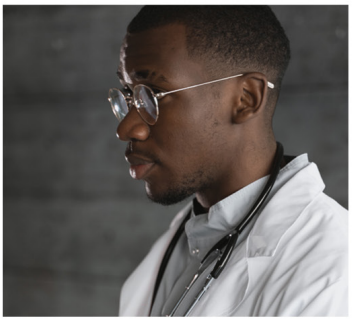
ESOT

Volume 35 | Issue 8
August 2022

Transplant International









Diversity, equity and inclusion in transplantation

Transplant International

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Transplant International

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ESOT

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ISSN 1432-2277
ISBN 978-2-8325-5272-8
DOI 10.3389/978-2-8325-5272-8

Transplant International

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TRANSPLANT TRIAL WATCH
published: 01 August 2022
doi: 10.3389/ti.2022.10706

Transplant Trial Watch

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Keywords: liver transplantation, paediatric, systematic review, donor management, brain dead donors, randomised controlled trial

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

SYSTEMATIC REVIEW

Liver Transplantation for Pediatric Hepatocellular Carcinoma: A Systematic Review.

by Kakos, C. D., et al. Cancers (2022); 14(5): 02.

Aims

This study aimed to summarise all available evidence on the clinicopathological characteristics and oncological outcomes following liver transplantation (LT) among pediatric hepatocellular carcinoma (HCC) patients.

Interventions

Electronic databases including MEDLINE, Scopus, Cochrane Library, and Web of Science were searched. Studies were screened and data were extracted by two independent reviewers.

Participants

67 Studies were included in the review.

Outcomes

The main outcomes were overall survival, disease-free survival and posttransplant complications.

Follow-Up

5 years.

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Received: *15 June 2022*
Accepted: *23 June 2022*
Published: *01 August 2022*

Citation:
Knight SR (2022) Transplant Trial Watch. Transpl Int 35:10706. doi: 10.3389/ti.2022.10706

CET Conclusion
This is a well-written report of a well-conducted systematic review in paediatric liver transplantation. Multiple databases were searched, and studies and data were extracted by two reviewers in duplicate. Sixty-seven studies reporting 245 patients in total were included from many different countries worldwide, published between 1985 and 2020. Each included study may have had only a few patients, range 1–25, with most studies reporting 1–2 patients only. The authors provide a general comment about the quality of included studies, and it would have been better to see individual studies formally quality assessed and possibly stratified for quality or by era of treatment. At mean follow up of 38.6 months, tumour recurrence was reported in 16.2% of patients, most commonly in the lungs and liver. 5-year disease free survival was 84.5%. At mean follow up of 46.8 months, overall survival was 84.8%, with tumour recurrence being the most common cause and this fits with the expected rate of tumour recurrence. 5-year overall survival was 74.3%. Liver transplantation to treat HCC in children offers long-term survival, and grafts from live donors showed a significant improvement compared to deceased donor grafts.

Trial Registration
www.researchregistry.com (reviewregistry1310).

Funding Source
No funding received.

RANDOMISED CONTROLLED TRIAL

Hemodynamic Effects of High-Dose Levothyroxine and Methylprednisolone in Brain-Dead Potential Organ Donors.

by Van Bakel, A. B., et al. Transplantation (2022) [published ahead of print].

Aims
The aim of this study was to examine whether high-dose levothyroxine, high-dose methylprednisolone, or a combination of the two hormones, when administered early in the course of donor management, would lead to improvements in donor hemodynamics, allowing significant reduction in vasopressor support.

Interventions
Participants were randomly assigned to receive high-dose levothyroxine, high-dose methylprednisolone, a combination of both, or no hormonal therapy (control).

Participants
199 Consecutive adult organ donors.

Outcomes
The primary outcome was the difference in vasopressor requirement to maintain goal hemodynamics among the four treatment groups. Secondary mechanistic outcomes included the assessment of thyroid hormone (TH) levels, cortisol levels and markers of inflammation (C-reactive protein [CRP] and multiple cytokines). Secondary clinical outcomes were the number, types, and proportion of organs procured versus consented, rate of transplantation of procured organs, and patient and graft outcomes of organ recipients exposed to the various treatments.

Follow-Up
120 days.

Jadad Score
3.

Data Analysis
Available case analysis.

Allocation Concealment
No.

Trial Registration
ClinicalTrials.gov—NCT04528797.

Funding Source
Non-industry funded.

