ($p = 0.04$). The BDIS estimate was higher in NMP [8.02 (7.40–8.65)] than in SCS [5.39 (4.52–6.26), $p < 0.0001$] regardless of time. One patient in each group developed ischemic cholangiopathy, with a BDIS of 6 for the NMP-preserved liver. In six other NMP grafts, BDIS ranged 7–12 without development of ischemic cholangiopathy. In conclusion, BDIS increases over time, and the higher BDIS in NMP did not increase ischemic cholangiopathy. Thus, BDIS may overestimate this risk after liver NMP.

Keywords: liver transplantation, normothermic machine perfusion, ischemic cholangiopathy, bile duct injury, liver viability assessment

TOP 5% CONGRESS ABSTRACT

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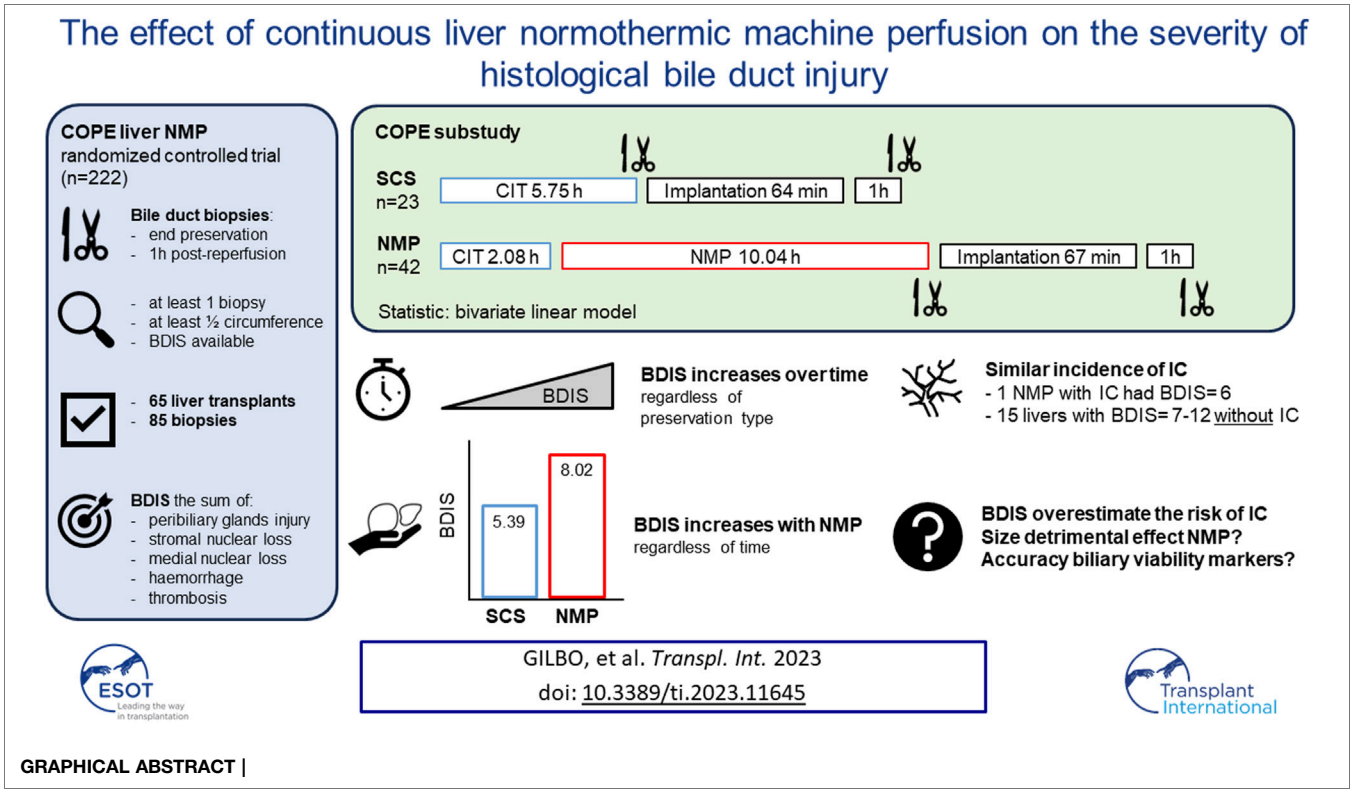
Abbreviations: BDIS, bile duct injury score; DBD, donation after brain death; DCD, donation after circulatory death; IC, ischemic cholangiopathy; NMP, normothermic machine perfusion; SCS, static cold storage.



GRAPHICAL ABSTRACT |

INTRODUCTION

Biliary complications are a significant cause of morbidity after liver transplantation, particularly in the form of non-anastomotic strictures of the biliary tree, also referred to as ischemic cholangiopathy (IC) [1].

The pathogenesis of IC involves ischemic-reperfusion injury, immune-mediated damage, cytotoxic insults, and defective biliary regeneration [1]. Additionally, livers procured from donation after circulatory death (DCD) donors [2] are more prone to developing IC than those procured from donation after brain death (DBD) donors, due to the additional hit of warm ischemic injury during the donation process [1]. Static cold storage (SCS) is inadequate in maintaining the integrity of the biliary epithelium, leading to epithelial loss at the end of SCS in up to 86% of livers [3]. After reperfusion, this injury progresses, affecting the peribiliary vascular space [4] and damaging the stem cell niche of the peribiliary glands [5]. Histological injuries such as epithelial loss, mural stroma necrosis, intramural haemorrhage, peribiliary vascular injury, thrombosis, and loss of peribiliary glands, have been identified as predictors of IC [5]. This formed the basis for the histological bile duct injury score (BDIS) [4–6], which has been used to stratify the risk of IC.

To address the need for improved preservation and reduce complications after transplantation of high-risk livers [7], alternative preservation methods, like continuous liver normothermic machine perfusion (NMP), have gained interest. Liver NMP involves the *ex situ* perfusion of the graft with an oxygenated, nutrient-enriched, erythrocytes-based perfusate kept at 37°C [8]. Two randomized controlled trials demonstrated that continuous NMP reduces ischemic-reperfusion injury (as measured by post-transplant transaminase release) of low to intermediate-risk livers [9, 10]. Although in a porcine DCD model continuous NMP has shown promising results in preserving the histology and promoting biliary regeneration [11], the results from currently available randomized controlled trials are inconclusive on the prevention of IC after transplantation. The consortium for organ preservation in Europe (COPE) trial on liver NMP did not find any difference in the incidence of IC between NMP and SCS, but it was not powered for this research question [9]. In contrast, Markmann et al. showed a significant reduction in the incidence of ischemic biliary complications, which were however defined as biliary strictures or leakage [10]. Furthermore, in early clinical series on end-ischemic NMP [12, 13] up to 30% of liver grafts transplanted after NMP viability assessment based on perfusate biochemistry [14] developed IC, suggesting that NMP does not prevent biliary injury. This prompted the definition of criteria to select livers at low risk of developing IC based on biliary biomarkers, which were identified utilizing BDIS as a surrogate endpoint for IC [6]. Although these criteria are increasingly being used in clinical practice, the impact of liver NMP on the severity of histological bile duct injury or its correlation with the development of IC remains unknown. Therefore, this study aims to investigate the influence of preservation methods on biliary injury severity, specifically

utilizing the histological BDIS in a subset of liver transplants included in the COPE trial comparing liver NMP to SCS [9].

PATIENTS AND METHODS

Study Design

Figure 1 provides a visual representation of the design of this substudy of the COPE trial. The COPE multicentre randomized trial run between June 2014 and March 2016, and considered whole livers from DBD and DCD donors aged ≥16 years. Livers were randomized 1:1 to be preserved using SCS or liver NMP started at the donor's site with the OrganOx Metra device (OrganOx Ltd., Oxford, United Kingdom). Eligible recipients were at least 18 years old and listed for a solitary liver transplant, excluding those with fulminant liver failure. Participants were consented while on the waiting list, with the consent including the recording of anonymized data on donor, recipient, transplant, and perfusion characteristics, as well as the collection of biological samples for biobanking. Transplant centres from the United Kingdom (Addenbrooke's Hospital, Cambridge; King's College Hospital, London; Queen Elizabeth Hospital, Birmingham; and Royal Free Hospital, London) and Belgium (University Hospitals of Leuven, Leuven) collected samples of the extrahepatic bile duct, stored in a central biobank. Bile duct biopsies were obtained at the end of liver preservation and after 1 hour of reperfusion in the recipient. Only liver transplants with at least one biopsy consisting of at least half circumference of the bile duct were considered. The study aimed to investigate the impact of preservation (SCS or NMP) on BDIS and explore interactions with donor types. Additionally, donor, recipient, and transplant characteristics influencing BDIS severity were explored. Ischemic cholangiopathy was defined as the unequivocable evidence of extra-anastomotic biliary strictures with a patent hepatic artery observed at a protocol magnetic resonance cholangiopancreatography at the 6-month post-transplantation [9]. Histological sections were assessed by experienced liver pathologists, and BDIS scores were compared between preservation groups. The substudy was approved by the Research Ethics Committee London-Dulwich, United Kingdom (ref: 14/LO/0182).

Normothermic Machine Perfusion

The OrganOx Metra device was used for automated NMP. NMP continued until the transplant team was ready to implant the liver, with a minimum duration of 4 h and a maximum of 24 h. Details on device, perfusate composition, and perfusion settings were already reported by Nasralla et al. [9].

Histopathology

Two experienced liver transplant pathologists (DN and RB) assessed whole slide images of formalin fixed and paraffin embedded extrahepatic bile duct biopsies. Images were scanned at ×20 magnification on a 3DHistech scanner at 0.276 µm/pixel. Assessment focused on the completeness of bile duct section (circumferential, more than half circumference, half circumference, less than half circumference, fragment only, no bile duct tissue). To minimise sampling error, only bile ducts that included at least 50% of the circumference were included, as changes vary around the circumference of the bile duct. The pathologists evaluated the slides in a blinded manner, using a modified version of the Hansen [4]—op den Dries [5] score. The scoring focused on grading injury to deep peribiliary glands (0, normal; 1, mild injury; 2, moderate injury; 3, severe injury), stromal nuclear loss (0, normal; 2, focal loss <10%; 2 moderate loss 10%–50%; 3, extensive loss >50%), loss of nuclei in the media of arteries/arterioles (0, normal; 1, focal—occasional arteries/arterioles; 2, moderate—more than occasional arteries/arterioles; 3, extensive), the extent of haemorrhage (0, none; 1, few scattered RBCs; 2, <25%; 3, 25%–50%; 4, >50%) and presence of thrombi (Y/N). The scoring excluded assessment of the epithelial lining and superficial peribiliary glands, which were not associated with IC in previous case series [5]. The pathologists underwent calibration and agreement on definitions and cut-offs before assessing the study samples. The BDIS was calculated as sum of the scores for each histological feature [6]. Only complete cases, where all features could be graded, were considered for BDIS calculation.

Statistical Analyses

Categorical data are presented as number (percentage), while continuous variables are reported as median (IQR). Fisher exact test and Mann-Whitney U tests were used for comparing categorical and continuous characteristics, transplant data, and outcomes between the SCS and NMP groups, respectively. Kaplan-Meier estimates and log-rank tests were used to assess overall and graft survival, with cumulative incidence curves used to visualize graft loss (considering patient death without preceding graft loss as a competing event). Between-group comparisons utilized Gray's test.

To compare BDIS between SCS and NMP, a bivariate linear model was employed, considering preservation (SCS, NMP) and donor type (DBD, DCD) as fixed factors and centre as a random factor. This model accounted for missing biopsy values and utilized an unstructured 2 × 2 covariance matrix for BDIS scores at the two timepoints. This model returned BDIS estimate (i.e., mean from a multivariate regression model for longitudinal measures) with a 95% confidence interval. The model was also used to examine changes in BDIS over time and to assess the interaction between preservation type and time. Subgroup analyses for DBD and DCD patients and exploration of the interaction between donor type and preservation type were performed. A *post hoc* sensitivity analysis included only liver transplants with increasing BDIS over time.

To evaluate the relationship between donor, recipient, and transplant characteristics with BDIS, bivariate linear models were used for each variable, allowing for differences in the linear relationship between the two timepoints. Regression coefficients were reported for each timepoint and averaged. No corrections for multiple testing were applied; therefore, these *p*-values should be interpreted as exploratory. Variables significantly associated with BDIS in the latter analyses were combined in a multivariable model. SAS software, version 9.4, was used for all analyses.

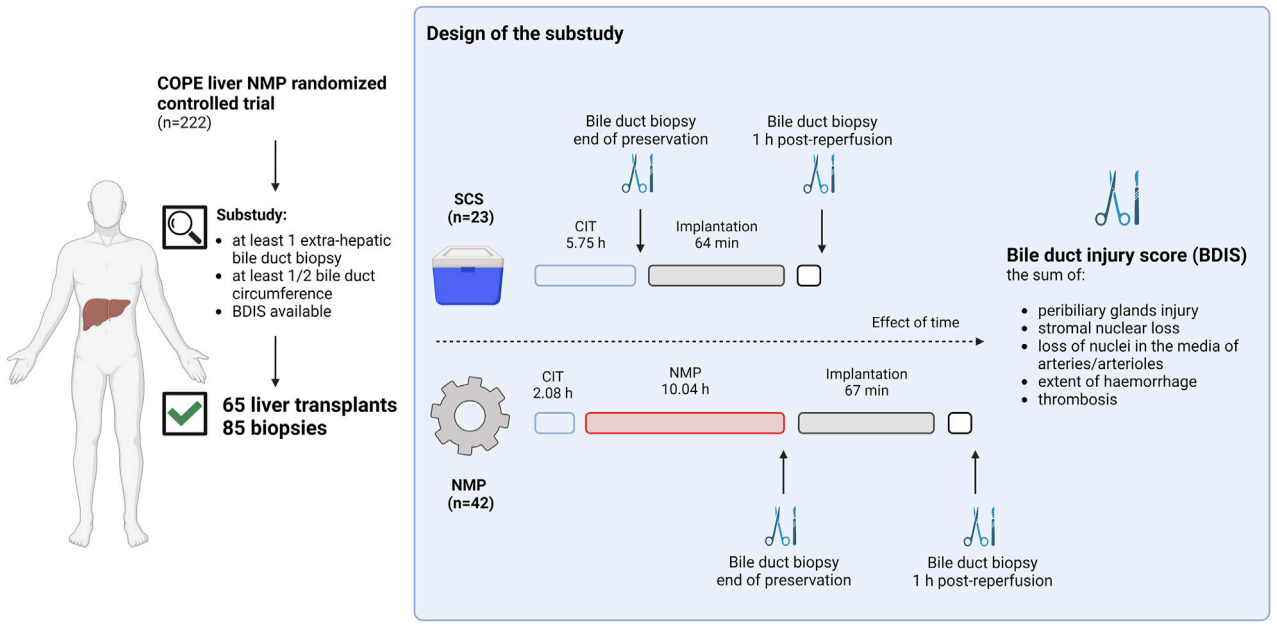


FIGURE 1 | Schematic representation of the study design. Liver transplants included in the consortium for organ preservation in Europe (COPE) randomized controlled study on liver normothermic machine perfusion (NMP) with at least one biopsy of the extrahepatic bile duct consisting of at least ½ duct circumference were included in the substudy. Bile duct biopsies were collected at the end of preservation or 1 hour after reperfusion in the recipient. In liver preserved with static cold storage (SCS) biopsies at the end of preservation were taken after a median of 5.75 h from organ flush in the donor, whilst in liver preserved with NMP these were taken after a median of 12.12 h from organ flush. Two experienced pathologists blinded for group allocation scored H&E stained slides to grade the bile duct injury score (BDIS) as the sum of peribiliary glands injury, stromal nuclear loss, loss of nuclei in the media of arteries and/or arterioles, extent of haemorrhage, and thrombosis. Only complete cases where all features could be scored were considered for the final analysis. The BDIS was compared between group. Additionally, the effect of time, donor type, and other donor, recipient, transplant, and perfusion characteristics on the BDIS were also explored. Created with Biorender.com.

RESULTS

Study Population

The COPE trial included 222 liver transplants. Bile duct biopsies were unavailable for 134 transplants, and an additional 21 were excluded because the biopsies consisted of <50% of bile duct circumference. Finally, four biopsies belonging to two subjects were excluded because some feature of the BDIS could not be scored due to artifacts (**Figure 2**). In total, 65 transplants were included in this study and 85 bile duct biopsies were evaluated. Of these, 42 livers (56 biopsies) were preserved using continuous NMP, and 23 livers (29 biopsies) were preserved using SCS. In the NMP group 30/42 (71.43%) livers were procured from DBD donors and 12/42 (28.57%) from DCD donors, whilst in the SCS group 14/23 (60.87%) livers were procured from DBD donors and 9/23 (39.13%) from DCD donors (p = 0.38).

The included subjects were well matched in terms of donor, recipient, and transplant characteristics. However, there were significant differences in the cause of death and the highest concentration of sodium in the donor, and in cold ischemic time [NMP: 2.17 (1.83–2.33) hours, SCS: 5.75 (5.08–7.) hours; p < 0.001] (**Table 1**). In DCD livers, donor warm ischemic time was 23.50 (21.00–28.50) minutes in the NMP group and 24 (23–27) minutes in the SCS group (p = 0.89). The most frequent indication for transplantation was alcoholic liver cirrhosis in both groups, and recipients were transplanted with a median lab MELD of 13 (10–18) points in the NMP group, and 11 (9–16) points in the SCS group (p = 0.44).

In line with the findings from the COPE trial, the peak concentration of aspartate transaminase within 7 days post-transplantation was lower in the NMP group [381 (196–906) IU/dL] than in the SCS group [741 (474–2,221) IU/dL, p = 0.01; **Table 1**]. Additionally, the mean arterial pressure after reperfusion was higher in NMP [76 (64–89) mmHg, SCS: 57 (52–66) mmHg; p < 0.001] and the requirement for vasopressors infusion lower [22/42 (53.66%)] than SCS-preserved livers [18/23 (81.82%), p = 0.03], as a result of less frequent post-reperfusion syndrome [NMP: 6/42 (14.29%), SCS: 8/23 (34.78%); p = 0.055]. There was no difference in 1 year patient or graft survival (**Supplementary Figure S1**). Two patients in the COPE trial developed IC after transplantation, one in each study arm. A bile duct biopsy was available only for the NMP-preserved liver (at 1-h post-reperfusion). Therefore, the SCS-preserved liver that develop IC was excluded from this substudy.

Excluded cases had a significantly higher donor BMI, lower EuroTransplant-donor risk index, higher donor sodium, longer cold ischemic and portal vein anastomosis time, and more frequent need for vasopressor pre-reperfusion than transplants included in this substudy (**Supplementary Table S1**).

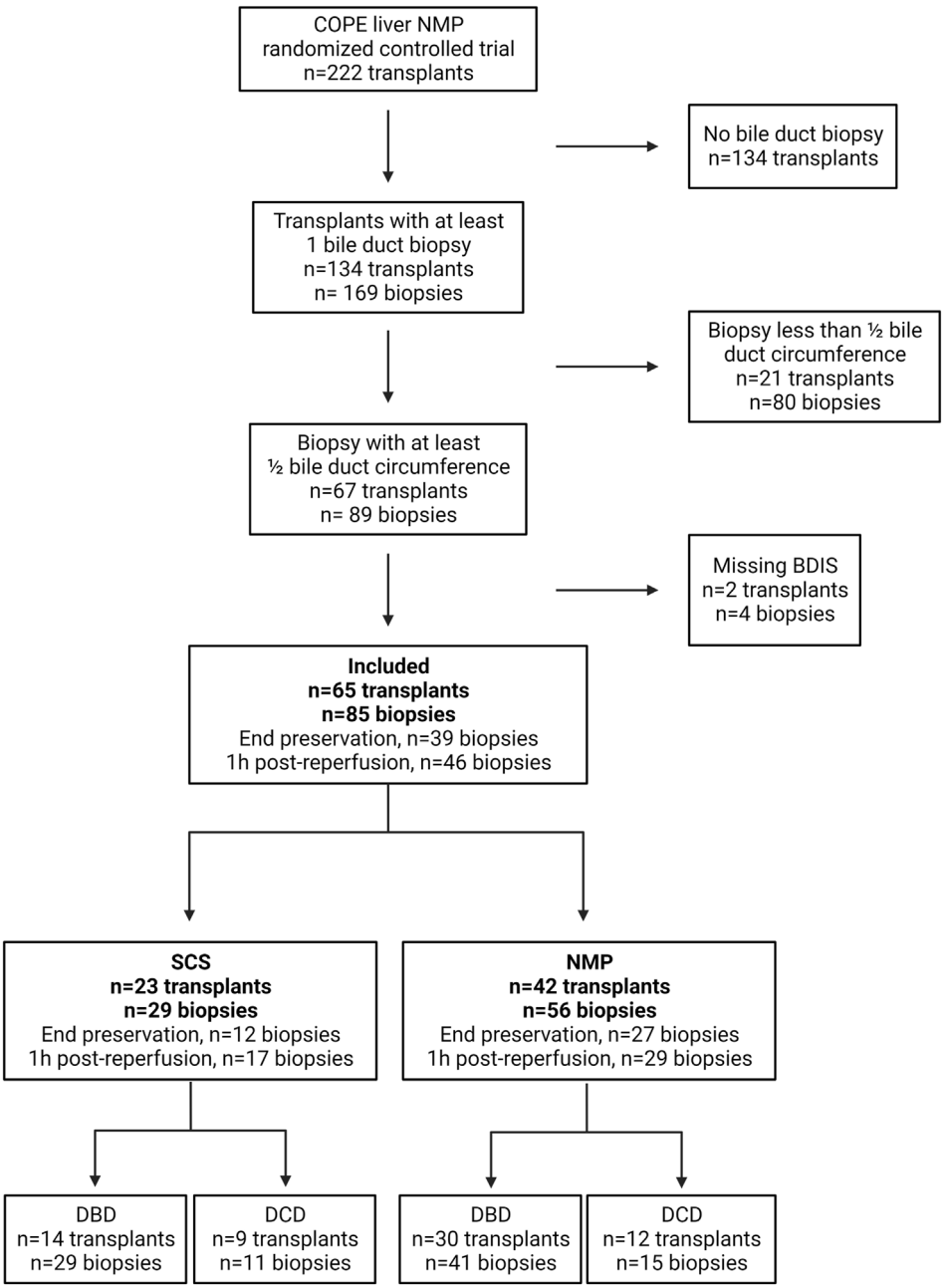


FIGURE 2 | Diagram depicting patients' inclusion in a substudy of the consortium for organ preservation in Europe (COPE) randomized controlled trial on liver normothermic machine perfusion (NMP). BDIS, bile duct injury score; DBD, donation after brain death; DCD, donation after circulatory death; SCS, static cold storage. Created with Biorender.com.

Does the Type of Liver Preservation Influence Histological Bile Duct Injury?

The severity of BDIS changed significantly over time during the transplant process, regardless of the type of preservation (p = 0.04; **Table 2**). Specifically, BDIS increased after graft reperfusion in most transplants, but in four livers (two in each group) the BDIS was found to be markedly improved after 1-h post-reperfusion compared to corresponding biopsies at the end of preservation (**Supplementary Figure S2**). Further re-evaluation of these four pairs revealed signs of sampling injuries. Notably, there was a pronounced loss of stromal nuclei and more severe injury to the deep peribiliary glands and arteries (**Supplementary Figure S3**) in biopsies at the end of preservation. This degree of stromal change is suggestive of localised clamp injury, which has artificially increased the BDIS at the end of preservation.

TABLE 1 | Donor, recipient, and transplant characteristics of the study population.

	SCS (*n* = 23)	NMP (*n* = 42)	*p*-value
Donor demographics			
Donor Type, *n* (%)			
DBD	14 (60.87%)	30 (71.43%)	0.38
DCD	9 (39.13%)	12 (28.57%)	
Total donor warm ischemia time,[a] min	24 (23–27)	23 (21–29)	0.89
Donor age, years	56 (47.56–62.78)	57 (45.30–72.81)	0.58
Donor gender, n (%)			
Male	14 (60.87%)	20 (47.62%)	0.31
Female	9 (39.13%)	22 (52.38%)	
Donor BMI, Kg/m^2	24 (–27)	25 (–27)	0.57
Donor blood group, n (%)			
A	12 (52.17%)	23 (54.76%)	0.62
AB	1 (4.35%)	1 (2.38%)	
B	3 (13.04%)	2 (4.76%)	
0	7 (30.43%)	16 (38.10%)	
Donor admitted to the ICU, *n* (%)	23 (100%)	42 (100%)	—
Length of donor ICU stay, days	2 (2–6)	2 (2–4)	0.47
Donor cause of death, *n* (%)			0.04
Others	3 (13.04%)	5 (11.90%)	
Trauma	4 (17.39%)	0 (0.00%)	
Hypoxia	3 (13.04%)	10 (23.81%)	
Cerebrovascular accident	13 (56.52%)	27 (64.29%)	
DRI, points	1.77 (1.36–2.68)	1.42 (1.17–2.66)	0.37
ET-DRI, points	2.00 (1.70–2.49)	1.76 (1.53–2.11)	0.30
History of diabetes, n (%)	1 (4.35%)	5 (11.90%)	0.31
History of smoking, n (%)	11 (47.83%)	13 (30.95%)	0.18
History of alcohol consumption, n (%)	6 (26.09%)	5 (12.20%)	0.16
History of cardiac disease, n (%)	6 (28.57%)	4 (11.43%)	0.11
Vasopressors use, n (%)	14 (63.64%)	24 (57.14%)	0.62
Dopamine, n (%)	0 (0%)	3 (12.50%)	0.17
Dobutamine, n (%)	0 (0%)	2 (8.33%)	0.27
Noradrenaline, n (%)	11 (78.57%)	18 (75.00%)	0.80
Vasopressin, n (%)	9 (64.29%)	14 (58.33%)	0.72
Highest AST, IU/L	28 (22–66)	52 (29–66)	0.37
Highest ALT, IU/L	31 (19–48)	32 (19–57)	0.99
Highest GGT, IU/L	34 (22–162)	47 (25–114)	0.55
Highest bilirubin, μmol/L	8 (4–18)	9 (5–17)	0.60
Highest sodium, mEq/L	148 (142–154)	141 (138–145)	0.01
Donor hepatectomy time, minutes	43 (30–57)	31 (24–36)	<0.001
Cold ischemic time, hours	5.75 (5.08–7.23)	2.08 (1.83–2.33)	<0.001
Duration NMP, hours	—	10.04 (6.25–12.09)	
Recipient demographics			
Transplant centre, n (%)			0.06
Cambridge	4 (17.39%)	4 (9.52%)	
King's College	1 (4.35%)	5 (11.90%)	
Birmingham	10 (43.48%)	29 (69.05%)	
Royal Free	5 (21.74%)	2 (4.76%)	
Leuven	3 (13.04%)	2 (4.76%)	
Recipient age, years	57.40 (52.51–62.44)	54.26 (43.01–62.66)	0.33
Recipient gender, n (%)			0.17
Male	18 (78.26%)	25 (59.52%)	
Female	5 (21.74%)	17 (40.48%)	
Recipient BMI, kg/m^2	25 (24–29)	26 (23–31)	0.49
Recipient blood group, n (%)			0.90
A	11 (47.83%)	21 (50.00%)	
AB	1 (4.35%)	3 (7.14%)	
B	3 (13.04%)	3 (7.14%)	
0	8 (34.78%)	15 (35.71%)	
Blood group match, n (%)			1
Identical	22 (95.65%)	39 (92.86%)	
Compatible	1 (4.35%)	3 (7.14%)	

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TABLE 1 | (*Continued*) Donor, recipient, and transplant characteristics of the study population.

	SCS (*n* = 23)	NMP (*n* = 42)	*p*-value
Creatinine, mmol/L	70.00 (53.00–94.00)	70.50 (55.00–93.00)	0.95
Bilirubin, μmol/L	23.00 (8.00–32.00)	30.00 (10.00–63.00)	0.19
INR	1.30 (1.20–1.70)	1.28 (1.20–1.60)	0.38
Lab MELD, points	11.00 (9.00–16.00)	13 (10.00–18.00)	0.44
Indication to transplantation, n (%)			0.75
Alcoholic cirrhosis	10 (43.48%)	12 (28.57%)	
Budd Chiari	1 (4.35%)	1 (2.38%)	
Caroli's syndrome	0 (0.00%)	1 (2.38%)	
Hemocromatosis	4 (17.39%)	7 (16.67%)	
HAT	0 (0.00%)	2 (4.76%)	
Ornithine transcarbamylase deficiency	1 (4.35%)	0 (0.00%)	
Polycystic liver disease	1 (4.35%)	3 (7.14%)	
Biliary cirrhosis	2 (8.70%)	4 (9.52%)	
Sarcoidosis	1 (4.35%)	5 (11.90%)	
Secondary sclerosing cholangitis	3 (13.04%)	7 (16.67%)	
Transplantation			
Steatosis, n (%)			0.38
None	10 (43.48%)	12 (29.27%)	
Mild	10 (43.48%)	16 (39.02%)	
Moderate	2 (8.70%)	10 (24.39%)	
Severe	1 (4.35%)	3 (7.32%)	
Liver weight, g	1,461 (1,267–1,658)	1,354 (1,140–1,641)	0.66
Porto caval bypass, n (%)	7 (38.89%)	9 (22.50%)	0.50
Veno-venous bypass, n (%)	1 (5.88%)	1 (2.44%)	0.51
Vena cava anastomosis, n (%)			0.66
Cava replacement	3 (13.04%)	4 (9.52%)	
Piggyback	20 (86.96%)	38 (90.48%)	
Portal vein anastomosis time, min	33 (28–40)	32 (24–45)	0.60
Hepatic artery anastomosis time, min	32 (26–39)	34 (26–41)	0.72
Total implantation time, min	64 (59–75)	67 (50–95)	0.76
Intra-operative immunosuppression, n (%)			0.44
None	14 (60.87%)	23 (54.76%)	
Others	1 (4.35%)	0 (0.00%)	
Methylprednisolone	8 (34.78%)	18 (42.86%)	
Basiliximab + methyprednisolone + tacrolimus	0 (0.00%)	1 (2.38%)	
Outcomes			
Peak AST within 7 days, IU/L	741 (474–2,221)	381 (196–906)	0.01
Peak ALT within 7 days, IU/L	710 (268–1,316)	348 (173–1,044)	0.06
Peak Bilirubin, μmol/L	74 (31–136)	66 (33–128)	0.99
Peak GGT, IU/L	578 (348–870)	551 (355–751)	0.70
Peak INR	1.75 (1.40–2.10)	1.70 (1.46–1.96)	0.79
AST, IU/L			
at 7 days	41 (29–91)	57 (35–127)	0.30
at 30 days	19 (15–41)	21 (13–38)	0.77
at 6 months	21 (18–35)	26 (21–34)	0.35
ALT, IU/L			
at 7 days	89 (59–190)	128 (70–327)	0.93
at 30 days	26 (18–43)	30 (21–57)	0.23
at 6 months	20 (14–30)	16 (16–43)	0.14
Bilirubin, μmol/L			
at 7 days	29 (15–72)	36 (17–100)	0.50
at 30 days	14 (8–21)	13 (7–19)	0.37
at 6 months	8 (5–15)	9 (6–14)	0.98
GGT, IU/L			
at 7 days	328 (240–723)	525 (353–719)	0.68
at 30 days	196 (63–319)	195 (122–473)	0.32
at 6 months	30 (11–205)	61 (42–222)	0.26
INR			
at 7 days	1.1 (1–1.2)	1.12 (1–1.3)	0.50
at 30 days	1.1 (1–1.2)	1.1 (1–1.2)	0.99
at 6 months	1 (1–1.1)	1.13 (1–1.23)	0.054

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TABLE 1 | (*Continued*) Donor, recipient, and transplant characteristics of the study population.

	SCS (*n* = 23)	NMP (*n* = 42)	*p*-value
Post-reperfusion syndrome,[b] n (%)	8 (34.78%)	6 (14.29%)	0.055
Post-reperfusion mean arterial pressure, mmHg	57 (52–66)	69 (64–89)	<0.001
Post-reperfusion vasopressor, n (%)	18 (81.82%)	22 (53.66%)	0.03
Post-reperfusion lactate, mmol/L	3.60 (3.20–5.10)	3.60 (2.60–4.40)	0.46
1-year patient survival, % (95% CI)	91.30 (69.50–97.80)	95.10 (81.80–98.80)	0.65
1-year graft survival, % (95% CI)	91.30 (69.50–97.80)	90.50 (76.60–96.30)	0.83
Graft loss at 1-year, % (95% CI)	8.70 (1.40–24.60)	9.50 (3.00–20.70)	0.60

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DBD, donation after brain death; DCD, donation after circulatory arrest; DRI, donor risk index; ET-DRI, EuroTransplant donor risk index; GGT, gamma glutamyl transferase; INR, international normalized ratio; MELD, model for end-stage liver disease.
[a]Total donor warm ischemic time in DCD, donors is measured from the withdraw of life sustaining therapy to cold flush.
[b]Post-reperfusion syndrome was defined as > 30% drop in mean arterial pressure persisting for > 1 min within 5 min of reperfusion.

TABLE 2 | Multivariate regression model for longitudinal measures estimating the effect of preservation type on the histological bile duct injury score.

BDIS	SCS (*n* = 23)	NMP (*n* = 42)		
	Estimate[a] (CI)	Estimate[a] (CI)	*p*-value	Bonferroni
Main effect preservation type[b]	5.39 (4.52; 6.26)	8.02 (7.40; 8.65)	<0.0001	—
End preservation	5.17 (3.96; 6.39)	7.25 (6.44; 8.06)	0.006	0.006
1 h post-LT	5.61 (4.49; 6.73)	8.80 (7.94; 9.66)	<0.0001	<0.0001
Main effect time[c]				0.04
Interaction effect[d]				0.25

[a]Estimate represents the mean from a multivariate regression model for longitudinal measures.
[b]Main effect preservation type represents the overall effect, regardless of the timepoint.
[c]Main effect time represents estimates the changes over time in BDIS, regardless of preservation type.
[d]Interaction effect investigate if the evolution of BDIS, over time differs between preservation types.

The type of liver preservation significantly affected the severity of BDIS, regardless of time ($p < 0.001$; **Table 2**). The overall BDIS estimate was significantly higher in the NMP group [8.02 (95% CI: 7.40, 8.65)] than in the SCS group [5.39 (95% CI: 4.52, 6.26), $p < 0.0001$]. This difference was significant both at the end of preservation [NMP: 7.25 (95% CI: 6.44, 8.06), SCS: 5.17 (95% CI: 3.96, 6.39); $p = 0.006$] and at 1-h post-reperfusion [NMP: 8.80 (95% CI: 7.94, 9.66), SCS: 5.61 (95% CI: 4.49, 6.73); $p < 0.001$] (**Figure 3**). There was no evidence that the size of BDIS change in time depends on preservation type (interaction effect, $p = 0.25$). Representative images of bile ducts with low or high BDIS are provided in **Figure 4**. A *post hoc* sensitivity analysis excluding the four transplants with BDIS improving after reperfusion confirmed these findings (**Supplementary Table S2**).

The NMP-preserved liver that developed IC after transplantation had a BDIS of 6 on a circumferential bile duct biopsy taken 1-h post-reperfusion. There were 15 other livers (6 NMP, 9 SCS) with a circumferential bile duct biopsy taken 1-h post-reperfusion with a BDIS >6 (range 7–12) that did not develop IC.

Does the Effect of Type of Preservation Differs Among Donor Types?

There was no difference in BDIS estimate between DBD [7.1 (95% CI: 6.4, 7.9)] and DCD liver grafts [7.0 (95% CI: 5.9, 8.1), $p = 0.87$]. The BDIS estimate in NMP was higher than in SCS in both DBD and DCD transplants (**Supplementary Table S3** and **Supplementary Figure S4**). There was no evidence that the effect of preservation type on histological injury of the bile duct differs between DBD and DCD (interaction effect, $p = 0.989$).

Characteristics Influencing the Severity of BDIS

To investigate which factor influences the severity of bile duct injury, we used bivariate linear models with BDIS as endpoint, and tested donor, recipient, transplant, and perfusion characteristics (**Table 3**, **Supplementary Table S4**). Donor type and donor warm ischemic time did not affect BDIS. The log-transformed highest concentration of gamma glutamyl transferase in the donor and cold ischemic time showed significant associations with BDIS. Donor blood group also influenced the severity of bile duct injury, with AB group donors associated with the lowest BDIS. Additionally, donor history of smoking or alcohol intake and the use of dopamine correlated with histological injury severity. Recipient-related characteristics did not show associations with BDIS. Blood group mismatch, NMP duration, bile volume during perfusion, implantation time, and hemodynamic post-reperfusion did not impact BDIS. An additive multivariable model including significant variables from univariate analysis showed that time, type of preservation, and donor blood group independently influence bile duct injury as measured by BDIS (**Table 3**).

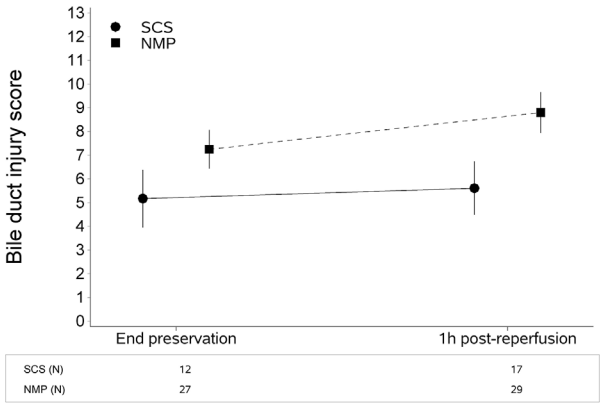

FIGURE 3 | Continuous liver normothermic machine perfusion (NMP) is associated with higher bile duct injury score compared to static cold storage (SCS). This difference is significant both at the end of preservation and 1 hour after reperfusion. The plot shows estimates (mean from the multivariate regression model) with confidence intervals. The bile duct injury score was estimated with a multivariate regression model for longitudinal measures (**Table 2**).

DISCUSSION

In this study, we provide evidence of the differential impact of different liver preservation modalities on the histological injury to the extrahepatic bile duct. Using 85 biopsies collected during the COPE trial comparing 121 NMP to 101 SCS livers, we showed that the BDIS increases significantly over time, regardless of preservation modality or other donor or transplant characteristics. Interestingly, although continuous liver NMP was associated with significantly higher BDIS, this did not lead to higher incidence of IC in the COPE trial. Next to the effect of time and preservation type, donor blood group emerged as a factor that may influence the severity of histological bile duct injury.

Although the results of our study revealed significant differences in BDIS between NMP and SCS groups, the size of this difference (almost three points) should be placed in context. In this study, BDIS increased significantly over time, independently of the preservation strategy used. As the duration of preservation was longer in the NMP group (>12 h) than in the SCS group (5.75 h, **Figure 1**), the bile duct biopsies taken after preservation and 1-h post-reperfusion captured different stages of the increase of biliary injury severity over time in the two groups. Consequently, a direct comparison of biopsies after preservation and 1-h post-reperfusion between the two groups overestimates the effect of NMP on BDIS as it does not adjust for the additional damage caused by the longer preservation time in the NMP group. In other words, while the difference in BDIS estimates between NMP and SCS was 2.63 points (**Table 2**), the real magnitude of the contribution of NMP to BDIS increase may have been smaller since preservation times were inherently different in the two groups. Nonetheless, our results clearly showed that continuous liver NMP is independently associated with higher BDIS. The fact that a liver graft undergoes two hits of reperfusion during NMP ("on pump" and in the recipient) may explain the exacerbation of BDIS. However, the overestimation of the detrimental effect of liver NMP on BDIS may explain the comparable incidence of IC

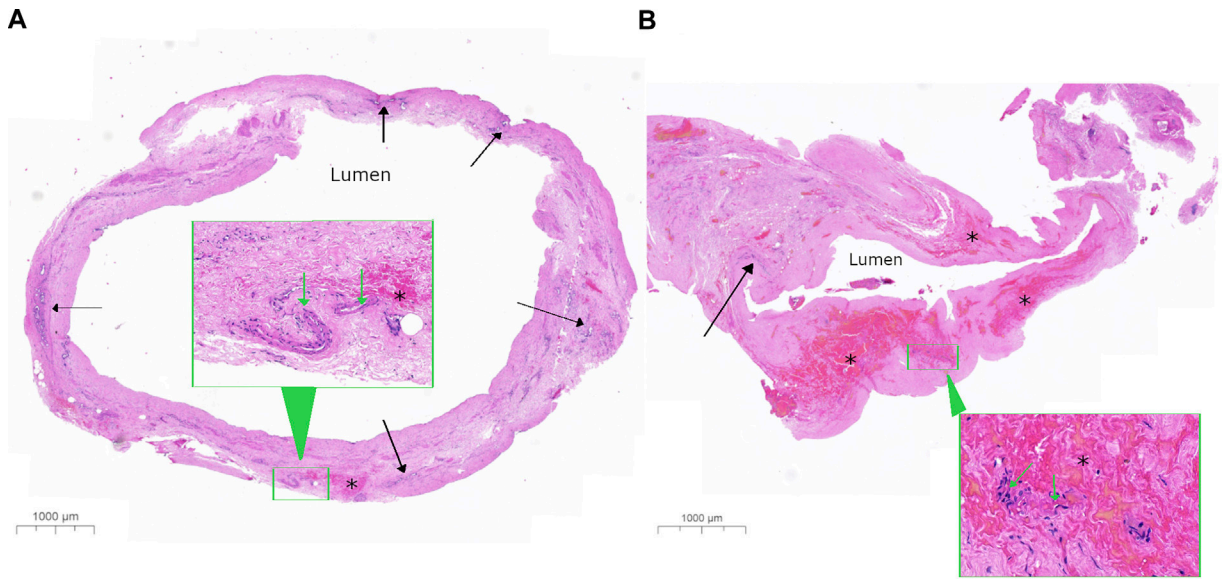

FIGURE 4 | Representative histological image of bile ducts with low and high bile duct injury score. Low-power images show a complete transverse section from a bile duct with **(A)** a low bile duct injury score (BDIS) of 4 and **(B)** a high BDIS of 12. The stroma of the bile duct wall appears normal in **(A)** but appears amorphous pink with no nuclear detail in **(B)**. In **(A)**, the deep perinuclear glands (solid arrow) look relatively normal compared to **(B)** where only a few damaged peribiliary glands are visible with nuclear staining that is not readily identifiable as glands at this power. Additionally, there is focal interstitial haemorrhage (*) in **(A)** compared to extensive interstitial haemorrhage in **(B)**. The insets in both **(A,B)** show higher-power images of the areas outlined in a green rectangle to demonstrate that the arteries have good nuclear detail in **(A)** with less loss of nuclei in **(B)**, which are difficult to assess in this haemorrhagic area.

TABLE 3 | Results from univariate and multivariate analysis exploring characteristics influencing the severity of the histological bile duct injury score.

Univariate analysis

	Average of both timepoints			
	Beta (SE)	***p*-value**	**Mean (95%CI)**	***p*-value**
Donor demographics				
Donor type				0.87
DBD			7.1 (6.4; 7.9)	
DCD			7.0 (5.9; 8.1)	
Total donor warm ischemia time[a] (min)	0.034 (0.056)	0.56		
Donor age	0.029 (0.019)	0.14		
Donor gender				0.98
Male			7.1 (6.3; 7.9)	
Female			7.1 (6.2; 8.0)	
Donor BMI	0.066 (0.060)	0.28		
Donor blood group				0.02
A			6.5 (5.8; 7.3)	
AB			4.5 (1.3; 7.6)	
B			8.9 (6.7; 11.1)	
0			7.9 (6.9; 8.8)	
Length of donor ICU stay	0.108 (0.144)	0.46		
Donor cause of death				0.16
Others			7.5 (5.8; 9.1)	
Trauma			4.9 (2.5; 7.3)	
Hypoxia			7.9 (6.6; 9.2)	
Cerebrovascular accident			6.9 (6.2; 7.7)	
DRI	0.154 (0.379)	0.69		
ET-DRI	0.898 (0.623)	0.16		
History of diabetes				0.63
No			7.2 (6.5; 7.8)	
Yes			6.7 (4.9; 8.5)	
History of smoking				0.02
No			7.6 (6.9; 8.3)	
Yes			6.2 (5.3; 7.2)	
History of alcohol consumption				0.02
No			7.4 (6.7; 8.0)	
Yes			5.5 (4.1; 7.0)	
History of cardiac disease				0.15
No			6.7 (6.0; 7.4)	
Yes			7.9 (6.4; 9.4)	
Vasopressor use				0.45
No			7.5 (6.6; 8.4)	
Yes			7.0 (6.3; 7.8)	
Dopamine				0.76
No			7.1 (6.3; 7.9)	
Yes			6.6 (4.0; 9.3)	
Dobutamine				0.34
No			7.0 (6.2; 7.8)	
Yes			8.6 (5.1; 12.2)	
Noradrenaline				0.56
No			7.4 (5.9; 9.0)	
Yes			6.9 (6.0; 7.8)	
Vasopressin				0.70
No			7.3 (6.0; 8.5)	
Yes			6.9 (5.9; 8.0)	
Highest AST	0.002 (0.008)	0.76		
Highest AST (log2)	0.449 (0.471)	0.35		
Highest ALT	–0.001 (0.006)	0.89		
Highest ALT (log2)	0.150 (0.250)	0.55		
Highest GGT	0.005 (0.003)	0.12		
Highest GGT (log2)	0.523 (0.231)	0.03		
Highest Sodium	–0.075 (0.039)	0.06		
Highest Bilirubin	0.011 (0.025)	0.67		
Highest Bilirubin (log2)	0.248 (0.171)	0.15		
Cold ischemia time (h)	–0.451 (0.112)	0.0001		

(Continued on following page)

TABLE 3 | (*Continued*) Results from univariate and multivariate analysis exploring characteristics influencing the severity of the histological bile duct injury score.