CLINICAL IMPACT SUMMARY

The haemodynamic instability seen in many brain dead (DBD) donors is thought in part to result from disruption in the hypothalamo-pituitary axis, resulting in reduced levels of thyroid hormone and vasopressin [1]. For this reason, donor management often includes supplementation of thyroid hormones and vasopressin, and use of corticosteroids. Existing evidence as to the benefits of hormone replacement in the DBD donor is conflicting, with potential benefits of thyroid hormone and desmopressin administration seen in observational registry studies not borne out in prospective randomised controlled trials [2, 3].

In a recent issue of Transplantation, Van Bakel et al. report the results of a prospective randomised controlled trial of donor management in 199 brain-dead organ donors [4]. Donors were randomised to four groups: high-dose levothyroxine, high-dose methylprednisolone, combination therapy and no hormonal therapy. Vasopressor requirements were assessed using a

validated score (the vasoactive-inotropic score; VIS). The reduction in VIS from baseline was significant in the methylprednisolone and combination groups, but no improvement was seen in the levothyroxine alone or control groups.

Unlike many donor intervention studies, the investigators were careful to report organ utilisation and graft outcomes for all groups. No differences were found between groups, although the study was not powered for these outcomes.

Of note, the study was not blinded and this may have contributed to significant crossover from other arms to the combination arm and possibly impacted inotrope use. However, the findings above were confirmed in both intent-to-treat and per-protocol analyses.

Overall, these results support the existing RCT evidence that thyroid hormone replacement alone does not improve cardiovascular stability in DBD donors, and that the largest impact on stability comes from corticosteroid use.

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

SK has received consultancy fees from OrganOx Ltd., for research design in the past.

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EDITORIAL
published: 24 August 2022
doi: 10.3389/ti.2022.10781

Editorial: Equity in Transplantation: A Commitment for Progress in Troubled Times

Thierry Berney[1,2], Ifeoma I. Ulasi[1,3,4], Chloë Balleste[5,6], Paulo N. Martins[7], Maria Irene Bellini[1,8], Hannah A. Valantine[9] and Luciano Potena[10]*

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Keywords: diversity and inclusion, equity, discrimination, gender equality, ethnicity, transplantation

In the last few months, we have witnessed a series of events jeopardizing basic human rights in parts of the world that used to stand for them. In one of the world's oldest democracies, essential woman's rights, basic aspirations of the LGBT community, voting rights of underprivileged populations, and the right to equitable healthcare are being suppressed or grossly challenged. As the world attempts to recover from the disarray brought by the COVID 19 pandemic, nationalist parties targeting migrants and other minorities as scapegoats, are increasingly entering the parliaments and governments of countries with democratic traditions. As the Ukraine-Russia conflict roars in the heart of Europe, 20 more countries are experiencing significant civil wars, terrorist insurgencies, or ethnic violence (1). According to the World Bank, more than 50% of the population lives below the poverty line in 19 countries and some of the wealthiest western economies have more than 15% meeting the poverty criteria (2). We are experiencing worldwide a worrisome increase in attacks and discrimination based on gender, race, ethnicity, sexual orientation, gender identity, nationality, religion, education, and other features of diversity that characterize a human being.

Transplantation is a therapeutic strategy founded on an altruistic gift. In this troublesome context we, who are involved in transplantation, have more than ever an urgent and specific duty to safeguard the value of this gift by acting to ensure equity in the delivery of care, preserve the value of diversity and inclusion, and remove the biases that limit access to transplantation.

At Transplant International, we firmly believe that diversity is the essence of humankind and inclusion is the engine that drives and sustains the quality of our work. Whether from the transplant patient or the transplant professional standpoint, we believe that equal access to healthcare, as well as to professional development and academic career are self-evident rights, and that ensuring the implementation of these principles is the duty and responsibility of the leaders in the relative microcosm that is transplantation.

From the patient perspective, the issues to tackle are manifold and were highlighted in the call to action launched by ESOT on the occasion of its 40th anniversary (3). As a few examples among many: conditions, such as diabetes, obesity, and hepatitis B/C, are more prevalent in certain racial and ethnic groups, which negatively impacts donation and transplantation rates in disproportionately high numbers (4); patients with higher income and education have greater access to transplantation (5); immigrants face barriers in access to transplant services, including lower awareness and a lack of full healthcare coverage (6); women donate more organs than they receive, while men making up the majority of organ transplant recipients, in particular, because of psychological and socio-economic factors (7); there are significant regional and national variations in the number of transplants performed. In many countries, transplant centers are not evenly distributed, in favor of wealthier areas. This is even

Editorial

OPEN ACCESS

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Received: *20 July 2022*
Accepted: *22 July 2022*
Published: *24 August 2022*

Citation:
Berney T, Ulasi II, Balleste C, Martins PN, Bellini MI, Valantine HA and Potena L (2022) Editorial: Equity in Transplantation: A Commitment for Progress in Troubled Times. Transpl Int 35:10781. doi: 10.3389/ti.2022.10781

more critical in emerging economies, let alone least developed countries, where access to transplantation is often non-existing.

The devil can sometimes hide in the details. A universal and easy measure of kidney function, the eGFR (estimated glomerular filtration rate) has been calculated for decades with a modifier for "black people," introducing in effect a bias leading to systemic underestimation of kidney disease severity in black patients and delaying their access to kidney transplantation (8). The board of directors of the US Organ Procurement and Transplantation Network (OPTN) has very recently (June 2022) abolished the modifier for black people in the calculation of eGFR, in a commendable effort to remove one of the obstacles to timely kidney transplantation in a population disproportionately affected by end-stage kidney disease (8). This specific issue will be reviewed in more detail in Transplant International in the near future.

Regarding professional careers, the field of transplantation does not fare any better than other fields in medicine and medical sciences. A recent survey revealed alarmingly high rates of ethnic and gender disparity, lack of mentorship, and very low rates of female leadership in the liver transplantation field (9); in terms of first and senior authorship, gender disparity has improved over the past 20 years, but is still blatantly obvious (10); finally, the editorial boards of journals, including in the field of transplantation, still have gross imbalances in their compositions in terms of gender and ethnic equity (11-13).

As stated in the Transplant International website, "we value engagement and inclusion at all stages of science communication and dissemination, from the submission of research manuscripts, through the editorial and review process and on to publication." The gender-balanced editorial board (14) "welcomes submissions from applicants of all ethnicities, nationalities, religions, gender identities, sexual orientations or other individual status, and are committed to eliminating the influence of any bias in our processes." To bring this commitment further, and following the call for action launched at the opening ceremony of the 2021 ESOT congress in Milan and the mandate of the ESOT Action Day announced at the celebration of ESOT 40th anniversary (3), Transplant International is pleased to announce the launching of a Special issue on "Diversity, Equity and Inclusion in Transplantation" (15).

The scope of this issue is not only to highlight the problems currently limiting inclusion and equity in transplantation, but to propose evidence-based solutions, that could guide changes in policies and practices. We encourage all members of the transplantation community to show their commitment to this far-reaching cause and contribute to this endeavour.

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

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

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FORUM
published: 05 August 2022
doi: 10.3389/ti.2022.10590

Comments on: Differential IgG4-Producing Plasma Cell Infiltration in Non- and Post-Transplant Plasma Cell Hepatitis

Isabel Aguilera[1]* *and Jose Manuel Sousa*[2]

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Keywords: IgG4, PC-rich R, GSTT1, liver transplant, plasma cells

A Forum discussing:

Differential IgG4-Producing Plasma Cell Infiltration in Non- and Post-Transplant Plasma Cell Hepatitis
by Horwich BH, Liang TZ, Dodge JL, Chopra S, Kahn JA and Saito T (2022). Transpl Int 35:10182. doi: 10.3389/ti.2022.10182

We read with interest the article by Horwich et al. about IgG4-producing plasma cells. The aim of the study was to use IgG4-positivity as a differential biomarker for distinct clinical presentations of plasma cell hepatitis before and after liver transplantation. They found a high degree of IgG4-PC infiltration more frequently associated with plasma cell rejection (PCR) than other types of AIH and concluded that IgG4-positivity might serve as a valuable diagnostic tool in the post-LT setting.

It is very gratifying to see a confirmation of our previous report regarding the presence of IgG4 PCs in plasma cell-rich rejection (PC-rich R) biopsies. Our group identified the cellular profile associated with PC-rich R, and quantified the number of cells per mm^2 of tissue by using a Computer-Assisted System Technology (newCAST™). The relative proportion of the main cell types was assessed. The results showed an important representation of $IgG4^+$ PCs with a mean value of 5.9% (0.5%–19.8%) of the total number of immune cells in the inflammatory infiltrates found in portal areas (1).

A search in the scientific literature is complicated since *de novo* autoimmune hepatitis, first described in 1998 (2), has received many different names throughout these years until, in a recent update, the Banff Working group recommended to replace all these terms by "plasma cell-rich rejection" (PC-rich R) (3). We agree with the authors that AIH and PC-rich R are histologically very difficult to distinguish but fortunately, we have now a very specific serology pattern.