Univariate analysis				
	Average of both timepoints			
	Beta (SE)	***p*-value**	**Mean (95%CI)**	***p*-value**
Recipient demographics				
Recipient age	–0.039 (0.027)	0.15		
Recipient gender				0.93
Male			7.1 (6.4; 7.8)	
Female			7.0 (6.0; 8.1)	
Recipient BMI	0.068 (0.053)	0.20		
Recipient blood group				0.06
A			6.5 (5.7; 7.3)	
AB			5.7 (3.4; 8.0)	
B			8.9 (6.9; 10.9)	
0			7.7 (6.7; 8.6)	
Blood group match				0.76
Identical			7.1 (6.4; 7.7)	
Compatible			7.5 (5.0; 9.9)	
Creatinine	0.006 (0.009)	0.50		
Bilirubin	0.004 (0.004)	0.37		
Recipient Bilirubin (log2)	0.296 (0.180)	0.11		
INR	0.007 (0.681)	0.99		
INR (log2)	–0.197 (0.838)	0.82		
Lab MELD	0.062 (0.053)	0.25		
Transplantation				
Steatosis				0.46
None			6.9 (5.8; 7.9)	
Mild			6.8 (5.8; 7.7)	
Moderate			7.9 (6.5; 9.3)	
Severe			8.0 (5.5; 10.5)	
Liver weight	0.001 (0.001)	0.17		
Duration NMP (min)	–0.002 (0.001)	0.054		
Volume Bile NMP (mL)	0.003 (0.004)	0.46		
Porto caval bypass				0.03
No			7.6 (6.8; 8.3)	
Yes			6.0 (4.7; 7.2)	
Veno-venous bypass				0.23
No			7.2 (6.6; 7.9)	
Yes			5.5 (2.4; 8.6)	
Vena cava anastomosis				0.04
Cava replacement			5.2 (3.4; 7.1)	
Piggyback			7.3 (6.7; 7.9)	
Portal vein anastomosis time (min)	–0.002 (0.018)	0.90		
Hepatic artery anastomosis time (min)	0.010 (0.016)	0.53		
Total implantation time (min)	0.004 (0.011)	0.75		
Outcomes				
Post-reperfusion syndrome[b]				0.28
No			7.3 (6.6; 7.9)	
Yes			6.5 (5.2; 7.7)	
Post-reperfusion Mean Arterial Pressure	0.029 (0.015)	0.06		
Post-reperfusion vasopressor				0.54
No			7.4 (6.6; 8.2)	
Yes			7.0 (6.2; 7.9)	
Post Reperfusion Lactate	0.118 (0.253)	0.64		
Multivariate analysis[c]				
	Beta (SE)	***p*-value**		
Time		0.01		
End preservation	ref.			
1 h post-reperfusion	1.276 (0.480)			
Preservation type		0.002		
SCS	ref.			
NMP	3.828 (1.173)			

(Continued on following page)

TABLE 3 | (*Continued*) Results from univariate and multivariate analysis exploring characteristics influencing the severity of the histological bile duct injury score.

Univariate analysis				
	Average of both timepoints			
	Beta (SE)	***p*-value**	**Mean (95%CI)**	***p*-value**
Cold ischemic time, h	0.256 (0.224)	0.26		
Donor highest serum GGT, log2	0.251 (0.198)	0.21		
Donor blood group		0.03		
A	–1.014 (0.577)	0.09		
AB	–3.463 (1.411)	0.02		
B	1.302 (1.185)	0.28		
0	ref.			
Donor history of smoking		0.29		
No	ref.			
Yes	–0.617 (0.577)			
Donor history of alcohol consumption		0.19		
No	ref.			
Yes	–0.961 (0.725)			

N.B the relationship between indication to transplantation and BDIS, could not be explored due to the small sample size in each individual indication.
The complete analysis is reported in ***Supplementary Table S4****.*
ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DBD, donation after brain death; DCD, donation after circulatory arrest; DRI, donor risk index; ET-DRI, EuroTransplant donor risk index; GGT, gamma glutamyl transferase; INR, international normalized ratio; MELD, model for end-stage liver disease.
[a]*Total donor warm ischemic time in DCD, donors is measured from the withdraw of life sustaining therapy to cold flush.*
[b]*Post-reperfusion syndrome was defined as > 30% drop in mean arterial pressure persisting for > 1 min within 5 min of reperfusion.*
[c]*Result from an additive multivariable multivariate linear model for repeated measures, not considering interactions with time (due to sample size but also given the non-significant univariable results for these interaction terms). Dopamine use in the donor has been exclude as covariate because of excessive missing values. The model has been fitted on 75 observations.*

in the COPE trial despite significantly higher BDIS in the NMP group.

Additionally, our study raises concerns about the validity of BDIS as a surrogate endpoint of IC in perfused livers, and about currently defined cholangiocellular viability criteria. Three reports on bile duct histology during liver transplantation highlighted the univariate association between arteriolonecrosis, epithelial loss, stromal necrosis, injury to the peribiliary glands and the risk of IC after transplantation [3–5]. However, to the best of our knowledge no additional study has investigated whether these histological features remain independently associated with the risk of IC when adjusted for other well-known risk factors. In this study, we report that higher BDIS does not necessarily lead to increased IC after transplantation. This finding is in line with the observation that although more than 80% of liver grafts exhibit histological injury to the biliary epithelium at the end of SCS [4], only 10%–15% develop IC after transplantation, indicating that this injury can be recovered [15]. Therefore, determining first the contribution of bile duct histological injury to the overall risk of IC is crucial to elect BDIS as surrogate endpoint of this complication. Nevertheless, in a series of end-ischemic NMP of human livers, Matton et al. postulated that a BDIS score >4.75 points identifies high-risk grafts for IC, and cholangiocellular viability criteria based on bile biochemistry were developed to identify liver grafts likely to exceed this threshold [6]. The BDIS was calculated by adding up the score assigned to each histological alteration considered, implicitly assuming that they contribute to the risk of IC equally. However, the individual contribution of each histological lesion has never been investigated in multivariate analysis. Therefore, whether an additive BDIS is an accurate representation of biological events leading to IC remains unknown. Recently, de Jong et al. examined the histological aspect of the extrahepatic bile duct in livers transplanted after end-ischemic NMP [16]. They concluded that the currently defined cholangiocellular criteria correlate well with the histological damage, particularly of peribiliary glands and vascular plexus. These findings are not surprising as these criteria were specifically designed for this purpose, but they do not provide information on their accuracy since the study by de Jong et al. suffered from selection bias. Conversely, our study demonstrated that livers with BDIS scores considerably higher than the 4.75 threshold [6] can still have excellent outcomes. Indeed, while the NMP-preserved liver that developed IC displayed a BDIS score of 6 at 1 hour after reperfusion, 15 other grafts (9 SCS and 6 NMP) exhibited even higher BDIS scores (up to 12) at the same time point without developing IC. Although speculative, this observation, along with the absence of increased incidence of IC in the NMP group, suggests that BDIS overestimates the risk of IC in NMP-preserved livers. While we acknowledge that our findings may not be directly translatable to end-ischemic NMP, current cholangiocellular viability criteria may be too restrictive, potentially leading to unnecessary discarding livers that would remain free from IC.

This study also explored the factors influencing the BDIS. Time, preservation type, and donor blood group were found to be independent determinants of the score (**Table 3**). In this subset from the COPE liver NMP trial, DCD donors did not influence the BDIS. The results from the main trial showed that liver NMP exert a stronger protective influence on DCD grafts [9]. Considering that most DCD livers were preserved with NMP in this substudy, it is possible that liver NMP could have mitigated the adverse impact of DCDs on BDIS. However, due to the low number of DCD grafts in this substudy, the role of donor type on the severity of BDIS in livers preserved with NMP warrants further

investigations. Cholangiocytes express ABO-antigens and a previous study by Sanchez-Urdazpal et al. reported increased biliary complications after ABO-incompatible transplants, possibly due to enhanced immunological damage [17]. However, donor blood group AB was associated with a significant reduction of BDIS in our study. We did not include ABO-incompatible transplant and blood group matching (identical vs. compatible) did not influence BDIS. Therefore, we have currently no explanation for the protective role of donor blood group AB. However, due to the small number of AB group grafts ($n = 2$) and the lack of correction for multiple testing, these results should be interpreted as exploratory.

This study has some limitations. Not all centres involved in the COPE trial participated in this substudy, and not all transplants were included, which may limit the generalizability of the results to the entire trial population. Excluded cases had a significantly longer cold ischemic time, a known risk factor for biliary injury [18]. However, it is unlikely that the small median difference in cold ischemic time (1.28 h, **Supplementary Table S1**) would have reversed the results. Due to sampling issues, most biopsies did not include the entire bile duct circumference. To strike a balance between sample size and reliable evaluation, only biopsies with at least half circumference were considered for the BDIS. Although misinterpretation of injury severity cannot be ruled out, there was no difference in the proportion of biopsies with at least half circumference between the two groups (**Supplementary Table S5**). Nevertheless, complete bile duct circumferences were evaluated for the NMP liver that developed IC and other 15 with higher BDIS, eliminating this risk. Moreover, this study emphasizes the need for improved standardization of sampling techniques in future studies investigating BDIS. It is crucial to sample an adequate length of the extrahepatic bile duct above the biliary cannula tip to increase the likelihood of obtaining a representative whole circumference sample. Nonetheless, our findings provide a strong rationale to reassess BDIS as a surrogate endpoint for IC and re-evaluate current cholangiocellular viability criteria accuracy.

In conclusion, histological bile duct injury worsens over time regardless of the preservation method. Continuous NMP is associated with higher BDIS, but the magnitude of this effect remains uncertain due to limitations inherent to machine perfusion trials logistic. However, the more severe histological injury during continuous NMP does not necessarily lead to increased IC. Therefore, BDIS may overestimate this risk in NMP-perfused livers, making it less suitable as a surrogate endpoint for cholangiocellular viability criteria definition. Understanding the biological significance of bile duct injury and cholangiocellular biology during liver NMP is crucial for improving donor liver risk assessment. Further investigations exploring the biological responses of cholangiocytes from different donor types to NMP could shed light on these intricate mechanisms. To this end, the evaluation of bio-banked liver tissue samples from the COPE trial using single-cell -omics studies is being considered, which holds promise for unravelling the complexities of bile duct injury and optimizing liver graft preservation and selection.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving humans were approved by Research Ethics Committee London-Dulwich, United Kingdom (ref: 14/LO/0182). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

NG participated in study design, statistical planning, results interpretation, writing of the paper. DN and RB participated in data analysis, results interpretation, critical revision of the manuscript. SF participated in statistical planning, data analysis, results interpretation, critical revision of the manuscript. LL participated in results interpretation, critical revision of the manuscript. PF, RP, and DM participated in study design, results interpretation, revision of the manuscript. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

PF is a co-founder, chief medical officer, and consultant to OrganOx Limited and also holds shares in the company. PF was not involved in the selection, recruitment, or transplantation of patients in the original COPE trial on liver NMP.

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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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2023.11645/full#supplementary-material

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ORIGINAL RESEARCH
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Excellence in Organ Utilisation—A Quantitative and Qualitative Evidence Base for a New Approach in the UK

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The Department of Health and Social Care in England established an Organ Utilisation Group, to collate and analyse evidence regarding the organ transplantation care pathway, make recommendations on how to reduce inequity of access, make the best use of available resources, and drive innovation in organ transplantation. The group consulted with national and international experts and stakeholders, sought views from service providers across the transplant care pathway, and heard from over 600 people, including over 250 patients, carers, and donors. The group uncovered new evidence about where improvements are needed—particularly in relation to patient experience and inequities in access. The final report suggests a new direction for organ transplantation services in the United Kingdom, with action required at local, regional, and national levels. Ultimately, it is expected to increase transplant activity through increased organ utilisation and improve patient experience, outcomes, and empowerment whilst also supporting the transplant clinical community.

Keywords: organ utilisation, equity, patient and clinical engagement, transplant strategy and policy, NHS transplant service

INTRODUCTION

Over the last decade, around the world, most public facing programmes for transplantation have focused on the act of deceased donation or, where cultural mores make this challenging, living donation to allow a lifesaving or life enhancing transplant to occur [1].

There have been some remarkable successes in these programmes and there are some similarities in the way in which infrastructure for donation is augmented, often built on lessons learned from the Spanish system. These bring about improvement in donor numbers. But there are also national differences—not least in the ratio of deceased to living donation, organ specific "transplant per million population" achievements and the ratio of donation after death confirmation by neurological means (often termed Donation after Brain Death—DBD) compared with donation after death confirmation by circulatory cessation (often termed Donation after Circulatory Death—DCD) [1].

The last few years have also seen the trend of the increasing age of donors and increasing obesity in affluent countries [2]. The latter can bring problems in particular forms of donation such as liver and heart. Also, reflecting age and disease characteristics of the whole population, there is increased comorbidity in donors [3]. This has required transplant clinicians to investigate the safety and utility of using organs from patients with infection, tumour, and disease affecting other areas of the body [4–6]. There is an important principle of consent from transplant recipients who are being asked to accept an organ with a different risk profile compared with those that were transplanted a few years ago.

In May 2020, in the midst of the pandemic, England moved to a "deemed consent" basis for organ donation. The change in legislation [7]—which had strong public and clinical support—together with a

TOP 5% CONGRESS ABSTRACT

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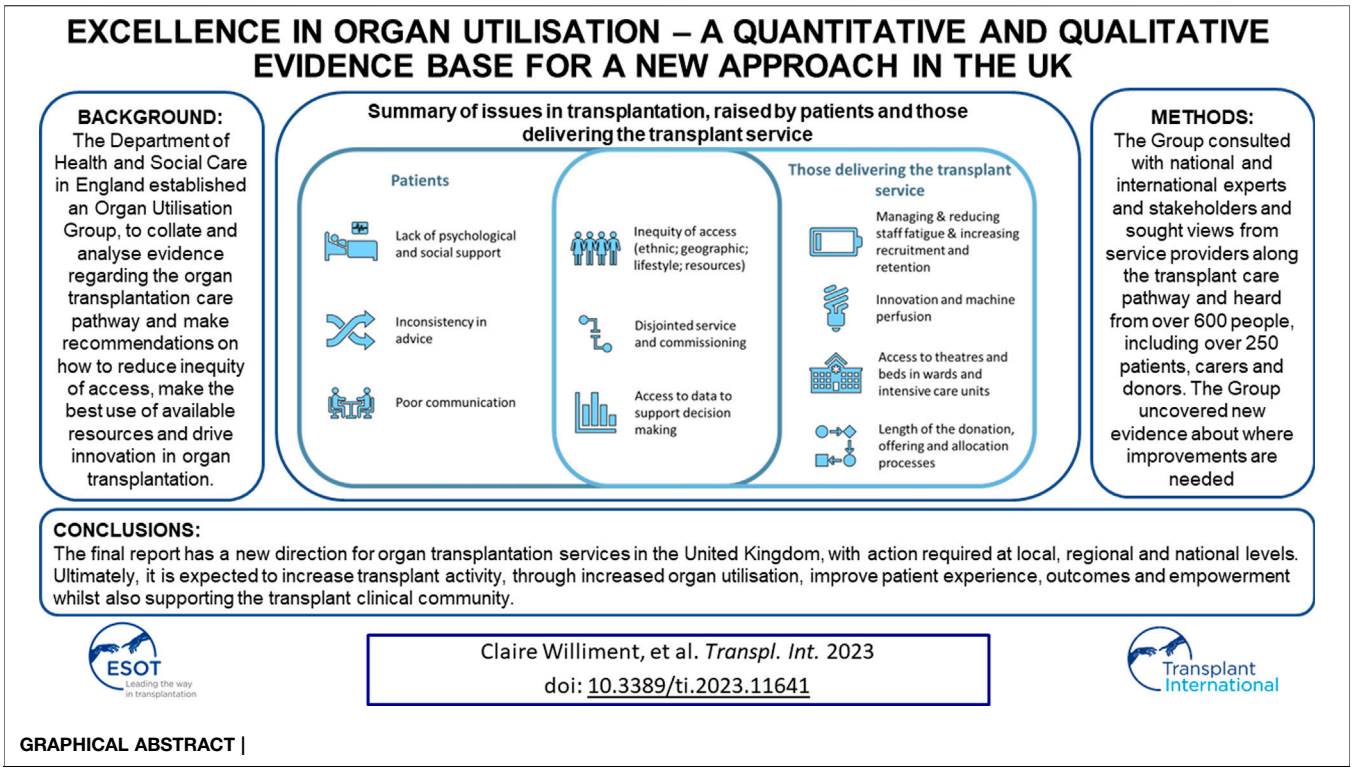

GRAPHICAL ABSTRACT |

wish to honour the choice of donors and their families, has led to a close examination of organ utilisation across the United Kingdom.

It was noted that, as in many countries, comprehensive planning arrangements have been put in place for organ allocation algorithms. Yet, a particular offer for a named patient is often made in the small hours of the morning, the final decision to accept or not frequently rests with a single clinician, and there is variable input from the patient themselves. The risk appetite of a particular clinician will naturally vary from time to time and based on the recent experience of that clinician in transplantation.

Preliminary examination of the UK wide data demonstrated differing acceptance rates from centre to centre and in access to innovative techniques that enhance utilisation.

MATERIALS AND METHODS

The Department of Health and Social Care (DHSC) established an Organ Utilisation Group (OUG), comprised of a range of subject matter experts and Chaired by NHS England's Medical Director, to make recommendations on how to maximise the potential for organ transplantation from living and deceased donors, through making the best use of available resources, driving improvements to the infrastructure, and supporting innovation. Each person (whether a leader, member, or participant in a meeting or event) either added this project to their normal daily tasks or gave their time freely. All meetings were held online, which also enabled broader participation and accessibility.

The OUG undertook work to identify the barriers to transplantation, examining national and international practice. This included patient focus groups, site visits, meetings with expert advisors, and reviews of the available data and literature. **Figure 1** summarises the activities undertaken.

The OUG received responses from national and international transplant service providers, patients, carers, commissioners, professional organisations, charities, and patient representative groups through a range of routes:

- 97 responses to online call for evidence
- 248 responses to online patient survey
- 4 patient focus groups held with a total of 27 delegates
- 58 delegates at stakeholder workshop
- Meetings with international colleagues from 6 countries
- 22 members of the Stakeholder Forum
- Senior transplant leaders from 7 countries
- 10 site visits with representatives including senior management, clinical leaders, transplant surgeons, intensive care, recipient co-ordinators, physicians, psychologists, social care workers
- Wide range of stakeholder meetings, including: psychologists; social care workers; histopathology; Histocompatibility and Immunogenetics; transplant teams; clinical advisory groups; digital data provision experts; commissioners; Government transplant advisory groups; NHS Blood and Transplant organ-specific patient advisory groups; patient representative groups (including patient charities and support groups); community leaders (e.g., faith/belief leaders, community-specific champions).

The online call for evidence was open to the public and stakeholder groups and the OUG invited charities, patient, and

FIGURE 1 | Organ utilisation group engagement and evidence gathering activities.

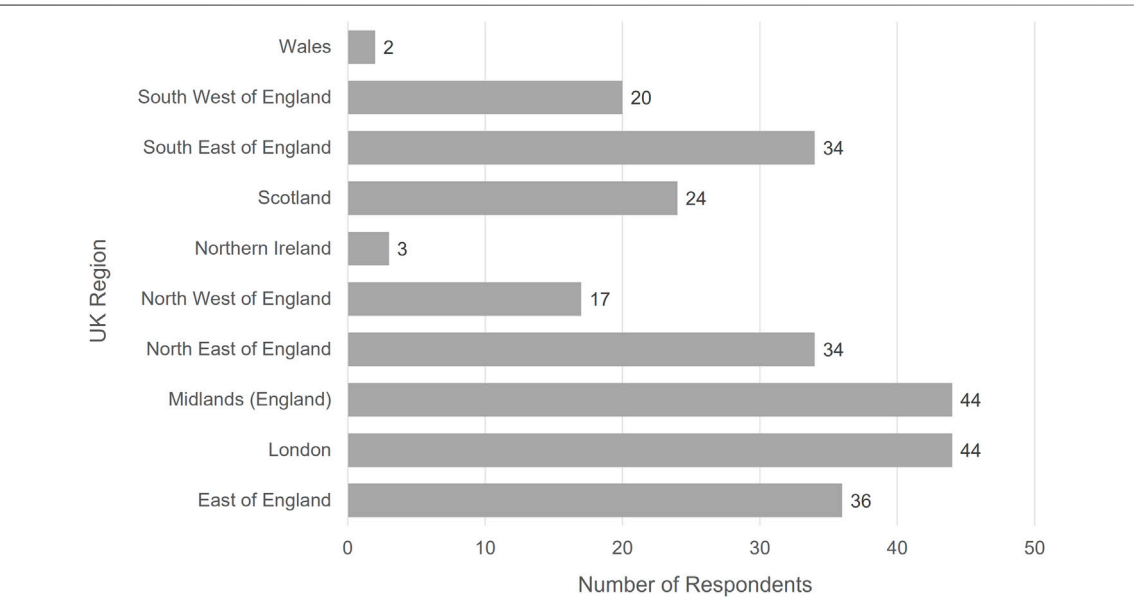

FIGURE 2 | Geographical region of where respondents to the online patient survey received the majority of their care.

clinical representative organisations to share with their members. It is therefore not possible to know the final number of people who received the survey and responded.

There was a remarkable consistency of views among patients, transplant teams and managers, backed by the data analysis, about the problems with transplantation and the opportunities to deliver improvements.

Data were extracted from the UK Transplant Registry held by NHS Blood and Transplant (NHSBT). This includes data on all patients waiting for or in receipt of a solid organ transplant in the United Kingdom. The number of organs donated per deceased donor were calculated, between 1 October 2020 and 31 March 2023. In order to evaluate the unwarranted variation across centres, offer decline rates were calculated by centres using offers from DBD donors, between 1 April 2019 and 31 March 2022, who had at least one heart retrieved, offered directly, and resulting in a transplant. Adult risk-adjusted median waiting times by centre were calculated for patients listed for a kidney

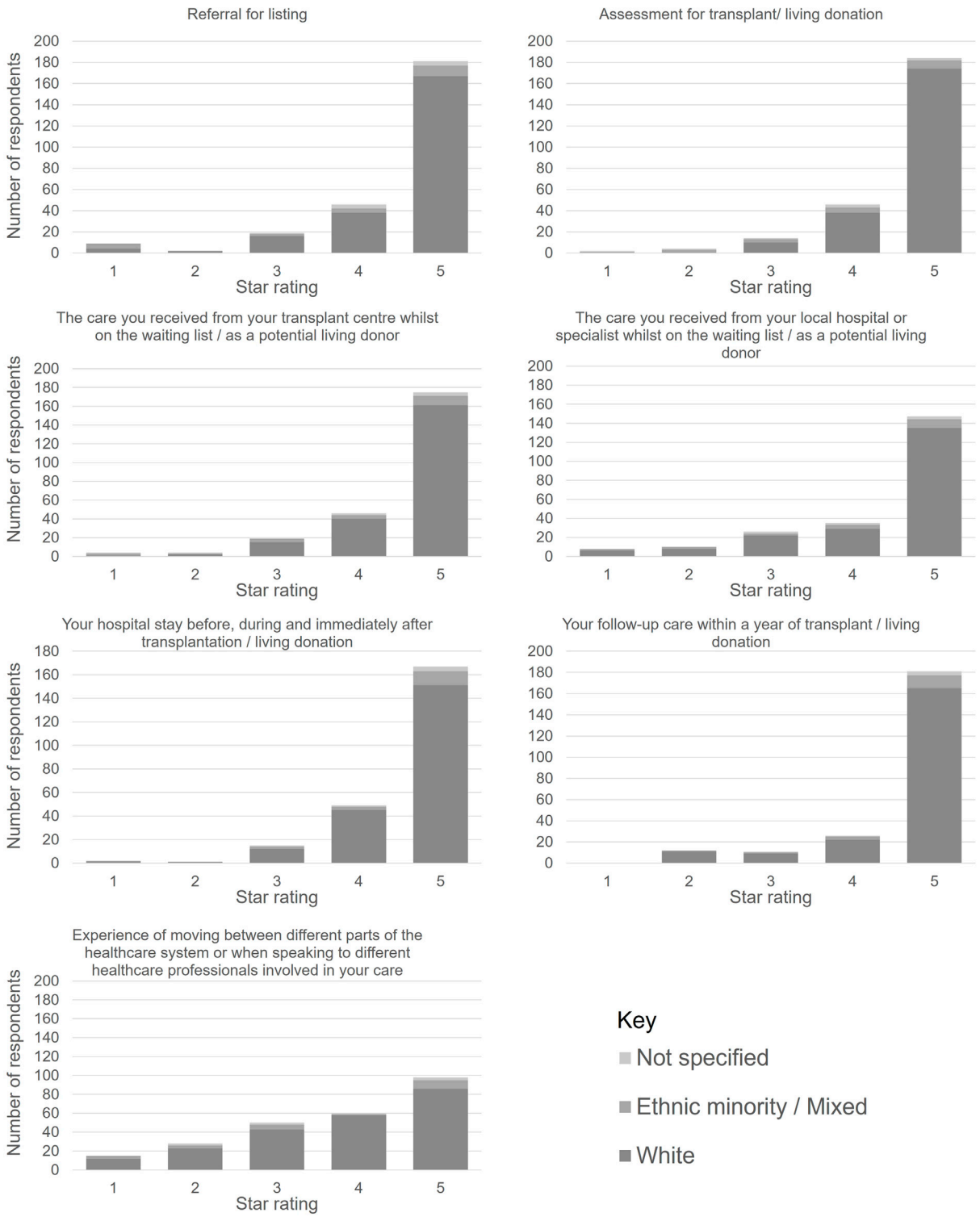

FIGURE 3 | Responses to the online patient survey with satisfaction rates for care received along the transplant care pathway.

between 1 April 2016 and 31 March 2019 using a Cox-proportional hazards model. Risk-adjusted death censored graft survival following deceased donor pancreas transplant between 1 April 2013 and 31 March 2017 was estimated using a Cox-proportional hazards model. Risk-adjusted 5 years patient survival from listing for adult elective liver registrations between

TABLE 1 | Summary of challenges in organ utilisation raised through the online call for evidence.

Challenge	N
Workforce (Staffing; fatigue; recruitment; sustainability)	20
Access to theatre and/or intensive care units	20
Data access (digital; imaging)	8
Risk aversion	7
Length of donation process	5
Lack of psychological support	5
Commissioning structure	4
Access to waiting lists	4
Offering process	3
Allocation process	3
Machine perfusion	3
Lack of patient education	3
Use of extended criteria organs	2
Workforce for research	2
Retrieval	2
Living donor liver transplantation	2
Pathology	2
Scouting	1
Inequity of access	1
Multi-Disciplinary Teams	1
Islet	1
Donation process	1

TABLE 2 | Summary of opportunities for improving organ utilisation raised through the online call for evidence.

Opportunity	N
Machine perfusion/novel technology	26
Data provision	10
Standards/guidance	7
Buddying scheme	6
Commissioning structure	6
Structured decline review scheme	5
Pathology (PITHIA)	4
Patient choice/education	4
Scouts	3
Bring donation & Transplant communities closer	3
Team restructure	3
Psychological support	3
workforce/job description	3
Shared decision making	2
Strategic direction/leadership	2
Theatre/ITU access	2
Ethics Committee	1
Allocation	1
Paediatric liver	1

1 January 2010 and 31 December 2021 were estimated using a Cox-proportional hazard model.

RESULTS

Feedback From an Online Call for Evidence

The OUG issued an open, online, call for evidence. The transplant community welcomed the opportunity to engage and the following responses were received:

- 74 Separate Respondents providing 93 responses in total.
- 107 challenges (+7 not applicable to OUG remit).
- 73 opportunities (+4 not applicable to OUG remit).
- 5 additional responses submitted via means other than the survey

Respondents were well dispersed across the UK. A chart of the residency of the individual giving a response is noted in **Supplementary Figure S1** of the **Supplementary Material**.

Respondents were asked to categorise their comments as either a "challenge" or "opportunity" to improve the service. Frequently, respondents gave much more detailed information over and above a simple categorisation of an issue. The overall categorisation is summarised in **Tables 1**, **2**.

Particular focus was given to three aspects of the service:

1. Commissioning of referral for transplantation and the transplant procedure itself, especially the UK system of commissioning renal transplantation.
2. Standardisation of meetings that examined the decline of organs and peer review of units. The data available to units regarding the outcome of declined organs was mentioned frequently.
3. Damage of organs during retrieval—both avoidance of such injury to improve utilisation and better resolution of different views between retrieval and transplant surgeons.

Feedback From Patients and Family Members/Carers

An online survey was issued in February 2022, to seek views from people who were waiting for, or had, transplants, and their families/carers. A key aim was to capture views from "less heard voices"—particularly Asian and Black female patients. Respondents were asked to rate different aspects of their care using a "star" rating, where 1 star was poor quality of care and 5 stars the highest quality of care. The survey was anonymous and covered both deceased and living donation. Respondents were given the option to record their ethnicity, but this was not a required field for completion.

There were 258 responses received from people from across the UK (see **Figure 2**). Of the respondents:

- 193 had received a transplant.
- 26 were on the waiting list.
- 42 were family members/carers of those either on the waiting list or have received a transplant.
- 252 were answering as or on behalf of an adult, with 6 people answering on behalf of a child.
- 19 respondents had received a kidney/liver transplant from a living donor. Of these respondents, 14 people received their organ from a family member or friend, and 1 person received their organ from someone who responded to a media/social media appeal.

A summary of the responses received to the survey is provided in **Figure 3**. Overall, patients were very satisfied with the levels of care received along the care pathway. The only exception was their experience of moving between different service providers as they progressed along the care pathway.

TABLE 3 | OUG focus group participants.

Focus group	Organ type	Participants
Focus Group 1	Kidney	1 Asian; 5 Black; 2 White delegates 1 parent of paediatric patient with special needs 1 representative of adult special needs patient 2 male and 6 female delegates
Focus Group 2	Lung	5 White delegates 1 male and 4 female delegates Pre- and post-transplant 1 patient who had been a child at the time of listing
Focus Group 2	Kidney	6 Black delegates 2 male and 4 female delegates Pre- and post-transplant 2 delegates on the waiting list
Focus Group 4	Liver	8 White delegates 4 male and 4 female delegates Pre- and post-transplant Experience of transplant during COVID

The OUG held online patient focus groups in 2021, Chaired by OUG patient representatives. Delegates were invited via patient representative groups. To support open, honest feedback, participants were anonymous, and feedback was not attributable to any specific patient. There were 27 participants across 4 focus groups as noted in **Table 3**.

The OUG was keen to hear from "less heard voices"—particularly female, Black, and Asian patients. The Group experienced challenges in finding people willing to discuss their transplant experience. Patient representative groups were approached to identify people to participate, and patients and family members/carers were self-selected. It is therefore possible that the experiences and views raised may not be representative of the wider patient population, as most patients who participated had experienced specific challenges that they wished to raise and were confident in highlighting their experiences. Their self-selective nature of participation meant that some groups were strongly skewed towards particular conditions, which may not be representative of the wider patient pathway.

Feedback From Those Involved in Delivering the Transplant Service

The OUG held an online workshop in October 2021, to provide stakeholders with the opportunity to advise on the key challenges and opportunities in transplant services. Delegates were invited to use the online voting mechanism "Mentimeter" [8], with 71 delegates participating in the voting. Delegates were asked to rate the performance of aspects of the transplant system using a sliding scale, where ratings closer to the left indicate significant issues/difficulties with a specific service that needed to be addressed. Ratings closer to the right would mean that the service consistently worked well. Delegates identified "organ offering and acceptance", "information sharing" and "organ retrieval" as having the most significant issues. There were no areas that delegates advised were consistently working well (see **Figure 4**). Respondents identified resourcing, workforce, patient support and technology as the key issues and challenges (see **Figure 5** for more information).

Contact was made with donation and transplant experts in 7 countries (Austria, Australia, Canada, France, Netherlands, Spain, and the USA). It was agreed that the issues described in the UK were often present in these other countries—further collaborative work is planned [9]. The following key similarities were noted:

- Maximising utilisation potential.
- Risk appetite and centre variation—not possible to eliminate, but should seek to reduce the amplitude.
- Utilisation rates driven by local enthusiasts.
- Few instances of any national level oversight of the whole care pathway.
- Workforce burnout and recruitment/retention issues especially post-pandemic.

Supplementary Table S2 in the **Supplementary Material** provides a summary of the responses including lessons learned and successful initiatives.

An online meeting was held with UK national clinical leads for transplant services to seek views on the challenges and opportunities. These focussed on four key areas:

i. Trust (Individual Hospital) involvement—there was a need for hospital Boards to take ownership of the issues regarding transplantation and do more to support both patients and clinical teams.
ii. Addressing risk aversion—there was a need to do more to support those who take reasonable risks and address logistical barriers to those who are willing to accept higher-risk organs.
iii. Workforce—transplant teams have to work unsociable hours with little reward. There was an increasing trend for surgeons to leave the UK to work in other countries.
iv. Resources—Intensive care capacity was raised as a particular issue to be addressed.

More detailed feedback is provided in **Supplementary Table S3** of the **Supplementary Material**.

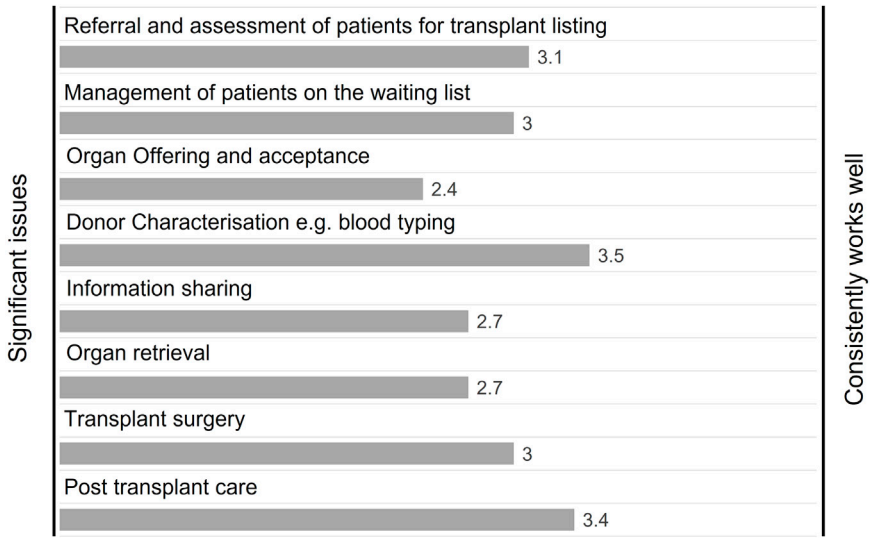

FIGURE 4 | Workshop delegate responses to the question "Rate the current performance of aspects of the transplant system" (n = 71).

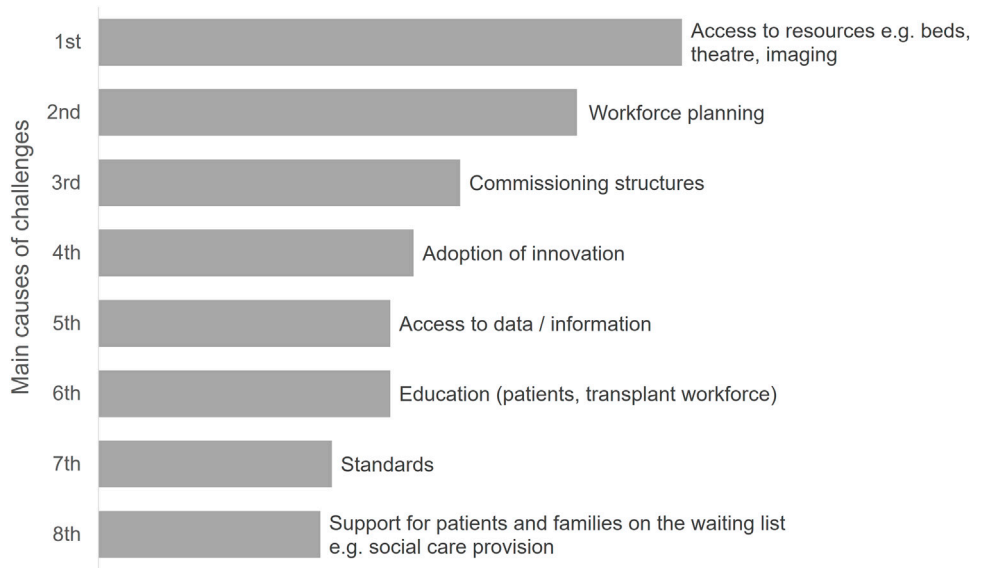

FIGURE 5 | Workshop delegate responses to the question "What do you consider are the main causes of challenges in organ transplantation?" (n = 71).

Views from clinical teams were also sought at the UK National Organ Utilisation conference in May 2022. Delegates included representatives from across the transplant service. Delegates gave a clear steer that changing the culture would have the greatest impact on organ utilisation (see **Figure 6**).

The majority of patients raised the importance of psychological and social care support and where this was lacking, the negative impact on experience for patients and their families, and patient outcomes. Patients expressed frustration regarding poor communication. This included the timeliness of communication and the lack of effective communication along the care pathway. For example, a lack of timely, effective sharing of notes between different providers. Patients noted that there was inconsistency in advice received—particularly relating to medication and diet—between different providers and regions. This caused concern and anxiety. Female patients also noted a lack of available advice regarding issues such as sexual and reproductive health.

Those delivering the transplant service noted concerns in the workforce, particularly relating to staff fatigue, difficulties in recruitment and the high rate of staff attrition. They raised frustration at the lack of ability to quickly adopt proven innovation and machine perfusion technologies as standard practice, noting that this was limiting the numbers of organs that could be utilised. There was significant variation in access to theatres, beds, and key staff, which limited a hospital's opportunity to accept offered organs. The length of

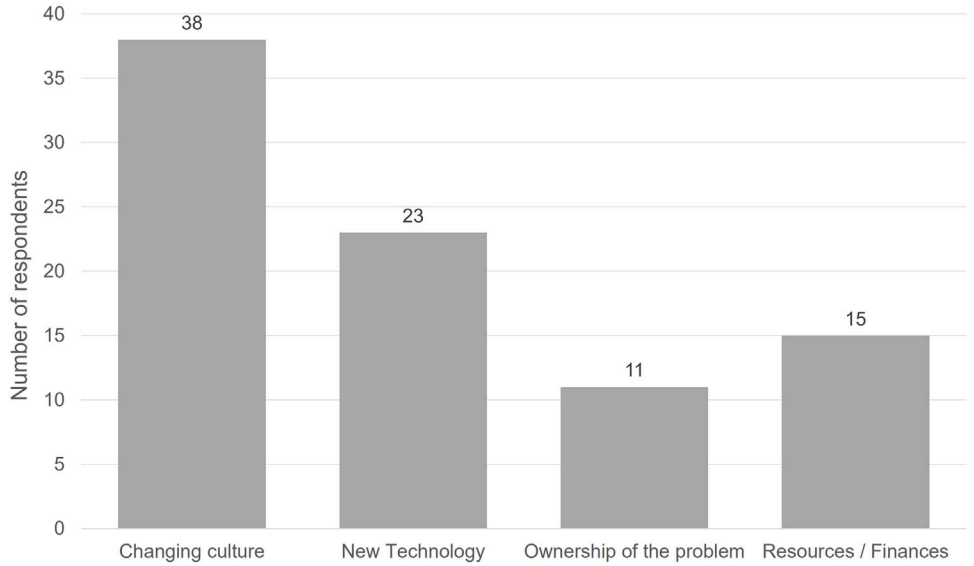

FIGURE 6 | National Organ Utilisation Conference delegate responses to the question "What change would have the most positive impact on organ utilisation?"

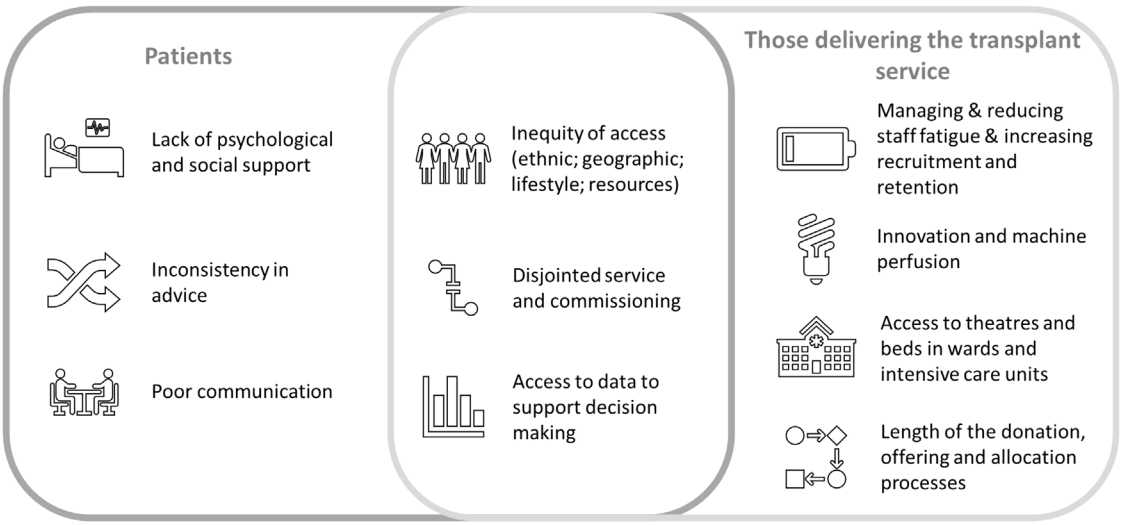

FIGURE 7 | Summary of issues in transplantation, raised by patients and those delivering the transplant service.

the donation, offering, and allocation process was also a cause of frustration and limited the ability to forward plan and secure local resources for the transplant procedure.

Both groups expressed concern regarding inequity of access to transplantation services across a range of factors, including ethnic, geographic, lifestyle, and resources. There were concerns regarding the disjointed service along the care pathway, which they believed could be partly attributable to having to move between different commissioners and providers. Finally, they advised that there was a lack of timely access to data to support their decision-making regarding organ acceptance. For patients, this included the need to ensure that data was provided in an easily understandable format, tailored to meet their needs. A summary of the issues in transplantation raised by patients and those delivering the service is provided in **Figure 7**.