PC-rich R is a true rejection process that starts with the recognition of a donor antigen expressed in the graft by the recipient immune system. This is due to a genetic mismatch when the recipient lacks any copy of the Glutathione S-transferase T1 (GSTT1) gene and the donor carries at least one copy of this gene (4–6). Some of these mismatched patients develop a specific immune response by producing GSTT1 donor-specific antibodies, which is a required but not sufficient condition to develop PC-rich R. We have characterized anti-GSTT1 antibodies and the predominant IgG subclasses were IgG1 and IgG4 (7). Interestingly, IgG4 appear again involved in PC-rich R, this time as donor-specific antibodies.

It is clear that rAIH and PC-rich R represent distinctive clinical entities. The results presented in the article by Horwich et al. and the knowledge of the GSTT1 genetic mismatch with subsequent

Forum

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***Received:** 22 April 2022*
***Accepted:** 21 June 2022*
***Published:** 05 August 2022*

Citation:
Aguilera I and Sousa JM (2022) Comments on: Differential IgG4-Producing Plasma Cell Infiltration in Non- and Post-Transplant Plasma Cell Hepatitis. Transpl Int 35:10590. doi: 10.3389/ti.2022.10590

production of anti-GSTT1 antibodies (especially IgG4) should facilitate differential diagnoses between PC-rich R and other inflammatory post-transplant pathologies that have been particularly difficult when pre-LT disease was uncertain as mentioned by the authors.

AUTHOR CONTRIBUTIONS

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

FUNDING

This study was supported by FEDER funds and by the Spanish Ministry of Economy, Instituto de Salud Carlos III, Grant 17/01403.

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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FORUM
published: 05 August 2022
doi: 10.3389/ti.2022.10679

Reply to: Comments on: Differential IgG4-Producing Plasma Cell Infiltration in Non- and Post-Transplant Plasma Cell Hepatitis

*Brian Harris Horwich, Jeffrey A. Kahn and Takeshi Saito**

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Keywords: IgG4, rejection, alloimmunity, autoimmunity, plasma cell hepatitis

A Forum discussing:

Comments on: Differential IgG4-Producing Plasma Cell Infiltration in Non- and Post-Transplant Plasma Cell Hepatitis
by Aguilera I and Sousa JM (2022). Transpl Int 35:10590. doi: 10.3389/ti.2022.10590

We would like to thank Drs. Aguilera and Sousa for their thoughtful commentary on our recent publication "*Differential IgG4-Producing Plasma Cell Infiltration in Non- and Post-Transplant Plasma Cell Hepatitis*." In particular, we would like to thank the authors for calling their important work to our attention.

Their identification of Glutathione S-transferase T1 (GSTT1) gene mismatch between donor and recipient, specifically Donor (−)/Recipient (+), as a potential predictor for developing plasma cell-rich rejection (PCR) was a critical breakthrough in this field. Additionally, their work also suggests that serologic evaluation of anti-GSTT1 antibodies may be a useful marker in PCR diagnosis and disease response to corticosteroid therapy (1). It is satisfying that the findings from our histopathologic assessment of post-transplant plasma cell hepatitis correlates with their observations (2).

As the authors' mentioned, the findings of our study and their prior work may be of particular clinical relevance in the evaluation of patients for whom a pre-liver transplantation (LT) diagnosis was not established (i.e., those in fulminant liver failure of unknown etiology). The current diagnostic algorithm does not provide adequate guidance with unclear pre-LT diagnosis, reflecting the fact that it is entirely clinical context-based, but not immuno-pathobiology-based diagnosis (3). Accordingly, the roles of Immunoglobulin subclass 4 (IgG4) immunostaining and serologic antibody testing are not well-established in differentiating PCR from recurrent autoimmune hepatitis (rAIH). This is despite prior literature demonstrating that PCR is not a immunologically homogenous entity by its current definition (4).

Consequently, our studies suggest a potential complementary approach to the evaluation of these individuals. One possible diagnostic algorithm could be evaluating the IgG4 Positivity by immunohistochemistry in combination with anti-GSTT1 antibody serologic testing. Based on the findings of our studies, high IgG4 Positivity and elevated anti-GSTT1 antibodies would be highly suggestive of PCR. Conversely, low IgG4 Positivity and absent anti-GSTT1 antibodies may be confer a diagnosis of rAIH. A study in which IgG4 Positivity and anti-GSTT1 antibodies are

Forum

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Received: *29 May 2022*
Accepted: *21 June 2022*
Published: *05 August 2022*

Citation:
Horwich BH, Kahn JA and Saito T (2022) Reply to: Comments on: Differential IgG4-Producing Plasma Cell Infiltration in Non- and Post-Transplant Plasma Cell Hepatitis. Transpl Int 35:10679. doi: 10.3389/ti.2022.10679

Abbreviations: IgG4, immunoglobulin subclass 4; GSTT1, Glutathione S-transferase T1; LT, liver transplantation; PCR, plasma cell-rich rejection; rAIH, recurrent autoimmune hepatitis.

identified in the same subjects is warranted. Additionally, as our works only evaluated a combined 28 cases of PCR and rAIH, further studies with a larger cohort are needed (1, 2).