Statistical Evidence

There is unwarranted variation in access to transplantation, organ acceptance and post-transplant survival leading to inequities in care and treatment for patients. **Figure 8** highlights the differences between centres for various stages in the transplant pathway for all organs. Each chart shows a funnel plot for the different outcomes displayed. The average rate for the UK is shown as the horizontal thick black line with the dotted lines representing the upper and lower confidence limits. Each centre is represented by a dot. Where a centre falls above or below the dotted lines, this indicates that the centre has a statistically higher or

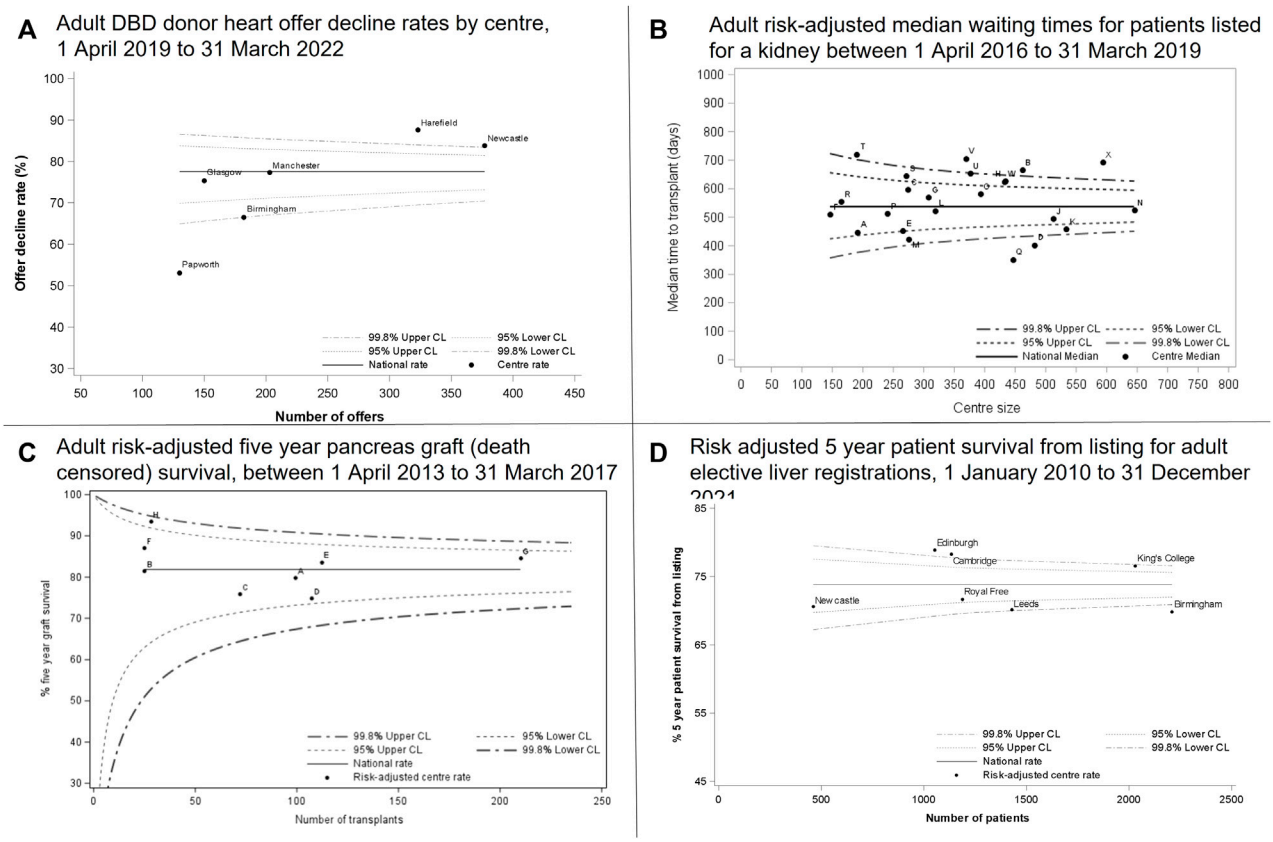

FIGURE 8 | Centre variation across offer decline rates, risk-adjusted median waiting times, graft survival and patient survival.

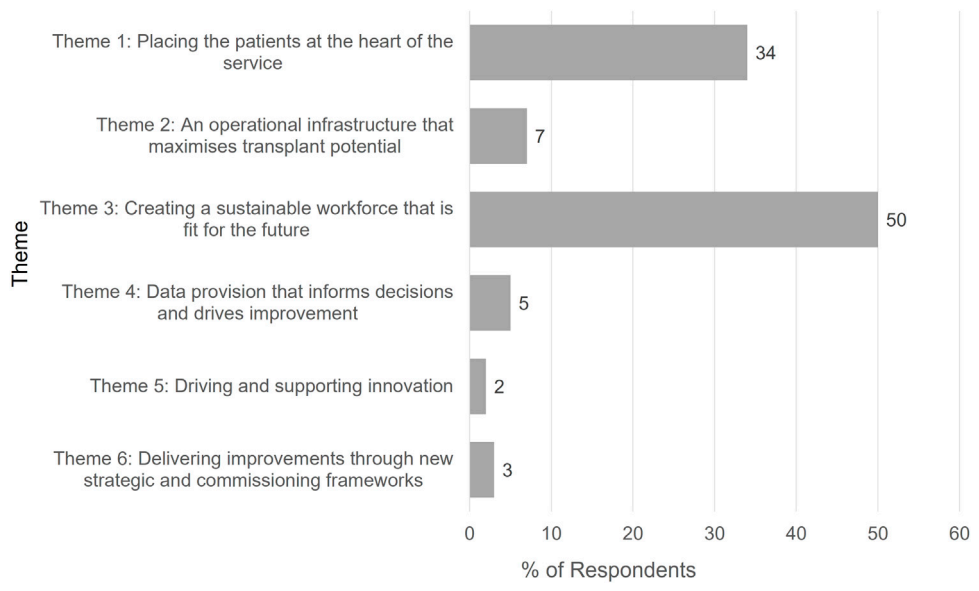

FIGURE 9 | Feedback from British Transplantation Society Conference Delegates to the Question "Which theme (from the OUG report) do you believe should be given the highest priority?"

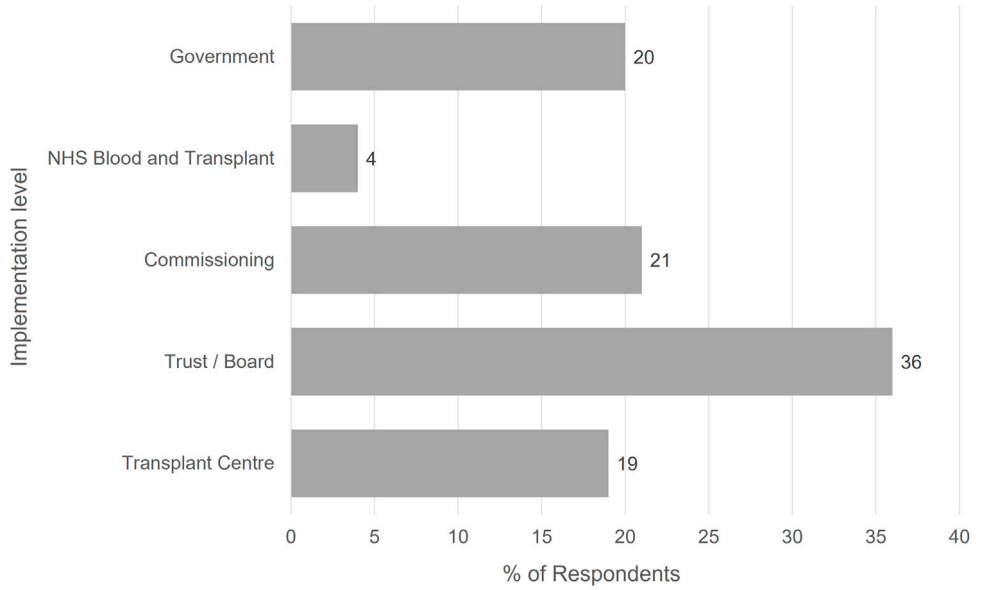

FIGURE 10 | Feedback from British Transplantation Society Conference Delegates to the Question "At what level are the biggest challenges to implementing the OUG recommendations?"

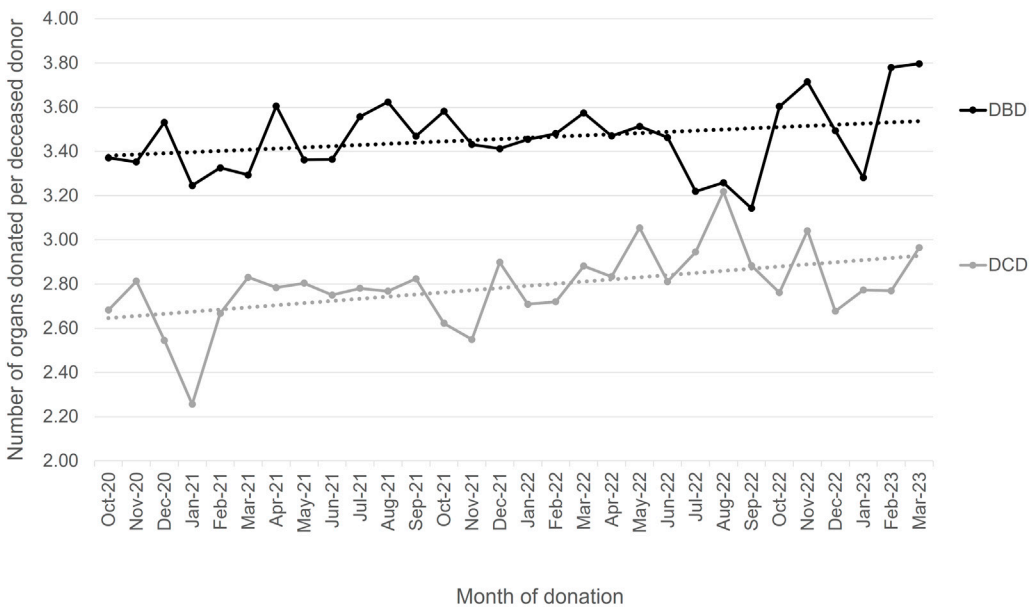

FIGURE 11 | Number of organs per donor by month and donor type with trendlines, 1 October 2020–31 March 2023.

lower than average rate compared to the UK rate. Chart A shows DBD donor heart offer decline rates ranging from 53% to 88% across centres. This shows a difference in appetite for accepting donor offers between centres. Chart B shows risk-adjusted median waiting times for patients listed for a kidney transplant. Risk-adjusted median waiting times range from 1 to 2 years across centres even after adjusting for patient demographics. Variation in acceptance rates can lead to unwarranted variation in waiting times. Chart C shows risk-adjusted five-year pancreas death censored-graft survival ranging from 75% to 93%. Although no centre has significantly poorer outcomes compared with the national rate, the variation can still impact the length of time a patients graft functions. Chart D shows 5-year risk-adjusted patient survival from listing for adult elective liver patients and ranges from 70% to 79% across the centres. It is important not only to look at post-transplant survival, but also survival from listing as this accounts for deaths on the waiting list as well as deaths post-transplant. Similar graphs are available for other organs in the NHSBT annual report [10] and demonstrate a similar pattern.

OUG Vision and Recommendations

The OUG final report includes a vision for transplant services, which focusses on the following issues [11]:

- To ensure a donated organ is transplanted into the intended recipient as rapidly as possible, through delivering a service that is:
  - Supporting and empowering patients (improved data that enables patients to understand their options and reflects the diversity of those on the transplant waiting list; giving patients a louder voice in shaping the services that they rely on).
  - Equitable (regardless of geography, socio-economic status, health literacy, culture or ethnicity).
  - Reducing unwarranted variations in practice (clearer expectations about roles and responsibilities; infrastructure enables adherence to best practice).
  - Driving cost savings to the NHS (increasing the number of transplants; maximising the efficient use of available resources).
  - Honouring the gift from donors (no opportunity missed for safely transplanting an organ into the intended recipient).
  - Supporting and empowering transplant teams (data, guidance and training provided in a timely, accessible manner).
  - Sustainable (resources; workforce).
  - Embedding innovation (supporting new techniques, technologies and evidence-based best practices).
  - Placing the UK as a world leader (organ transplant rates; forefront of research).

The published report [9] provides 12 recommendations spread across the following themes:

1. Placing the patients at the heart of the service.
2. An operational infrastructure that maximises transplant potential
3. Creating a sustainable workforce that is fit for the future.
4. Data provision that informs decisions and drives improvements.
5. Driving and supporting innovation.
6. Delivering improvements through new strategic and commissioning frameworks.

The recommendations provide imperatives for activity, with accompanying support actions to inform implementation (for details see **Supplementary Table S4** in the **Supplementary Material**).

Implementation

Feedback has been sought regarding the priorities for implementation. At the OUG seminar of the 2023 British Transplantation Society Annual Congress, delegates were asked to use an online survey tool to identify which of the report's themes should be given the highest priority. Delegates were only able to choose one theme. The responses received are provided in **Figure 9**, demonstrating that the need to create a sustainable workforce was considered the highest priority (50% of respondents), closely followed by placing patients at the heart of the service (34% of respondents).

Delegates were asked which of the main groups responsible for implementation of the OUG recommendations would have the biggest challenges. The responses are provided in **Figure 10**, demonstrating that Government, Commissioning, and Transplant centres were all identified as being equally challenging, but the highest level of challenge would be with local NHS Trust engagement and implementation.

Initial Impact of the OUG

The OUG work has already started to have an impact and deliver a number of benefits to transplant services.

The establishment of the OUG demonstrated a renewed interest in organ utilisation from the Government, with an aim to maximise the potential benefit of introducing Opt Out legislation and save more lives through the gift of organ donation. The publication of the report was accompanied by a Written Ministerial Statement from Minister Neil O'Brien, Parliamentary Under Secretary of State (Minister for Primary Care and Public Health). This included commitments to implementing the recommendations in full and delivering improvements to the transplant service [12].

Figure 11 shows the number of organs donated per donor and donor type for each month since the start of the Clinical Leads for Utilisation (CLU) schemes through to the OUG report publication and beyond. The superimposed linear trendlines show an increase by month for both DBD and DCD donors in the numbers of organs retrieved for the purpose of transplantation, with DCD increasing at a higher rate. Although not directly attributable, the CLU schemes along with directed interest in organ utilisation would have positively contributed to the increases seen.

DISCUSSION

The OUG report sets out a new strategy and direction for transplant services. It builds on a range of existing national and local initiatives, bringing them together to provide revised impetus, strategic direction, and national oversight. It also identifies a range of areas for new focus within transplantation, such as improvements in personalised care for patients.

The recommendations place the patient at the heart of the service and seek to honour the gift of donation through ensuring that organs are transplanted in a safe and equitable manner. The report aims to improve the experience of both service providers and users and improve utilisation rates.

The level of engagement with the OUG work—national and international—demonstrates the acknowledgement of transplant teams, providers, and patients, in the need for change and a will to work together to deliver improvements. The fact that the OUG was a Government initiative, with the report published by Ministers, will help to ensure national focus on implementation. However, the high levels of stakeholder engagement through the report development stages need to be maintained—indeed is even more important—for the implementation stage.

The limitations to the project included the difficulty in surveying all patient attitudes. Rather than surveys with a set threshold response rate, the evidence was sought via all major relevant patient groups, often encouraging anonymous reporting if that facilitated engagement. Specific focus groups, aided by leaders of Ethnic Minority groups,

helped in listening to "less heard voices" but coverage may not have been comprehensive. The scope of this project, partly by design to examine transplant processes, and partly the logistics of a report that was achievable, were limited and did not seek to include issues at referral nor in donation. That is not to say that these are not important; far from it. But the thrust of the report and evidence gathering is around the processes of transplantation.

The recommendations and supporting actions within the OUG report are complex and require action by multiple organisations, at national, regional, and local levels. The OUG remit was to deliver recommendations that would take up to 5 years to deliver. It will take time to map the multiple co-dependencies both across the 6 themes of the report and also with other work underway nationally and locally. This will support the identification of priorities for action.

It is acknowledged by all involved in this project that publication of a report will change little without recommendations being carried forward to support this work. Therefore, the English Department of Health and Social Care Ministers have established the Implementation Steering group for Organ Utilisation (ISOU), to bring together those with a role in implementation, agree priorities and timescales and then monitor and support implementation. Other countries in the UK have observers on this group and have indicated that they wish to carry out implementation in a similar manner. The group has senior policy and clinical Co-Chairs and membership includes providers, commissioners, patient and lay representation, as well as subject matter experts. The first ISOU meeting was held in April 2023—less than 2 months from the publication of the report—demonstrating the Government's commitment to implement the recommendations as quickly as possible.

There is work underway within ISOU to develop an implementation plan, with supporting Key Performance Indicators, to monitor progress and impact of the implementation approach. If successful, the following benefits will be realised:

- Increase in utilisation rates.
- Improved equity of access.
- Decrease in current rates of higher quality declines or lack of resources declines.
- Improved patient experience.
- Improved patient engagement.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical Approval was not required. Any patient participation was carried out as an online survey where patients had voluntarily put themselves forward or were there as representing a Patient organisation- or as discussion in focus groups where, again, any patients had volunteered to be part of the process.

AUTHOR CONTRIBUTIONS

CW and JF: Design of study, collection and analysis of data, involvement in engagement activity, overall policy recommendations, drafting. JJ: Design, collection and analysis of patient engagement data; drafting. LM: Design of study, data collection, collation and analysis, drafting. SP: Design of study; editing; analysis of collated evidence, policy decisions. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

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

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England Specialised Commissioning	Ms	Sarah Watson
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Commissioning	Mr	Stuart Davies
Commissioning	Ms	Teresa Magirr
Commissioning	Ms	Karen Quinn
Stakeholder Forum Chair	Ms	Fiona Loud
Stakeholder Forum Chair	Prof	Deirdre Kelly

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2023.11641/full#supplementary-material

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ORIGINAL RESEARCH
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Vigilance Data in Organ Donation and Solid Organ Transplantation in Germany: Six Years of Experience 2016–2022

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The reporting of serious adverse events (SAE) and serious adverse reactions (SAR) is an essential part of an effective vigilance and surveillance system (V&S) in organ donation and transplantation. All SAE and SAR reported to the German organ procurement organization (DSO) between 2016 and 2022 were analyzed. In case of a possible transmission of a disease to one or more recipients, an assessment of imputability was done according to the grading system of the US Disease Transmission Advisory Committee (DTAC). 543 SAE and SAR cases were reported to the DSO and analyzed in detail. 53 of the 543 reports (9.8%) were proven or probable (P/P) transmissions of infectious diseases, malignancies or other diseases to 75 recipients. Infections were the most frequently reported P/P disease transmission occurrences (30/53, 57%). In case of disease transmission, the mortality of the recipients was high (17/75, 23%), especially when a malignant disease was transmitted (11/22, 50 %). Donor-Derived disease transmission is a rare event (53/8,519; 0.6 %), but when it occurs can lead to significant morbidity and mortality.

Keywords: organ donation, organ transplantation, disease transmission, donor-transmitted cancer, serious adverse event, serious adverse reaction

TOP 5% CONGRESS ABSTRACT

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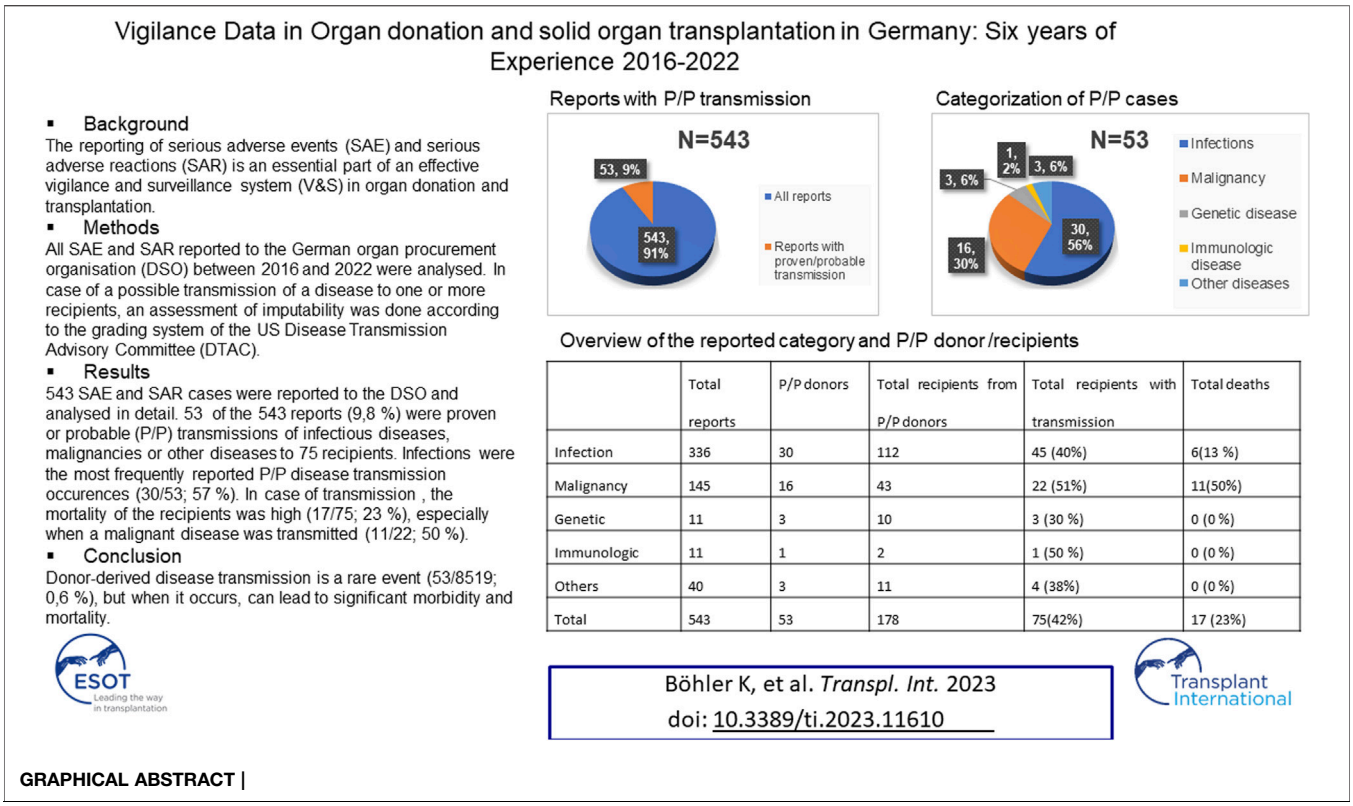
INTRODUCTION

Due to the shortage of organs for solid organ transplantation, different strategies have been developed to increase the donor pool, including the use of organs from expanded-criteria donors and from increased risk donors [1–3]. Compared to the high number of transplantations performed worldwide each year, the number of reported adverse outcomes seems low. Nevertheless donor-derived transmission of infectious diseases and malignancies pose an additional risk to the organ recipients with significant morbidity and mortality [4–9].

Abbreviations: BAL, broncho-alveolar lavage; BoDV-1, borna disease virus 1; CPVT, catecholaminergic polymorphic ventricular tachycardia; DDC, donor-derived cancer; DSO, Deutsche Stiftung Organtransplantation; DTAC, Disease Transmission Advisory Committee; DTC, donor-transmitted cancer; EFRETOS, European Framework for Evaluation of Organ Transplants; ET, Eurotransplant; EU, European Union; FISH, fluorescent *in situ* hybridization; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HHV-6 virus, human herpesvirus 6; HHV-8, human herpesvirus 8; MDR, multi drug resistant; OPCC, Organ Process Chain Committee; P/P, proven/probable; PDDTE, potential donor disease transmission events; RCC, renal cell carcinoma; SAE, Serious Adverse Event; SAR, Serious Adverse Reaction; SPP, species; SOP, Standard Operating Procedures; V&S, Vigilance and Surveillance.