AUTHOR CONTRIBUTIONS

BH participated in the conception and draft of the manuscript. JK participated in the composition of the manuscript. TS participated in generating the intellectual content and writing of the manuscript.

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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ESOT | Transplant International

GUIDELINES
published: 10 August 2022
doi: 10.3389/ti.2022.10511

European Guideline for the Management of Kidney Transplant Patients With HLA Antibodies: By the European Society for Organ Transplantation Working Group

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This guideline, from a European Society of Organ Transplantation (ESOT) working group, concerns the management of kidney transplant patients with HLA antibodies. Sensitization should be defined using a virtual parameter such as calculated Reaction Frequency (cRF), which assesses HLA antibodies derived from the actual organ donor population. Highly sensitized patients should be prioritized in kidney allocation schemes and linking allocation schemes may increase opportunities. The use of the ENGAGE 5 ((Bestard et al., Transpl Int, 2021, 34: 1005–1018) system and online calculators for assessing risk is recommended. The Eurotransplant Acceptable Mismatch program should be extended. If strategies for finding a compatible kidney are very unlikely to yield a transplant, desensitization may be considered and should be performed with plasma exchange or immunoadsorption, supplemented with IVIG and/or anti-CD20 antibody. Newer therapies, such as imlifidase, may offer alternatives. Few studies compare HLA incompatible transplantation with remaining on the waiting list, and comparisons of morbidity or quality of life do not exist. Kidney paired exchange programs (KEP) should be more widely used and should include unspecified and deceased donors, as well as compatible living donor pairs. The use of a KEP is preferred to desensitization, but highly sensitized patients should not be left on a KEP list indefinitely if the option of a direct incompatible transplant exists.

Keywords: kidney transplantation, guidelines, HLA antibodies, sensitization, incompatible

OPEN ACCESS

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Received: *16 March 2022*
Accepted: *14 June 2022*
Published: *10 August 2022*

Citation:
Mamode N, Bestard O, Claas F, Furian L, Griffin S, Legendre C, Pengel L and Naesens M (2022) European Guideline for the Management of Kidney Transplant Patients With HLA Antibodies: By the European Society for Organ Transplantation Working Group. Transpl Int 35:10511. doi: 10.3389/ti.2022.10511

INTRODUCTION

Although kidney transplantation rates have increased in many countries in recent years, highly sensitized patients typically spend longer waiting for a transplant, or may never receive one. This guideline is aimed at healthcare professionals who are faced with a patient with HLA antibodies, to provide advice regarding the most appropriate way to achieve a successful transplant.

The guideline does not include patients undergoing non-renal or multi-organ transplants, and does not consider pediatric recipients in detail.

This article provides a summary of the guideline; the full guideline can be accessed at: https://esot.org/wp-content/uploads/2022/07/WS06_Full-doc_07202022.pdf.

METHODS

A working group (WS06) was convened by the European Society of Transplantation (ESOT) as part of the Transplant Learning Journey Project, including healthcare professionals from across Europe with expertise in the field, patient group representatives and a member of the Centre for Evidence in Transplantation, University of Oxford, United Kingdom.

Six areas of interest were defined and are listed below:

- Definition of sensitization
- Comparison of practices across Europe for transplanting sensitized patients
- The place of kidney exchange programs for sensitized patients
- Desensitization strategies
- Outcomes after HLA incompatible transplantation
- Strategies for access to kidney transplantation for highly sensitized patients

For each, a standard systematic search strategy was predefined, using the PICO model to formulate clinical questions. Bibliographic searches were developed for each of the clinical questions by experienced staff from the Centre for Evidence in Transplantation. Systematic searches were conducted in the Transplant Library (www.transplantlibrary.com), Medline and Embase and consisted of a mixture of free text and controlled vocabulary terms.