GRAPHICAL ABSTRACT |

As organ donation and transplantation is a complex process involving many different institutions at various steps of the process, an effective vigilance and surveillance system (V&S) is of utmost importance for reducing risks to the recipients [10,11].

The EU-directive 2010/53/EU of 7 July 2010, on standards of quality and safety of human organs intended for transplantation, requires that the member states establish a rapid alert system to report, investigate, register, and transmit relevant and necessary information concerning serious adverse events (SAEs) and serious adverse reactions (SARs) to the involved transplantation centers and the national competent authorities [12].

In this context, the EU-directive defines a serious adverse event as "any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to the transmission of a communicable disease, to death or life- threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalization or morbidity" [12]. A serious adverse reaction is defined as "an unintended response, including a communicable disease, in the living donor or in the recipient that might be associated with any stage of the chain from donation to transplantation that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity" [12].

In short, an SAE refers to a serious risk of harm to the recipient although no harm has occurred or been identified yet, whereas an SAR refers to serious harm that has already occurred to one or more recipients and might be associated with the donor.

Setting up a V&S system must be distinguished from a quality management system in organ donation and transplantation. A quality management system sets up a whole range of predefined quality indicators such as occurrence of primary graft failure or in-hospital mortality post-transplant. In a V&S system there are no predefined indicators, instead there are different events and reactions in the whole chain of the process that are not previously known and may influence the quality and safety of organ donation and transplantation. The clear definitions of SAE and SAR described above must be complied with and well understood.

The different steps of a V&S system consist of alerting, reporting, assessing, and managing SAEs and SARs, followed by the surveillance of the recipients. To fulfill the different tasks, procedural rules are determined by the directive 2012/25/EU of 9 October 2012 [13].

According to this directive the member states have to appoint qualified and trained staff for the assessment and processing of the incoming reports, available 24 h/7 days/365 days. The dedicated staff has to alert without any delay the involved transplantation centers, organ procurement organizations, and in case of cross-border organ exchange, the national authorities. An initial report has to be sent to the above-mentioned institutions in order to set up preventive and/or therapeutic measures for the involved recipients. Furthermore, when additional information becomes available following the initial report, it shall be transmitted to the involved institutions. Within 3 months, a final report including the result of the assessment and

investigation, as well as the actions taken, should be provided to the relevant parties. If applicable in the individual case, preventive and corrective measures to avoid similar incidents in the future should also be included in the report [13].

In Germany, the organ procurement organization (Deutsche Stiftung Organtransplantation—DSO) is the delegated body assigned by the German competent authority (Federal Ministry of Health) responsible for managing and performing the V&S system in organ donation and transplantation.

On a national level, the regulation of the law of donation, removal, and transplantation of organs and tissues of 28th May 2014 implemented the V&S system according to both directives [14].

Analyses of reported SAEs and SARs should help with identifying risks in the process of donation and transplantation. Ideally, the risk analyses will be integrated into adaptations of new guidelines or standard operating procedures (SOP). Sharing the information of known SAE and SAR cases between all involved parties like donor hospitals, transplantation centers, procurement organizations, organ exchange organization, and national health authorities is crucial. All these efforts are important to enable maximal recipient safety and security.

MATERIALS AND METHODS

All incoming reports of SAEs and SARs were assessed by a special team of qualified and trained physicians of the DSO (SAE/SAR team of the DSO). The team consists of one executive physician, one staff physician, and nine physicians from the seven different German regional sections who also worked as organ procurement coordinators but with a focus on SAE and SAR. Furthermore, there was support from designated external experts in the field (e.g., virology, hematology, pathology) provided in a case-by-case decision to help review the cases. All procedural steps were carried out in accordance with the directive 2012/25/EU [13].

As a first step, the reports were grouped into five categories: pathogens/infections, suspected malignancies, genetic diseases, immunologic events/reactions, and other diseases.

All reports were classified as SAE or SAR according to the definitions of the directive [12]. For every reported SAR, an assessment of imputability was carried out, grading the probability that the transmission of an infectious disease, tumor, or other diseases to the recipient was linked to the transplantation of the donor organ into the following categories: proven, probable, possible, unlikely, excluded, or not assessable. The grading system is adapted from the US Disease Transmission Advisory Committee (DTAC) [4, 10]. *Probable* means "the following two conditions are met: Suspected transmission and laboratory evidence of the pathogen or the tumor in a recipient. And it meets at least one of the following conditions: Laboratory evidence of the same pathogen or tumor in other recipients and/or laboratory evidence of the same pathogen or tumor in the donor. If there is pre-transplant laboratory evidence, such evidence must indicate that the same recipient was negative for the pathogen involved before transplant" [4]. *Proven* means that all conditions are met. In the case of only one recipient a clear signature tying the donor and recipient together is necessary (i.e., fluorescent *in situ* hybridization (FISH) or DNA molecular analysis) [4].

In case of malignancy, a donor-transmitted cancer (DTC) was defined as present within the allograft at the time of transplantation and a donor-derived cancer (DDC) as developing within the donor cells following transplantation [5, 15].

RESULTS

From 1st January 2016 to 31st December 2022, 8,519 organ donors (5,995 organ donors from Germany, 2,524 donors from other European countries) donated 21,060 organs to 20,315 recipients. During this period, a total of 543 serious adverse events (SAEs) and serious adverse reactions (SARs) were recorded by the SAE/SAR team. In 418 (418/543, 77%) cases, the organ donation took place in Germany and in 125 cases (125/543, 23%) the organ donation took place in another European country and at least one recipient in Germany was transplanted.

365 of the reported cases (365/543, 67%) were classified as SAEs and 178 cases (178/543, 33%) as SARs. 336 reports were classified as pathogen/infection (336/543, 62%), 145 as suspected malignancy (145/543, 27%), 40 as other diseases (40/543, 7%), 11 as an immunologic disease (11/543, 2%), and 11 as a genetic disease (11/543, 2%) (**Table 1**).

In the pathogen/infection category, bacteria accounted for 169 cases (169/336, 50%), fungi for 114 cases (114/336, 34%), viruses for 48 cases (48/336, 14%), and parasites for five cases (5/336, 2%) (**Table 1**). In 68 of the 336 cases, more than one pathogen was found, resulting in a total of 412 pathogens (68/336, 20%).53 donors (53/8,519, 0.62%) transmitted a proven/ probable disease to 75 recipients (75/20,315, 0.37%). 17 of the 75 recipients with proven/probable transmitted disease died as a consequence (17/75; 23%) (**Table 1**).

The most common bacteria reported were *Staphylococcus* spp. (59 cases, including 16 methicillin-resistant *S. aureus* and 3 methicillin-resistant *S. epidermidis*) followed by *Klebsiella* spp. (25 cases, including 10 multidrug-resistant), *Enterococcus* spp. (21 cases, including 5 vancomycin-resistant *Enterococcus faecium*), *E. coli* (20 cases including 4 multidrug-resistant), *Acinetobacter* spp. (15 cases, including 10 multidrug-resistant), and *Pseudomonas* spp. (15 cases, including 4 multidrug-resistant). There were 7 reports with *Mycobacteria* (4 *Mycobacterium tuberculosis* and 3 *non-tuberculous Mycobacteria*). 67 of the recorded 209 bacteria (67/209, 32%) were multidrug resistant (MDR) pathogens (**Table 2**).

In 12 cases, bacteria were responsible for a proven/probable transmission of an infection: *Enterococcus faecium* (5 cases including 4 cases with vancomycin-resistant *E. faecium*), *Klebsiella pneumonia* (3 cases), *E. coli* (2 cases), *Streptococcus pneumonia* (1 case), and *Mycobacterium tuberculosis* (1 case). There were 20 recipients with clinical symptoms, but no fatal course (**Table 2**). In five recipients, the kidney needed to be removed because of a hemorrhage of the infected arterial anastomosis.

TABLE 1 | Different categories in all reported SAE/SAR cases.

	Total reports	P/P donors	Total recipients from P/P donors	Total recipients with transmission from P/P donors[a]	Total deaths from disease transmission[b]
Bacteria	169	12	43	20 (47%)	0 (0%)
Fungus	114	10	41	11 (27%)	2 (18%)
Virus	48	7	24	13 (54%)	3 (23%)
Parasite	5	1	4	1 (25%)	1 (100%)
Suspected Malignancy	145	16	43	22 (51%)	11 (50%)
Genetic	11	3	10	3 (30%)	0 (0%)
Immunologic	11	1	2	1 (50%)	0 (0%)
Others	40	3	11	4 (36%)	0 (0%)
Total	543	53	178	75 (42%)	17 (23%)

Abbreviation: P/P, proven/probable.

[a]*% = recipients with transmission/recipients from proven/probable (P/P) donors.*

[b]*% = death from disease transmission/total recipients with disease transmission.*

TABLE 2 | Summary of bacterial pathogens in all reported SAE/SAR cases.

Bacterial pathogen	All cases	MDR	Donor transmitted P/P	Recipients P/P	Death P/P
Staphylococcus spp.	59	19	0	0	0
Klebsiella spp.	25	10	3	6	0
Enterococcus spp.	21	5	5	10	0
E. coli	20	4	2	2	0
Acinetobacter spp.	15	10	0	0	0
Pseudomonas spp.	15	4	0	0	0
Mycobacteria	7	0	1	1	0
Other Bacteria	47	15	1	1	0
Total	209[a]	67	12	20	0

Abbreviation: spp., species; MDR, multi drug resistant; P/P, proven/probable.

[a]*In 40 cases more than one pathogen.*

In 10 cases, fungi (7 *Candida* spp., 2 *Aspergillus* spp., 1 *Cryptococcus*) were responsible for 10 proven/probable transmission to 11 recipients. Two of them died because of a hemorrhage of a mycotic aneurysm after kidney transplantation, in one additional case the kidney had to be removed. In all three cases *Candida albicans* was detectable at the renal allograft artery. In the case of the transmission of *Aspergillus fumigatus* one recipient developed an intracerebral aspergillosis and another recipient a pulmonary aspergillosis with the need of lobectomy (**Table 3**).

In 7 cases, proven/probable viruses were transmitted to 13 recipients, of which three died. There was one HCV transmission to five recipients, two HEV transmissions to two recipients, one HHV-6 transmission to one recipient (three-year-old child), one HHV-8 transmission to one recipient, and one Borna disease virus 1 (BoDV-1) transmission to three recipients. In the case of the BoDV-1 transmission, two recipients died, and one patient survived with neurological deficits. One recipient died after the transmission of HHV-8 virus from the donor (**Table 4**).

In one case, a parasite infection (*Toxoplasma gondii*) was transmitted to one recipient resulting in the death of the patient.

Of the 145 cases categorized as potential malignancy, 104 showed a malignant tumor after the final histopathological examination (104/145, 72%). 16 cases were classified as proven/probable transmission (16/104, 15%) to 22 recipients resulting in 11 deaths (11/22, 50%) (**Table 5**).

The mean time until the diagnosis was made in the 22 recipients was 6.3 months (0–36 months). The cases with the proven/probable malignancy transmission included three adenocarcinoma, two lymphoma, two melanoma, two renal cell carcinoma (RCC), two neuroendocrine lung cancer, two urothelial carcinoma, one angiosarcoma, one pleural mesothelioma, and one squamous cell carcinoma.

The most commonly reported malignant tumor was a RCC. RCC accounted for 43 of the 104 cases categorized as malignant (43/104, 41%), 16 of them were donor-derived with a mean time of 7.9 years after transplantation. In two cases a proven/probable transmission of the RCC to two recipients occurred. Also common were adenocarcinoma (11 cases, 3 donor-transmitted), urothelial carcinoma (9 cases, two donor-transmitted), lung cancer (8 cases, two donor-transmitted) and lymphoma (5 cases, two donor-transmitted) (**Table 5**).

Overall, in the 6 years from 2016 to 2022, 0.19% of the 8,519 donors (16/8,519, 0.19%) transmitted a proven/probable malignancy to 0.11% of all recipients (22/20,315, 0.11%).

There were three proven/probable transmissions of a genetic disease to three recipients: One catecholaminergic polymorphic ventricular tachycardia (CPVT) transmitted to the heart recipient, one hemochromatosis transmitted to the liver recipient, and one factor VII deficiency transmitted to the liver recipient. In the category of other diseases, one donor transmitted

TABLE 3 | Summary of fungal pathogens in all reported SAE/SAR cases.

Fungal pathogen	All cases	Donor transmitted P/P	Recipients P/P	Death P/P
Candida spp.	91	7	7	2
Aspergillus spp.	15	2	3	0
Mucor	3	0	0	0
Cryptococcus	2	1	1	0
Other	3	0	0	0
Total	114	10	11	2

Abbreviations: spp., species; P/P, proven/probable.

TABLE 4 | Summary of viral pathogens in all reported SAE/SAR cases.

Viral pathogen	All cases	Donor transmitted P/P	Recipients P/P	Death P/P
HBV	7	1	1	0
HCV	6	1	5	0
HEV	5	2	2	0
BoDV-1	1	1	3	2
HHV-6	1	1	1	0
HHV-8	1	1	1	1
Other	27	0	0	0
Total	48	7	13	3

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; BoDV-1, borna disease virus 1; HHV-6, human herpesvirus 6; HHV-8, human herpesvirus 8; P/P, proven/probable.

TABLE 5 | Summary of malignancies in all reported SAE/SAR cases.

Malignancy Type/ Location	All cases	Donor derived (DDC)	Donor transmitted P/P (DTC)	Total recipients from P/P donors	Total recipients with P/P Transmission[a]	Death from P/P Transmission[b]
RCC	43	16	2	5	2 (40%)	0 (0%)
Other malignancy	26	1	3	8	4 (50%)	3 (75%)
Adenocarcinoma	11	2	3	8	4 (50%)	3 (75%)
Urothelial carcinoma	9	6	2	8	2 (25%)	0 (0%)
Lung cancer	8	4	2	6	2 (33%)	1 (50%)
Lymphoma	5	0	2	5	4 (80%)	2 (50%)
Melanoma	2	0	2	4	4 (100%)	2 (50%)
Total	104	29	16	44	22 (50%)	11 (50%)

Abbreviations: DDC, donor-derived cancer; DTC, donor-transmitted cancer; RCC, renal cell carcinoma; P/P, proven/probable.
[a]*Recipients with transmission/all recipients from P/P donors.*
[b]*Death from P/P transmission/all recipients with P/P transmission.*

a membranous nephropathy to both kidney recipients, one donor transmitted a fibromuscular dysplasia to one recipient, and one donor transmitted a thrombotic microangiopathy to one recipient. Furthermore, one recipient developed an acute graft host versus disease after liver transplantation. None of these patients died.

DISCUSSION

In the 6 years from 2016 to 2022, donor-derived disease transmission occurred in 0.37% of all recipients (75/20,315; 0.37%). Compared to other risks of transplantation, such as 30-day mortality or delayed organ function, this risk can be considered relatively low. However, in the case of a proven/probable transmission of a disease to the recipient, the mortality is significant (overall 17/75, 23%), and in the case of a malignant tumor (11/22, 50%) [4, 5, 7, 16].

In the DTAC report on cases of potential donor disease transmission events (PDDTE) from 2008 to 2017, 15% of the cases resulted in a proven/probable transmission (335/2,185; 15%) [7]. In our series from 2016 to 2022, we had a rate of 10% proven/probable cases (53/543; 10%).

One explanation for this could be the relatively high proportion of SAE cases (365/543, 67%) in our series. For instance, our cases also included contaminated transportation fluid or antibiotic sensitive blood cultures in the donor. In most cases, there was no infection of the recipients attributable to the reported microorganisms. When the German V&S system was implemented, it was established to document all possible SAEs and SARs in order to learn if there is a clinical impact at all. For this reason, it is possible that our data reflect an overreporting of SAE cases with no relevance to the recipient.

Within these years we implemented, together with leading German transplant centers, a "white list" definition of which germs should be reported as SAE. On the other hand, omitting these cases may oversee possibly relevant information with clinical impact to the recipient. The guide to the quality and safety of organs for transplantation [10] and the European Framework for Evaluation of Organ Transplants project (EFRETOS) [11] published lists with detailed examples of various SAEs and SARs.

In the future, a more detailed evaluation of the different pathogens (multiresistant bacteria, fungi) and transmission routes (blood, broncho-alveolar lavage, transportation fluid) may potentially help to better assess the risks for transmission of an infectious disease from the donor to the recipient.

On the other hand, in all publications concerning SAEs and SARs, there is the potential problem of underreporting due to the fact that the reports are dependent on the donor hospitals or transplant centers providing information. Although it is mandatory to report potential SAEs or SARs to the DSO, it is not known exactly how many donor hospitals or transplant centers accomplish this task and adhere to the rule. In Germany (and in the other countries of the EU) there a no legal penalties in case of non-reporting of an SAE/SAR case. Audits of the entire organ procurement process chain including SAE/SAR reporting take place regularly at donor hospitals and transplant centers. However, a systematic monitoring process guaranteeing complete reporting of all SAEs/SARs occurring in the German hospitals and transplant centers is difficult to achieve, considering the almost 1,300 donor hospitals and more than 110 transplant programs in 46 transplant centers. Furthermore, if we compare the incidence of donor-transmitted cancer (DTC) to one or more recipients from our series (22/20,315; 0.11%) with the incidence of other cohorts (0.02%–0.06%) [5, 7, 16, 17] the result is not indicative of serious underreporting. The differences in rates of DTC could reflect a higher age of donors, existing co-morbidities, and a different reporting behavior of an active V&S system compared to a registry. Larger cohorts and longer follow-up times may still be needed [7]. At present, it seems that a combination of an active V&S system and a transplant registry at a national, or even better, at an international level could provide a better assessment of the risk for organ recipients [17].

Implementing an effective and reliable V&S system is essential in order to improve patient safety and transparency in the field of organ donation and transplantation. Different steps are necessary to reach this goal: the awareness of all parties for this topic where SAEs and SARs can occur, fast alert to the responsible institution (in Germany DSO), immediate information of the involved transplantation centers and donor hospitals, initiation of corrective and preventive measurements in the recipients, assessment of the clinical significance of SAEs or SARs, reporting to the medical community and, if appropriate, implementing new guidelines. For instance, recently, the Organ Process Chain Committee (OPCC) of Eurotransplant (ET) sent a letter to the national competent authorities including a list of microorganisms to be reported as SAEs or SARs when found in broncho-alveolar lavage (BAL) or transport fluids based on the German data reported [18]. In addition, patients on the waiting list can be better informed about possible risks of the organ transplantation. For this, all parties of a healthcare system have to be aware of the risk for SAE and SAR in organ donation and transplantation and feel responsible for reporting and sharing these cases. Although there is a legal obligation, there is no perfect "supervising" tool, yet.

At the same time V&S should not be used to punish a hospital when an SAE or a SAR has occurred. This is crucial for the acceptance of this alert system. A no-blame philosophy should lead the communication with all involved institutions and a constructive dialogue based on a partnership should be followed.

Taken together, the goal of an effective V&S system is to create a reliable and rapid alert system to all involved parties of the transplantation community, to assess the risk of transmission of infectious diseases or malignancy from organ donors to the recipients, to improve decision-making in terms of better risk evaluation of the donors, and to improve the safety of donation and transplantation of organs in general.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

KB, AB, and AR participated in study design, data analysis, writing and final approval and are accountable for the work.

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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All Expanded Criteria Donor Kidneys are Equal But are Some More Equal Than Others? A Population-Cohort Analysis of UK Transplant Registry Data

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Survival outcomes for kidney transplant candidates based on expanded criteria donor (ECD) kidney type is unknown. A retrospective cohort study was undertaken of prospectively collected registry data of all waitlisted kidney failure patients receiving dialysis in the United Kingdom. All patients listed for their first kidney-alone transplant between 2000–2019 were included. Treatment types included; living donor; standard criteria donor (SCD); ECD^{60} (deceased donor aged ≥60 years); ECD$^{50–59}$ (deceased donor aged 50–59 years with two from the following three; hypertension; raised creatinine and/or death from stroke) or remains on dialysis. The primary outcome was all-cause mortality, with time-to-death from listing analyzed using time-dependent non-proportional Cox regression models. The study cohort comprised 47,917 waitlisted kidney failure patients, of whom 34,558 (72.1%) received kidney transplantation. ECD kidneys (n = 7,356) were stratified as ECD^{60} (n = 7,009) or ECD$^{50–59}$ (n = 347). Compared to SCD, both ECD^{60} (Hazard Ratio 1.126, 95% CI 1.093–1.161) and ECD$^{50–59}$ (Hazard Ratio 1.228, 95% CI 1.113–1.356) kidney recipients have higher all-cause mortality. However, compared to dialysis, both ECD^{60} (Hazard Ratio 0.194, 95% CI 0.187–0.201) and ECD$^{50–59}$ (Hazard Ratio 0.218, 95% CI 0.197–0.241) kidney recipients have lower all-cause mortality. ECD kidneys, regardless of definition, provide equivalent and superior survival benefits in comparison to remaining waitlisted.

Keywords: expanded criteria donors, deceased donation, kidney transplant outcomes, epidemiology, ECD

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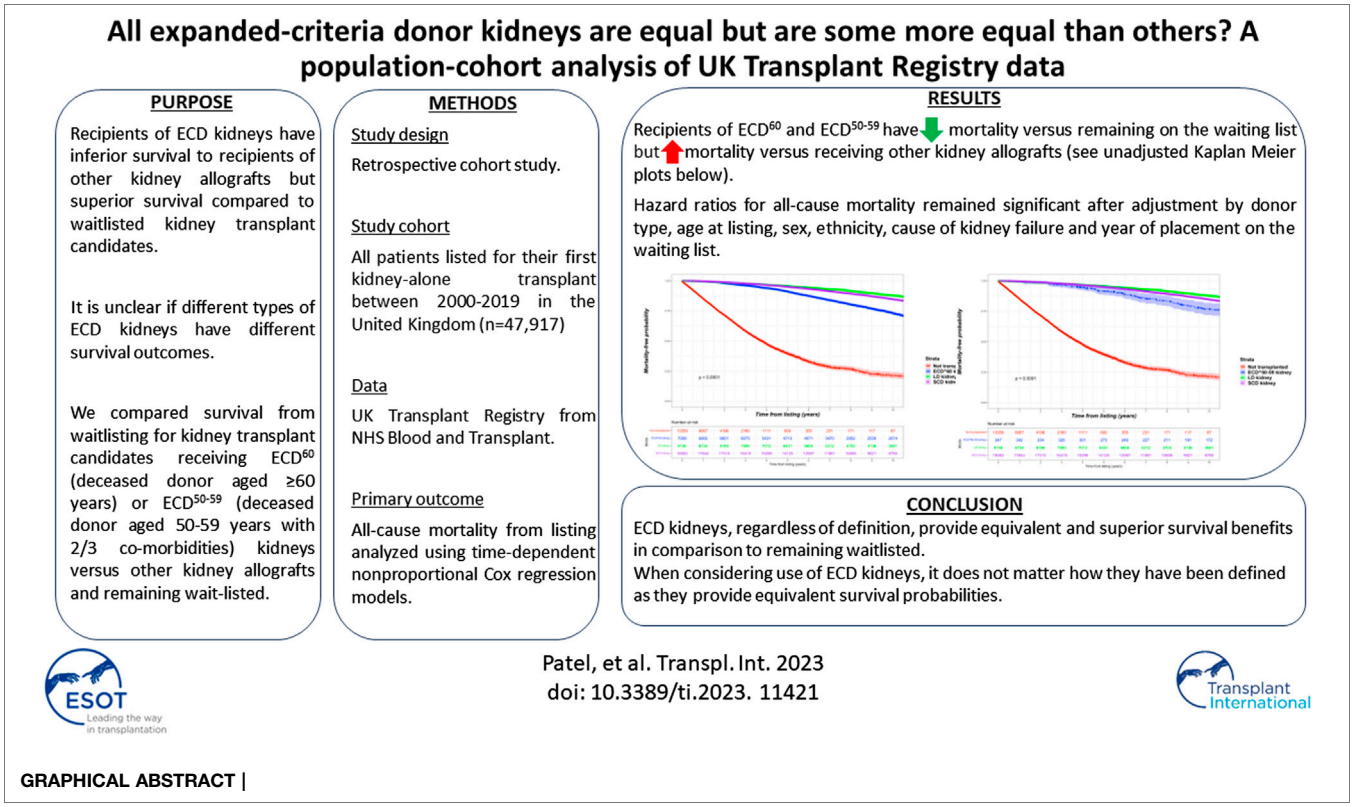

GRAPHICAL ABSTRACT |

INTRODUCTION

A broadening pool of donor kidneys are being utilized to bridge the gap between supply versus demand to facilitate more kidney transplantation. This includes expanded criteria donor (ECD) kidneys, which are defined based upon one of the following two conditions; either the deceased donor is aged ≥60 years or the deceased donor is aged between 50 and 59 years and fulfils any two of the following three criteria: 1) cause of death is cerebrovascular accident; 2) preexisting history of systemic hypertension; and 3) terminal serum creatinine >1.5 mg/dL (hereby referred to as ECD^{60} or ECD^{50-59}, respectively) [1]. Defined by historical data from the United States, ECD kidneys are associated with increased risk of graft failure compared with standard criteria donor (SCD) kidneys by 70% (relative hazard ratio 1.70) [2]. Although kidney donor profile index (KDPI) now provides transplant professionals with additional information, this basic stratification of SCD versus ECD kidney has been adopted in other countries including the United Kingdom in allocation of kidneys and counselling of patients.

Although studies confirm lower survival rates versus other kidney allografts, recipients of ECD kidneys have improved survival compared with waitlisted dialysis-treated patients. In a systematic review and meta-analysis of 48 published cohort studies, compared to remaining on dialysis any type of kidney allograft was superior from an all-cause mortality perspective and this included ECD kidney transplantation versus remaining waitlisted [3]. However, at present any potential kidney transplant candidate is counselled generically about the outcomes associated with ECD kidneys versus alternative options, with no differentiation made between different ECD kidney types. This is due to a lack of any comparative data comparing any patient and/or graft survival difference between the two ECD classifications. With ECD kidneys increasing as a proportion of all deceased donor kidneys, clarifying any survival difference between different types of ECD kidneys is important.

Therefore, the aim of this study was to compare survival for waitlisted kidney transplant candidates receiving ECD^{60} versus ECD^{50-59} kidney transplantation in comparison to other forms of kidney allografts or remaining on the waiting list.

MATERIALS AND METHODS

Study Cohort

A retrospective cohort study was undertaken of prospectively collected registry data related to all waitlisted kidney failure patients receiving dialysis in the United Kingdom. From 1 January 2000 until 30 September 2019 inclusive, all patients who were either listed and received their primary kidney-alone transplant versus those who were listed but never received a kidney transplant were included in the study. No formal sample size estimate was conducted as all eligible patient records were used. 31 December 2020 was considered the study end. The study is reported as per STROBE guidance [4].

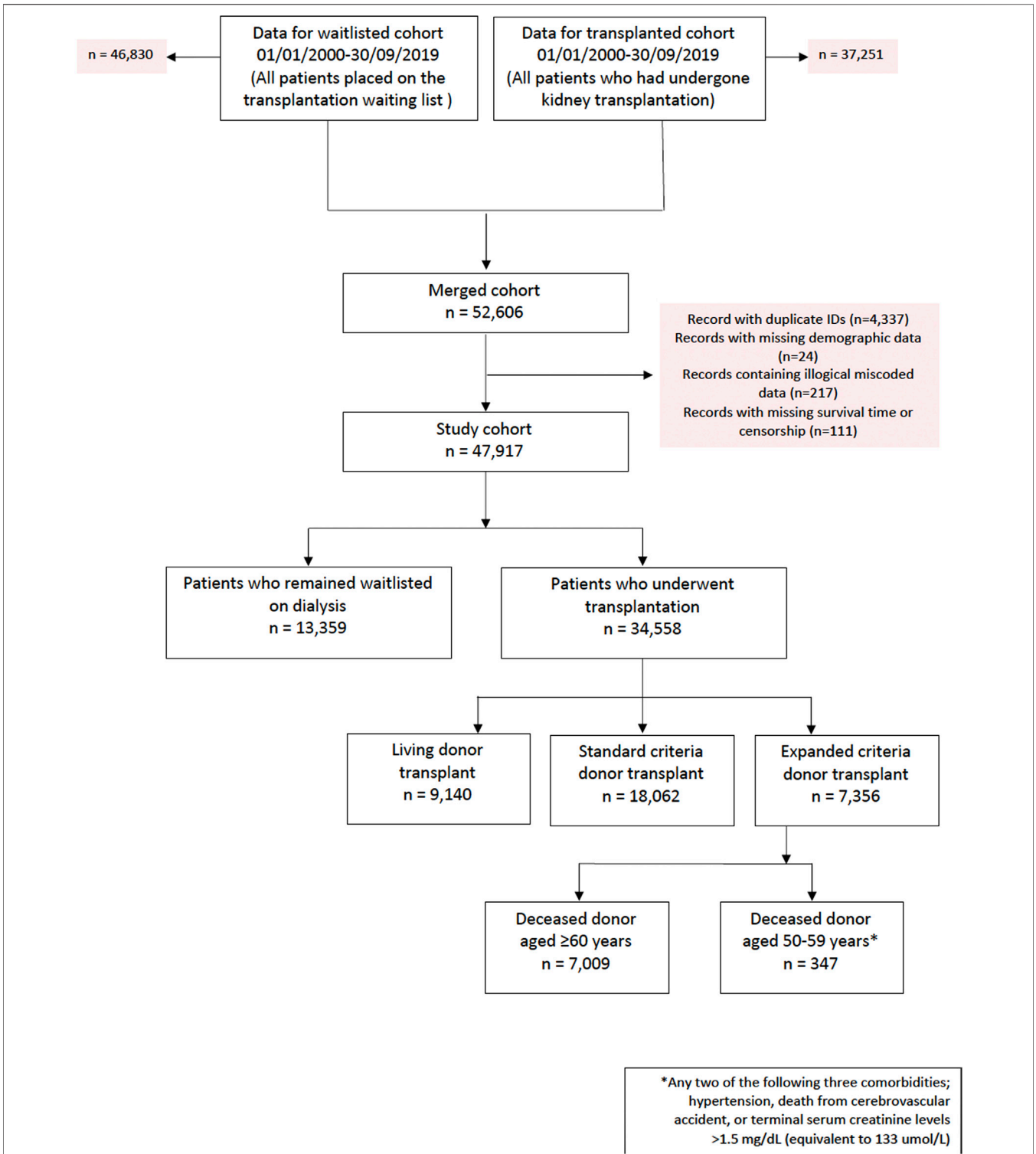

FIGURE 1 | PRISMA flowchart of study cohort.

Study Variables

The following study variables were available for all patients; age (at listing and at transplantation), sex, ethnicity [classified as white, black, Asian (Indo-Asian), other, known], primary cause of kidney failure (classified as diabetes, glomerulonephritis, hypertension, other separate, polycystic kidney disease, pyelonephritis/reflux nephropathy, unknown/missing), year of listing, and waiting time.

TABLE 1 | Baseline demographics of study cohort.

Variable		LD kidney	SCD kidney	ECD kidney	Dialysis	*p*-value
N		9,140	18,062	7,356	13,359	—
Median Age at waitlisting in years (IQR)		43 (23)	45 (19)	57 (15)	53 (21)	<0.001
Percentage (*n*) patients aged ≥60 years at listing		13.9% (1,271)	13.6% (2,461)	41.4% (2,046)	33.7% (4,408)	<0.001
Percentage (*n*) patients aged ≥65 years at listing		6.6% (605)	6.2% (1,120)	22.5% (1,653)	20.3% (2,708)	<0.001
Percentage (*n*) patients aged ≥70 years at listing		1.8% (167)	1.7% (299)	7.9% (580)	8.0% (1,069)	<0.001
Sex	Male	61.4% (5,611)	62.7% (11,326)	64.2% (4,719)	61.0% (8,143)	<0.001
	Female	38.6% (3,529)	37.3% (6,736)	35.8% (2,637)	39.0% (5,216)	
Ethnicity	White	82.6% (7,550)	75.3% (13,593)	75.2% (5,532)	71.6% (9,564)	<0.001
	Asian	8.8% (808)	13.4% (2,418)	13.5% (990)	15.5% (2,072)	
	Black	4.8% (436)	7.7% (1,383)	7.5% (554)	9.0% (1,198)	
	Other	2.8% (252)	2.7% (496)	3.0% (219)	3.1% (416)	
	Unknown	1.0% (94)	1.0% (172)	0.8% (61)	0.8% (109)	
Cause of kidney failure	Diabetes	7.2% (659)	7.5% (1,351)	12.3% (903)	27.6% (3,681)	<0.001
	Glomerulonephritis	6.6% (602)	6.8% (1,231)	6.3% (462)	3.8% (511)	
	Hypertension	4.7% (431)	5.3% (950)	6.7% (491)	4.7% (633)	
	Other Separate	31.8% (2,905)	27.2% (4,911)	24.7% (1,815)	20.9% (2,787)	
	Polycystic Kidney	8.9% (810)	11.5% (2,072)	12.4% (909)	6.3% (845)	
	Pyelonephritis/reflux	6.9% (629)	7.8% (1,411)	5.9% (431)	4.4% (592)	
	Unknown/Missing	34.0% (3,104)	34.0% (6,136)	31.9% (2,345)	32.3% (4,310)	

LD, living donor; SCD, standard criteria donor; ECD, expanded criteria donor; IQR, interquartile range.

Donor kidneys were stratified into living donors or any deceased donor (inclusive of donors after brain or circulatory death) further stratified into standard criteria donors (SCD), expanded criteria donor from deceased donors aged ≥60 years without comorbidities (ECD[60]) or expanded criteria donor from deceased donors aged between 50 and 59 years with two comorbidities among hypertension, death from cerebrovascular accident, or terminal serum creatinine levels >1.5 mg/dL (ECD[50–59]). The remaining waitlisted kidney transplant candidates did not proceed for transplantation and remained on dialysis.

Outcomes

The primary outcome of interest was all-cause mortality. The survival analysis was conducted according to the intention-to-treat principle; therefore, patients were not dropped from the analysis if they were removed from the waiting list or if transplantation subsequently failed. Secondary outcomes included death-censored graft loss.

Statistical Analysis

For baseline demographics, continuous variables were reported as medians and interquartile ranges (IQRs) and compared between groups using Mann-Whitney tests. Ordinal factors were also compared using Mann-Whitney tests, whilst nominal factors were analysed using Fisher's exact tests or Chi-square tests for those with two or more than two categories, respectively. Missing data underwent list-wise deletion.

Survival was analysed as time from initial placement on the waiting list to death, with data censored at loss of follow up or on 31 December 2020. Unadjusted survival-free probability was analysed by generation of Kaplan–Meier curves. After testing for violations of the proportional hazard assumption, time-to-death was modelled using non-proportional hazard Cox regression models with transplantation handled as a time-dependent covariate. Using this approach, all patients contribute data for time at risk (and death if it occurs) to the non-transplant group starting at study entry with those receiving a transplant switching time at risk (and death if it occurs) to the transplant group starting at the time of surgery (this forms the time-dependent transplant covariate in the model). Mortality hazard ratios were computed for the transplant recipients compared with those on the waiting list. We explored adjusted models factoring for age at listing, sex, ethnicity, cause of kidney failure and year of placement on the waiting list. An extended non-proportional hazard Cox regression model with both transplantation and graft loss handled as time-dependent variables was also included. Time to graft loss models were conducted using weighted Cox regression models and adjusted for age at listing, sex, ethnicity, cause of kidney failure, waiting time, year of placement of the waiting list, level of HLA mismatches, delayed graft function and 1-year rejection.

All analyses were done using R 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

Approvals

National Health Service Blood and Transplant (NHSBT) obtains informed consent from all patients undergoing solid organ transplantation in the United Kingdom for data collection and subsequent analyses. Study proposals are reviewed and approved by the kidney advisory group on behalf of NHSBT as IRB approval (ref: HD29035) before data dissemination.

RESULTS

Study Cohort

The original cohort obtained from NHSBT contained records from two datasets between 1 January, 2000 until 30 September, 2019; kidney failure patients listed who received a kidney

TABLE 2 | Characteristics of recipient receiving ECD kidneys.

Variable		All ECD kidney	$ECD^{50–59}$	ECD^{60}	*p*-value
Percentage (*n*)		100% (7,356)	4.7% (347)	95.3% (7,009)	—
Median Age at waitlisting in years (IQR)		57 (15)	49 (17)	58 (15)	<0.001
Median Age at transplantation in years (IQR)		60 (14)	53 (18)	60 (14)	<0.001
Sex	Male	64.2% (4,719)	65.4% (227)	64.1% (4,492)	0.614
	Female	35.8% (2,637)	34.6% (120)	35.9% (2,517)	
Ethnicity	White	75.2% (5,532)	71.% (247)	75.4% (5,285)	0.093
	Asian	13.5% (990)	14.4% (50)	13.4% (940)	
	Black	7.5% (554)	10.7% (37)	7.4% (517)	
	Other	3.0% (219)	2.3% 8)	3.0% (211)	
	Unknown	0.8% (61)	1.4% 5)	0.8% (56)	
Cause of kidney failure	Diabetes	12.3% (903)	7.5% (26)	12.5% (877)	0.008
	Glomerulonephritis	6.3% (462)	9.8% (34)	6.1% (428)	
	Hypertension	6.7% (491)	6.1% (21)	6.7% (470)	
	Other Separate	24.7% (1,815)	23.1% (80)	24.8% (1,735)	
	Polycystic Kidney	12.4% (909)	13.5% (47)	12.3% (862)	
	Pyelonephritis/reflux	5.9% (431)	7.8% (47)	5.8% (404)	
	Unknown/Missing	31.9% (2,345)	32.3% (112)	31.9% (2,233)	
Waiting time in days (IQR)		896 (988)	844 (1,128)	899 (978)	0.949

ECD, expanded criteria donor; IQR, interquartile range.

TABLE 3 | Non-proportional hazard Cox model of predictors for mortality after kidney transplantation with either dialysis or SCD as reference (fully adjusted model with transplantation handled as a time varying covariate).

Variable			HR (95% CI)	Variable		HR (95% CI)
$ECD^{50–59}$ kidneys	Treatment	Dialysis	1.000	Treatment	SCD	1.000
		$ECD^{50–59}$	**0.218 (0.197–0.241)**		$ECD^{50–59}$	**1.228 (1.113–1.356)**
		SCD	**0.177 (0.171–0.183)**		Dialysis	**5.644 (5.452–5.843)**
		LD	**0.145 (0.139–0.151)**		LD	**0.818 (0.790–0.848)**
ECD^{60} kidneys	Treatment	Dialysis	1.000	Treatment	SCD	1.000
		ECD^{60}	**0.194 (0.187–0.201)**		ECD^{60}	**1.126 (1.093–1.161)**
		SCD	**0.172 (0.166–0.178)**		Dialysis	**5.809 (5.615–6.008)**
		LD	**0.142 (0.137–0.149)**		LD	**0.827 (0.799–0.856)**

LD, living donor; SCD, standard criteria donor; ECD, expanded criteria donor; HR, hazard ratio; CI, confidence interval. Analysis adjusted by donor type, age at listing, sex, ethnicity, cause of kidney failure and year of placement on the waiting list.
Bold values indicate statistical significance.

transplant (n = 37,251) and kidney failure patients listed for transplantation (n = 46,830). After combining both datasets, duplicated records and/or cases with missing demographic data were excluded. This left 47,917 kidney failure patients to form our study cohort, of whom 34,558 (72.1%) subsequently received their first kidney transplant after waitlisting (living donors; n = 9,140, SCD; n = 18,062 and ECD; n = 7,356). From the deceased donor groups, 28.6% (n = 5,174) and 37.1% (n = 2,730) of SCD and ECD kidneys respectively were from donors after circulatory death. From the ECD recipient group, 7,009 were classified based upon donor aged ≥60 years (ECD^{60}) while 347 were classified based upon donor aged between 50–59 years and additional criteria met ($ECD^{50–59}$). This likely represents under ascertainment of $ECD^{50–59}$ kidney allografts: while data completeness for donor cause of death or age were excellent at 100%, data completeness was only 67.3% for donor creatinine, for example. As this is an integral aspect of our analysis, to account for this limitation we have performed sub-group analyses after removal of all missing creatinine values to ensure the primary findings are replicated. See **Figure 1** for the PRISMA flowchart of the study cohort.

Table 1 shows baseline demographics at the time of listing for the study cohort and identifies significant differences in baseline demographics between those that received different types of kidney allografts versus those that remained without transplantation. Most importantly, it confirms the significantly higher proportion of ECD kidneys allocated to older kidney transplant candidates. **Table 2** compares waitlisted kidney transplant candidates who received $ECD^{50–59}$ versus ECD^{60} kidneys. Kidney transplant candidates receiving $ECD^{50–59}$ versus ECD^{60} kidneys were younger (both at waitlisting and surgery) and had different causes of kidney failure.

Mortality Events

Overall, the kidney failure group that was listed but did not receive kidney transplantation had 4,003 deaths (42.8% of cohort) versus 6,695 deaths (24.0% of cohort) among the listed group that received kidney transplantation. For the transplant group, 1,127 deaths occurred after living donor transplantation

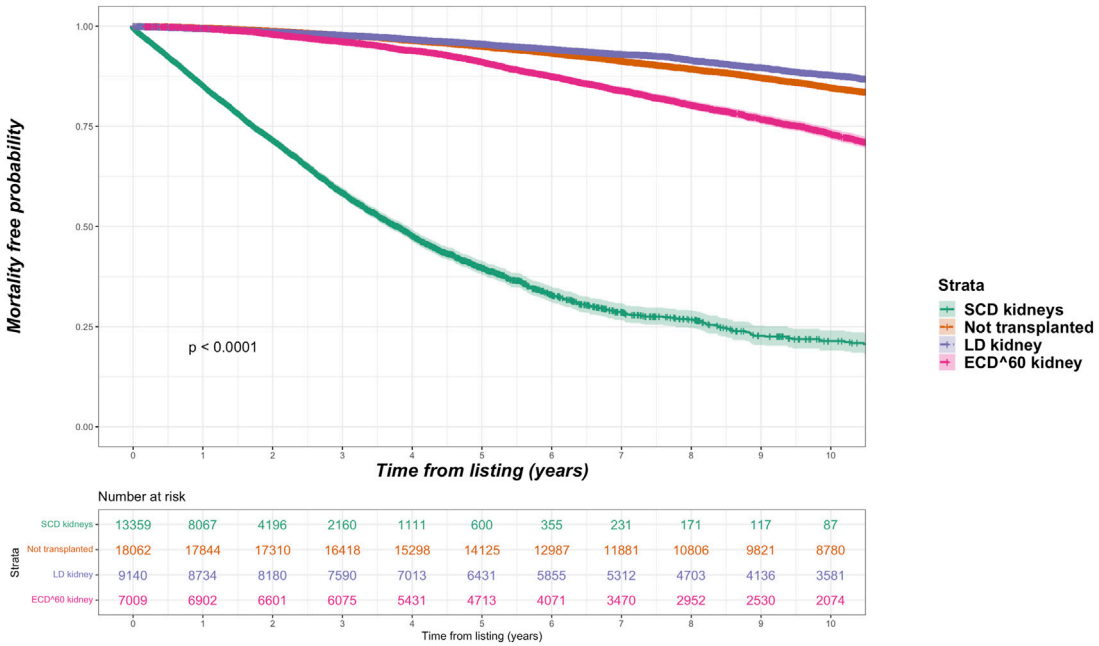

FIGURE 2 | Unadjusted Kaplan-Meir plot of mortality free survival comparing recipients of ECD^{60} kidneys versus all other kidney allografts versus remaining waitlisted on dialysis.

(14.1% of living donor cohort), 3,701 deaths after SCD transplantation (25.8% of SCD cohort) and 1,867 deaths after ECD transplantation (34.0% of ECD cohort). Among the ECD cohort, 103 deaths were in the ECD$^{50-59}$ cohort (4.7% of all deaths after ECD kidney transplantation) and 1,764 in the ECD^{60} cohort. The total period of follow up for the entire cohort was 349,964 patient-years, with median follow up after waitlisting of 5.8 years. Unadjusted Kaplan-Meir plots for mortality stratified by ECD^{60} or ECD$^{50-59}$ kidneys versus other treatment options are shown in **Figures 2**, **3**, respectively.

Unadjusted and Adjusted Graft Survival (Death-Censored) Using Weighted Cox Regression

Among the kidney transplant recipients (n = 34,375), there were a total of 6,893 (20.1%) death-censored graft losses over the follow up period. Graft losses stratified by donor type were living donor (n = 1,440, 15.8%), SCD (n = 3,658, 20.4%) and ECD (n = 1,795, 24.6%). Splitting ECD into the different classifications, graft losses occurred in 24.0% (n = 1,670) of ECD^{60} kidneys versus 36.2% (n = 125) of ECD$^{50-59}$ kidneys. Unadjusted Kaplan-Meir plots for death-censored graft loss stratified by ECD^{60} or ECD$^{50-59}$ kidneys versus other transplant treatment options are shown in **Figures 4**, **5**, respectively, with a comparison between the two ECD types shown in **Figure 6**.