Different members of the working group drafted each chapter, which was then reviewed by the whole working group. The initial recommendations were presented at an ESOT webinar open to all, on the 29th June 2021, and again *via* an ESOT Twitter chat on the 2nd August 2021, after which further refinements were made. An Expert Working Group, including interested healthcare professionals from across Europe, was convened on the 28th August 2021 (in Milan and online), when a draft of the final document was presented and discussed, with further refinements following this.

The detailed methodology, including the search strategies used and search dates, is presented in the full guideline (**Appendix**).

We have presented below a brief summary of each chapter listed above, along with our recommendations. Recommendations were graded according to the strength of the recommendation [strong (1) or weak (2)] and the quality of the evidence [high (A), moderate (B), low (C) or very low (D) (2)].

DEFINITION OF SENSITIZATION

High levels of donor-specific HLA antibodies (DSA) present at transplantation are associated with a high incidence of hyper-acute rejection (3,4), and can be induced by previous blood transfusions, pregnancies or transplants (5–7).

Historically, complement-dependent cytotoxicity (CDC) was the gold standard measure of HLA antibodies and the degree of sensitization was expressed as a percentage of panel reactive antibodies (%PRA). This %PRA was defined by the percentage of panel donors reactive with the patient serum in CDC. The % PRA was a relatively inaccurate assessment of sensitization, but often a PRA > 85% was considered the threshold for a highly sensitized patient (8).

A CDC crossmatch only detects complement-activating HLA antibodies. To also detect the non-complement fixing IgG subclasses IgG2 and IgG4, the Flow Cytometric crossmatch (FCM) was introduced in several laboratories (9,10). Donor-specific antibodies detectable in FCM, but not in CDC, appeared to be clinically relevant and were associated with graft rejection and graft loss in a proportion of recipients (11). In contrast to CDC reactive DSAs, antibodies detected in FCM were considered more as a risk factor than a contra-indication for transplantation.

Clinically irrelevant antibodies (including autoantibodies) reactive with other structures on lymphocytes can interfere in the outcome of both a CDC and a FCM crossmatch (12,13) leading to false positive results. Additionally, endothelial cells in the kidney can express alloantigens, which are not present on lymphocytes (14) and antibodies to these cannot currently be detected.

Solid phase assays were introduced more recently (15). Single antigen beads (SAB) have facilitated the detection and identification of specific HLA antibodies (16,17). Patient serum is tested against a mix of about one hundred different beads, each covered with HLA molecules of the same specificity. The degree of antibody binding to a specific bead is expressed as mean fluorescence intensity (MFI). This assay appears to be far more sensitive than CDC and FCM for detecting HLA antibodies and DSA. As a consequence, the proportion of sensitized patients has significantly increased after the introduction of solid phase assays (18).

The clinical relevance of antibodies detectable in SAB assays is still a matter of debate (19). Individual centers have tried to make correlations between the already established clinical relevance of CDC and FCM and the MFI values obtained in SAB (20).

Although no absolute thresholds can be defined, it is generally accepted that the highest MFI values predict a positive CDC crossmatch, although exceptions exist as some high MFIs are associated with a negative CDC (21). As the SAB assay is very sensitive, positive reactions are obtained, usually with a lower MFI, which do not correlate with a positive FCM or CDC crossmatch. The clinical value of such antibodies has been extensively studied with some conflicting results (22,23).

Most centers use a cut-off MFI of 1,000–1,500 (21) but there is no general agreement on this value. HLA antibodies are directed against specific epitopes expressed on the target HLA antigen, but individual epitopes can be shared by (many) different HLA alleles (24), which may lead to differing MFI for the same antibody. These, and other issues, can make it difficult to determine the clinical significance of a given antibody.

Recently, an attempt has been made to introduce more reliable parameters for the definition of the degree of sensitization based on the antibody specificities present in the patient and the HLA phenotypes of the actual organ donor population. Different names are now circulating for this novel parameter: vPRA (virtual PRA) (25), cPRA (calculated PRA) (26) and cRF (calculated reaction frequency) (27) but they all reflect the chance that a patient has HLA antibodies reactive with a donor derived from the actual organ donor population. HLA incompatible transplantation (HLAi) is defined by a positive CDC or FCM crossmatch at baseline, since we believe that desensitization is only required in these cases. If these crossmatches are not routinely performed, centers are advised to define locally MFI values corresponding to positive CDC or flow crossmatches to be used for the selection of patients to be desensitized.