In adjusted models, compared to receiving a SCD kidney, receiving any ECD kidney was associated with an increased risk for graft loss (HR 2.580, 95% CI 2.153–3.092, $p < 0.001$). After splitting ECD kidneys into the different classifications, compared to SCD kidneys both ECD^{60} kidneys (HR 2.638, 95% CI 2.202–3.161 $p < 0.001$) and ECD$^{50-59}$ kidneys (HR 1.836, 95% CI 1.179–2.859 $p = 0.007$) were associated with increased risk for graft loss. When compared to each other, ECD^{60} kidneys had equivalent risk for graft loss against ECD$^{50-59}$ kidneys (HR 0.905, 95% CI 0.597–1.373, $p = 0.640$).

Non-Proportional Hazards Cox Regression Model With Transplantation a Time-Dependent Covariate

In a non-proportional hazard Cox regression model using a time-dependent analysis, with transplantation handled as a time-dependent covariate, recipients of ECD^{60} kidneys had increased all-cause mortality compared to SCD kidneys (HR 1.126, 95% CI 1.093–1.161, $p < 0.001$) but lower all-cause mortality versus remaining on the waiting list (HR 0.194, 95% CI 0.187–0.201, $p < 0.001$) as per **Table 3**. Recipients of ECD$^{50-59}$ kidneys also had increased all-cause mortality compared to SCD kidneys (HR 1.228, 95% CI 1.113–1.356, $p < 0.001$) but lower all-cause mortality compared to remaining on the waiting list (HR 0.218, 95% CI 0.197–0.241, $p < 0.001$).

Non-Proportional Hazards Cox Regression Model With Both Transplantation and Graft Loss Time-Dependent Covariate

We conducted a non-proportional Cox regression analysis with both transplantation and graft loss factored as time-dependent covariates. In this extended model, compared to SCD kidney transplantation, both ECD^{60} (HR 1.102, 95% CI 1.084–1.120, $p < 0.001$) and ECD$^{50-59}$ (HR 1.201, 95% CI 1.139–1.266, $p < 0.001$)

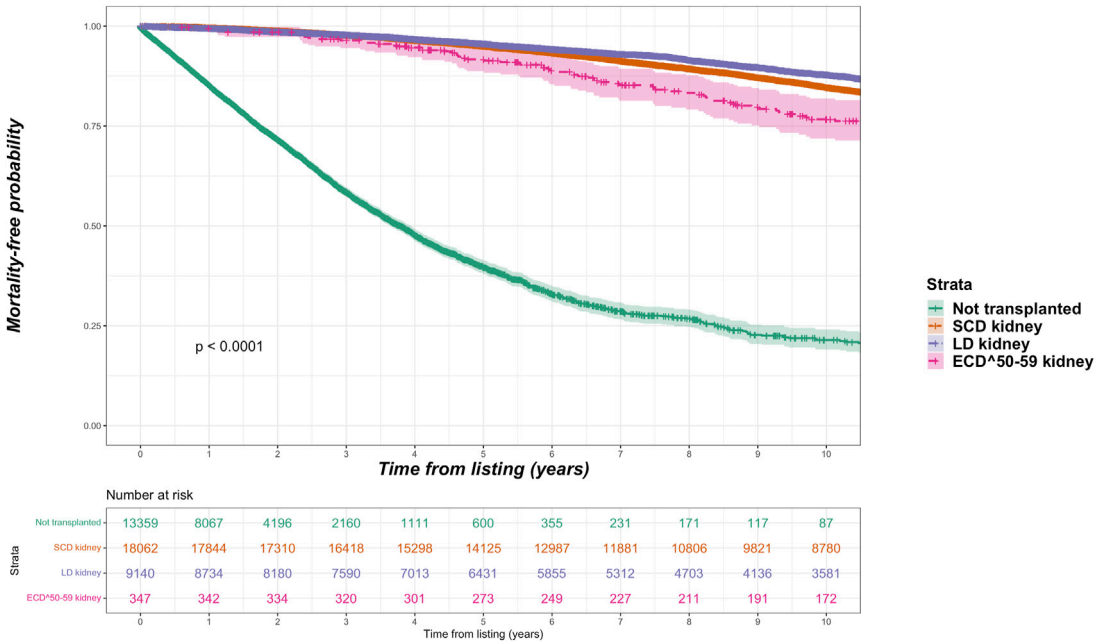

FIGURE 3 | Unadjusted Kaplan-Meir plot of mortality free survival comparing recipients of ECD$^{50–59}$ kidneys versus all other kidney allografts versus remaining waitlisted on dialysis.

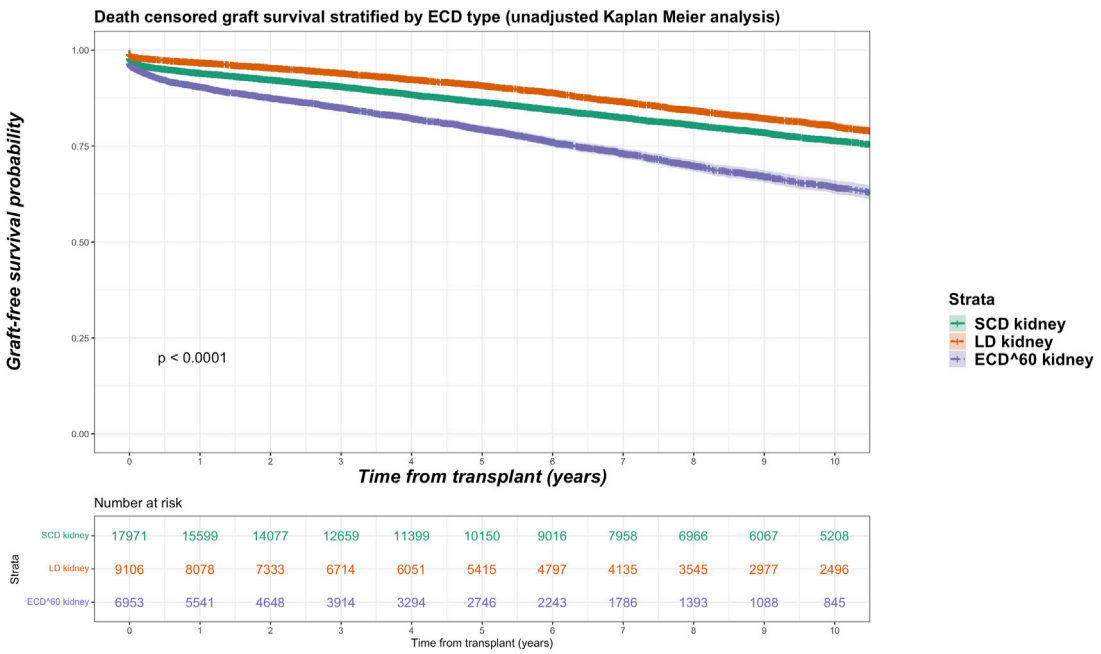

FIGURE 4 | Unadjusted Kaplan-Meir plot of graft loss free survival comparing recipients of ECD^{60} kidneys versus all other kidney allografts.

kidney recipients had increased risk for all-cause mortality, but lower all-cause mortality compared to remaining on dialysis (ECD^{60}: HR 0.198, 95% CI 0.192–0.204, $p < 0.001$ and ECD$^{50–59}$: HR 0.221, 95% CI 0.208–0.241, $p < 0.001$).

Sub-Analyses

In view of missing donor creatinine data, we undertook a sub-analysis excluding deceased donors with a missing donor creatinine to ensure no erroneous cross-over of ECD patients

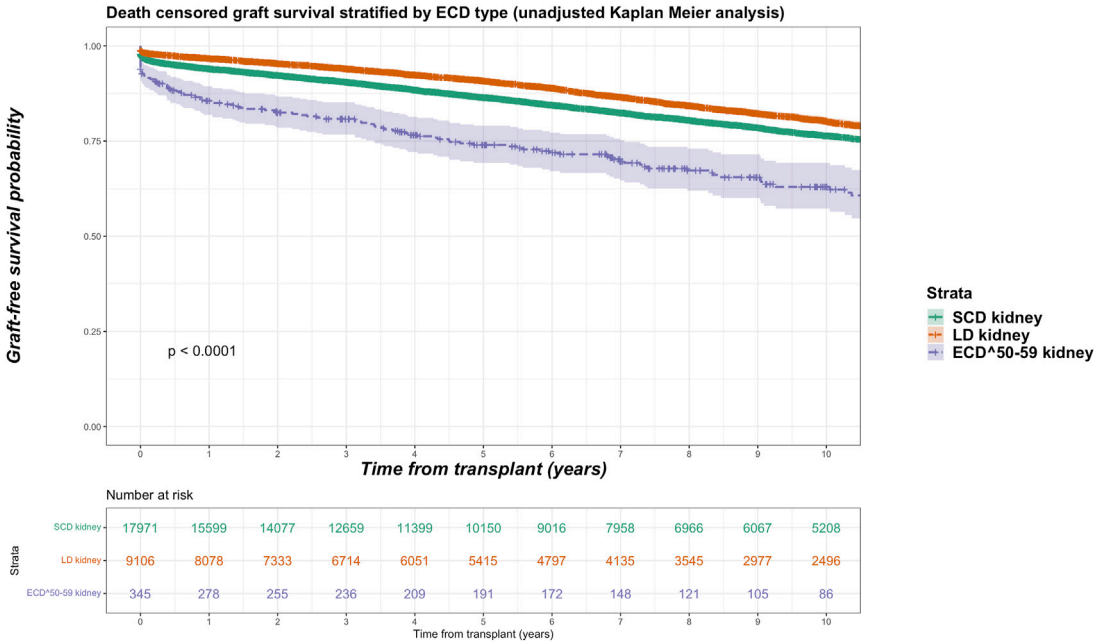

FIGURE 5 | Unadjusted Kaplan-Meier plot of graft loss free survival comparing recipients of $ECD^{50–59}$ kidneys versus all other kidney allografts.

as SCD patients (see **Supplementary Material**). No difference was observed from our primary analysis and we found no evidence that the results were skewed by missing donor creatinine data.

DISCUSSION

Since its emergence, ECD kidneys have been a valuable source of allografts to bridge the gap between supply versus demand for waitlisted kidney transplant candidates to proceed with transplantation versus remaining on dialysis. While ECD kidney transplantation generally provides survival benefits versus remaining on dialysis, no data exists to ascertain any difference in survival dependent upon which type of ECD kidney is implanted. To the best of our knowledge, this is the first analysis to investigate this in a population-cohort analysis and demonstrates the following important observations; 1) both ECD^{60} and $ECD^{50–59}$ kidneys demonstrate inferior patient and graft survival in comparison to SCD kidneys; 2) despite the inferior survival comparison to SCD kidneys, recipients of both ECD^{60} or $ECD^{50–59}$ kidneys have significantly lower all-cause mortality versus being waitlisted and never being transplanted, and; 3) there is no survival difference when comparing both ECD kidney allografts to each other.

The literature provides conflicting data with regards to survival benefits afforded by receiving ECD kidneys, especially among older kidney transplant candidates. The latter is important as our data confirms ECD kidney allocation is prioritized for older kidney transplant candidates to be the preferred recipient. A previous systematic review of published studies suggested ECD kidneys should be allocated for older (aged ≥40 years) kidney transplant candidates or those receiving their first allograft [5]. Prioritizing ECD kidneys for older recipients, by ignoring immunology-based allocation, has been a successful strategy implemented by the Eurotransplant Senior program and demonstrates favourable 5-year outcomes [6]. Our data are broadly consistent with these observations, showing survival benefit for ECD kidney transplantation versus remaining waitlisted independent of age. However, more recent study findings challenge this widely accepted opinion. Hellemans et al. [7] studied a Belgian cohort of 3,808 waitlisted kidney transplant candidates, of whom 3,382 subsequently received a deceased donor kidney transplant. Older recipients (aged ≥65 years) of ECD kidney transplants did not have a survival benefit when compared to remaining on dialysis in contrast to older recipients of SCD kidney transplants. All kidney transplant candidates had increased mortality risk post-operatively with subsequent survival benefit except for older recipients who received an ECD kidney transplant.

The outcomes from Hellemans et al. are surprising as previous studies suggest favorable all-cause mortality benefits from receiving ECD kidneys in European countries versus the United States. Querard et al. [8] conducted a systematic review and meta-analysis of 32 studies comparing survival outcomes between recipients of SCD versus ECD kidneys, with pooled 5-year patient survival probabilities 86.4% and 78.4%, respectively. A significant difference in mortality benefit was observed comparing European and North American studies, with 5-year pooled patient survival between SCD and ECD kidney recipients closer in European studies (90.3% and 85.3%, respectively) versus North American studies (83.6% and 73.4%, respectively). Despite this survival disparity, ECD kidney transplant outcomes remain favourable in the United States, where both Gill et al. [9] and Merion et al. [10] have observed prolonged time to survival benefits for recipients of ECD kidneys (especially among older and/or high-

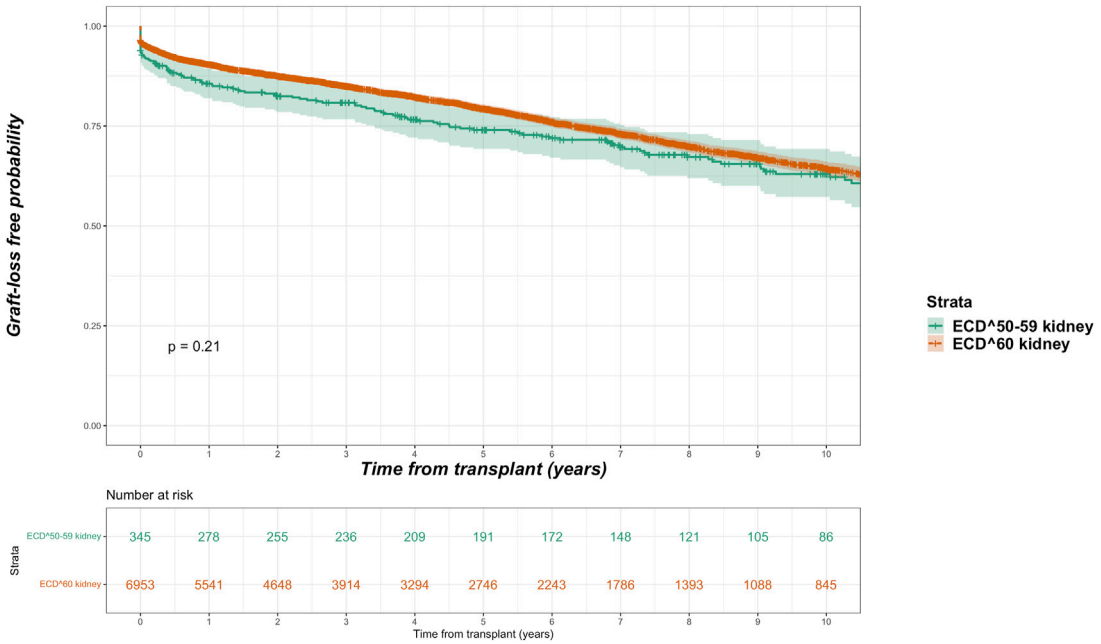

FIGURE 6 | Unadjusted Kaplan-Meir plot of graft loss free survival comparing recipients of ECD^{60} versus $ECD^{50–59}$ kidneys.

risk patients) but ultimate mortality advantage. Survival disparity may reflect differences in kidney failure survival, with high dialysis mortality observed in the United States skewing risk-versus-benefit ratios between the continents [11].

Considering the findings from Hellemans et al., our study is reassuring whilst providing new insights to the literature. This is important considering ECD kidneys now constitute over a third of deceased donor kidneys [12]. Our data confirms ECD kidneys, regardless of how they are defined, are a valuable source of deceased donor kidneys for waitlisted kidney transplant candidates. The survival difference between ECD^{60} and $ECD^{50–59}$ kidneys are negligible, especially when compared to remaining on the waiting-list. Our data also shows any survival benefit is independent of age at listing, which is important as many national organ offering systems prioritize ECD kidneys for older kidney transplant candidates and our results support this strategy regardless of ECD type. Both ECD kidneys are associated with increased risk for death-censored graft loss, as seen in our results and from published reports [8]. However, many studies do not factor graft loss as a time-dependent covariate in their post-transplant models for mortality. Our results are encouraging as they confirm, even with increased risk of graft loss, patient survival benefit from receiving an ECD kidney is clear. Regardless of these benefits, optimizing use of ECD kidneys for selected recipients may be prudent. For example, ECD kidney allograft survival may be improved in the absence of circulating donor-specific antibody ($p < 0.001$) and cold ischemic times <12 h ($p = 0.030$) according to a French study [13]. Optimal utilization of ECD kidneys may also be stratified by recipient age, with studies suggesting recipients aged ≥60 years [14] or ≥65 years [7] be prioritized. However, 10-year population-average effects using propensity scores suggest minimal absolute effect of only 8 months (95% CI 2–14 months) quicker time to graft failure attributed to ECD kidneys [7]. Therefore, the absolute risk difference between SCD and ECD kidneys in the long-term may be marginal when compared to remaining on the waiting-list.

One question our study cannot answer is whether a kidney transplant candidate should decline any ECD kidney and wait for a "better" deceased donor offer (e.g., a SCD kidney). Data from the United States shows the benefit of accepting "marginal" kidneys based upon specific recipient characteristics [15]. We suggest the certainty of outcomes associated with receiving an ECD kidney transplant, weighed against the uncertainty of outcomes regarding when an appropriate repeat deceased donor offer will emerge, must be carefully considered by any kidney transplant candidate. This is important as declined kidney offers are not benign events. Husain et al., in a cohort study analyzing 280,041 wait-listed kidney transplant candidates in the United States, observed approximately 30% of candidates receiving at least one deceased donor offer declined on their behalf eventually died or were removed from the waiting-list before receiving a kidney allograft [16]. Whilst data from the United Kingdom is more reassuring, with post organ decline deaths or removal from the waiting list occurring in 4% and 12% of kidney transplant candidates after 1-year or 5-year, respectively [17], there is no guarantee that declining a kidney allograft in the hope for a "better" kidney will be successful or facilitate timely transplantation. We believe that despite the survival differences observed in our analyses between SCD and any ECD kidney, our data should provide reassurance to kidney transplant candidates offered ECD kidneys. This is because those being offered an ECD kidney do not have a choice between an ECD versus a SCD kidney; their choice is between kidney transplantation versus no kidney transplantation. We believe this is the fundamental choice that kidney transplant candidates must consider, especially older candidates who are primed through national organ allocation algorithms to be prioritized for ECD kidney

offers. Considering the excess morbidity, mortality and costs related to dialysis therapies, limited financial resources from healthcare providers should focus on maximizing usage of all donated organs to avoid wastage of "marginal" organs which current evidence suggest provides a survival benefit to most (if not all) waitlisted kidney transplant candidates.

Our study benefits from being a contemporary analysis of a national population-cohort, compatible with the modern era of organ donation and kidney transplantation. The limitations of this study must be appreciated for accurate interpretation of the results. Missing donor-related data (e.g., terminal creatinine) means some deceased-donors may have been erroneously coded as SCD rather than ECD$^{50-59}$ kidneys, leading to an under-estimate. This must be interpreted as a significant limitation of this analysis, with the potential to skew results erroneously as donor creatinine is one of the three classification criteria for an ECD kidney. Future studies must aim to minimise such missing data for robustness. While acknowledging this limitation, we have undertaken additional sub-analyses to provide some validation of our primary findings but this limitation regarding missing data must be appreciated when interpreting our results. As an intention-to-treat analysis, we did not factor for waitlisted kidney failure patients who were suspended or removed from the waiting list due to lack of fitness. Censoring patients at delisting would have yielded an overestimation of survival on dialysis as data from the United Kingdom confirms increased mortality associated for waitlisted kidney failure patients who experience any period of suspension [18]. This analysis comprised waitlisted kidney transplant candidates who either had their primary transplant or remained on dialysis; therefore it provides no targeted evidence in the setting of advanced chronic kidney disease or a failed kidney transplant exploring repeat transplantation. Lack of data relating to medical co-morbidities limits interpretation of survival probabilities in the setting of specific health burdens, which may tip the balance of more borderline risk versus benefit calculations for older candidates and ECD kidneys. This is a critically important limitation that should be overcome for future analyses. The binary use of ECD kidneys is a crude distinction. While still utilized, the use of Kidney Donor Profile Indexes in the United States since 2014 is common but may not be directly translatable to European cohorts [19]. Finally, this analysis has focused solely upon survival benefits associated with transplant surgery for kidney failure patients and overlooks the importance of quality of life which was beyond the scope of this study but is under investigation elsewhere [20].

To conclude, in this contemporary national cohort study of kidney failure patients listed for transplantation, proceeding with any type of ECD kidney transplant affords a survival benefit to kidney transplant candidates versus remaining on dialysis. Although associated with increased mortality compared to recipients of other kidney allografts, which is an important consideration for waitlisted candidates with realistic chances for a timely SCD or living donor transplant, ECD kidneys for the majority offers a valuable opportunity of kidney transplantation. While our data is reassuring, the caveat remains that survival benefits at a population-level must be translated to individual kidney transplant candidates with personalized risk counselling. Further analyses would be beneficial to provide more nuanced survival probability investigations in the context of medical co-morbidities. However, our data should provide reassurance to clinicians involved in the care of kidney failure patients that kidney transplantation using ECD kidneys provides an excellent opportunity to improve survival probabilities.

DATA AVAILABILITY STATEMENT

Data for this analysis was acquired from the UK transplant registry, which is accessible upon reasonable request.

ETHICS STATEMENT

This was an approved registry analysis so no formal approval required.

AUTHOR CONTRIBUTIONS

Substantial contribution to concept: KP, AB, DC, TN, DD, and AS. Substantial contribution to design: KP, AB, and AS. Substantial contribution to analysis: DC and FE. Substantial contribution to interpretation: FE, TN, DD, and AS. Drafting of work: KP, AB, and AS. Final approval: KP, AB, DC, FE, TN, DD, and AS. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

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

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2023.11421/full#supplementary-material

Supplementray Figure S1 | Unadjusted Kaplan-Meir plot of mortality free survival comparing recipients of ECD50-59 kidneys versus all other kidney allografts versus remaining waitlisted on dialysis (missing donor creatinines excluded).

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