Recommendations

- A parameter, which is based on the HLA frequencies of the actual organ donor population, such as vPRA, cPRA or cRF, should be used to estimate the chance that a sensitized patient can be transplanted with a compatible donor without the need for any special treatment (1C).
- When defining unacceptable mismatches in highly sensitized patients on the basis of (weak) antibody reactivities in single antigen bead assays only, one should consider the poorly defined risk of antibody-mediated rejection (ABMR) in the light of a prolonged waiting time and associated mortality and morbidity (2D).

Areas for Further Research

- Further standardization of single antigen bead assays and their interpretation is recommended (1C).
- Better HLA matching on the basis of antibody epitopes rather than antigens and a restricted transfusion policy will probably diminish the number of highly sensitized patients, but more data are needed.

COMPARISON OF PRACTICES ACROSS EUROPE FOR TRANSPLANTING SENSITIZED PATIENTS

Both deceased and living donations are coordinated on either a national basis, or on behalf of a group of countries (http://www.accord-ja.eu/background). Eurotransplant (https://www.eurotransplant.org/) and Scandiatransplant (http://www.scandiatransplant.org/) each allocate donor organs for groups of countries. Larger donor pools would be expected to increase the likelihood of identifying a compatible donor for those who are hard to match. A survey of transplant practices around Europe was carried out during September and October 2021 for the purposes of this guideline, and the results form **Table 1**.

Deceased donor offering schemes can adjust for the increased waiting time of sensitized patients, either by increasing the weighting given to those who are hard to match, as in the UK Kidney Offering Scheme (https://www.odt.nhs.uk/transplantation/kidney/kidney-offering-and-matching/) or by the development of an Acceptable Mismatch (AM) program (28). Enrolment in an AM program is reserved for those more highly sensitized patients, whose chance of receiving an offer is otherwise low. For example, to be considered for enrolment in the Eurotransplant AM program, recipients will have been receiving dialysis for at least 2 years and have a PRA of >85%. The Eurotransplant AM program has enabled successful transplantation of highly sensitized patients with excellent outcomes (29).

The EUROSTAM project has compared data from five European registries to determine whether expanding the donor pool across different populations will result in increased rates of transplantation for those with >95% sensitization (27). In total, 195 (27%) of the 724 highly sensitized patients who had been registered for at least 5 years at each organization had an increased chance of a compatible kidney transplant offer in a different European pool. This makes a strong case for sharing kidneys between European countries and registries for selected difficult to transplant patients.

Kidney exchange programs (KEP) in Europe began in Switzerland in 1999 (30), and the Dutch and UK schemes were initiated in 2004 and 2007 respectively (31,32); the latter has performed the greatest number of transplants (33). Over the last decade, programs have been established throughout Europe (33). Approaches to exchange schemes vary; altruistic donation is permitted in the United Kingdom, but is not possible in France, Poland, Greece or Switzerland. Similarly, compatible pairs are included in the United Kingdom, but not in France or Portugal (33). The European Network for Collaboration on Kidney Exchange Programs (ENCKEP, https://www.eurotransplant.org/) was established in 2016. The program has contributed to aspirations for future developments, including modelling of European KEPs with the aim of future optimization (34).

No European country has a published national consensus on their optimal recommended management pathway for highly sensitized patients, although several European centers have published their protocols and outcomes following HLAi transplantation (35–38). The survey referred to above demonstrated substantial variability in the definition of sensitization, approaches to improve opportunities for deceased and living transplantation and perceived success of HLAi transplantation.

Recommendations

Organ Allocation

- We recommend an active policy of prioritizing highly sensitized patients for organ transplantation, using cPRA/cRF (1C).

TABLE 1 | Informal European survey of practices regarding transplantation, 2021.

Country or organization for deceased donor allocation	Population (million)	Living donation	Deceased donation		
		Is there access to a kidney exchange program?	Does the allocation scheme include prioritization for sensitized recipients?	Does the allocation scheme include an acceptable mismatch program?	Details
Eurotransplant (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, Netherlands, Slovenia)	137	Yes: Austria (with the Czechia and Israel), Belgium (20), Netherlands	Yes	Yes	Acceptable antigens are defined by the lack of antibody-reactivity in complement-dependent cytotoxicity assays using target cells mismatched for a single HLA antigen, or single antigen-expressing cell lines
ScandiaTransplant (Denmark, Finland, Iceland, Norway, Sweden, Estonia)	28.9	ScandiaTransplant Kidney Exchange Program launched April 2019	Yes	Yes, ScandiaTransplant Acceptable Mismatch Program (STAMP)[a]	Common waiting list and database system. STAMP patients have the highest priority for a deceased donor kidney
Czechia	10.7	Yes Recent expansion to include Austria and Israel	Yes	No	Patients are categorized according to their measured PRA: 0%–20%, 20%–80, and >80%, with higher priority for transplantation given to those with higher PRA values. Patients who have waited longer than 3 years for a transplant are prioritized, regardless of their PRA value DSA are allowed, based on local protocols for desensitization
France	67	Yes	Yes	Yes	Sensitized patients are prioritized according to waiting time and HLA compatibility
Greece	10.4	Yes	Yes	Yes	Patients are prioritized based on waiting time and HLA mismatch
Ireland	5	Yes—with the United Kingdom	Yes	Yes	All highly sensitized patients who are long waiting are screened to identify acceptable mismatches or windows in which they can be transplanted
Italy	60.3	Yes	Yes	Yes	The Italian national allocation scheme prioritizes at national level patients with PRA >90% and who have been on dialysis >8 years Recipients are selected according to a points score, based on - PRA - Age mismatch between donor and recipient - Recipient age - HLA mismatch - Time spent on dialysis - Time on waiting list
Latvia	1.9	Yes (21)			
Lithuania	2.9	Yes (22) established in 2013, although up to 2019, the system has not been used			Although Lithuania is not a member of international organ procurement and allocation organizations yet, they do collaborate with neighboring Nordic countries and exchange organs with Latvia, Estonia and Poland

(Continued on following page)

TABLE 1 | (*Continued*) Informal European survey of practices regarding transplantation, 2021.

Country or organization for deceased donor allocation	Population (million)	Living donation	Deceased donation		
		Is there access to a kidney exchange program?	Does the allocation scheme include prioritization for sensitized recipients?	Does the allocation scheme include an acceptable mismatch program?	Details
Poland	38	Yes	Yes	Yes	Prioritization for patients with a PRA >80%; increased weighting for patients with PRA 50–79
Portugal	10.2	Yes	Yes	No	Additional points for sensitized and highly sensitized patients
Russia	146.2		No Each transplant center has their own internal protocol	Yes Some kidney centers may transplant if there is an acceptable mismatch	There is no common waiting list in Russia or any kind of program like Eurotransplant. Each center has its own waiting list, their own algorithm for prioritizing patients for transplantation (although many use UNOS, Intermax or other classification systems to help decisions) and their own protocol for post-transplant follow-up Prioritization is based on donor and recipient risk index match, waiting time, and HLA mismatch
Slovakia	5.4	No	No	No	
Spain	46.8	Yes	Yes	No	One kidney of all brain death donors is offered to a National Prioritization Scheme for sensitized patients with a cPRA >98%. Kidney acceptance for an individual patient based on virtual crossmatch (23)
Switzerland	8.74	Yes	Yes	Yes	Prioritization for allocation is based on a continuum of increasing cPRA for each blood group. An MFI cut-off of 1,000 is used for both class 1 and class 2 DSA
Turkey	85.6	Yes	No	No	Allocation is according to a scoring system Criteria — Score HLA match — DR 150, B 50, A 5 Region — 1000 Center — 250 Recipient age (<11 years / 12–17/ ≥18 years — HLA match score multiplied by 2.5/1.5/1 Time on dialysis — 3 points for each month
United Kingdom	68	Yes	Yes	No	Absolute priority for those with cRF >100%, matchability score 10, waiting time >7 years Remaining patients prioritized on points score, based on i. Donor and recipient risk index match ii. Waiting time iii. HLA mismatch iv. Local region > non-local regions (of four national regions)

[a]*http://www.scandiatransplant.org/organ-allocation/Manual_STAMP_20_nov_2017_version_8.1.pdf.*
http://www.scandiatransplant.org/organ-allocation/Kidney_exchange_11_november_2020.pdf.

THE PLACE OF KIDNEY EXCHANGE PROGRAMS FOR HIGHLY SENSITIZED PATIENTS

The simplest form of a KEP is a two-way exchange involving two incompatible pairs who swap their donors to achieve a compatible transplant for both recipients (**Figure 1**). The closed loop between three or more incompatible pairs whose recipients find a compatible kidney by exchanging their donors, represents another basic form of kidney paired donation.

Unfortunately, for highly sensitized patients with a wide range of anti-HLA antibodies or for blood type O recipients, it is very hard to find a compatible match for each pair involved in a closed loop.

The option of a non-directed altruistic (or unspecified) donor (NDAD) who is willing to donate his/her kidney with no intended recipient, avoids the need to "close the loop." The NDAD's kidney is matched with the recipient of an incompatible pair whose living donor donates to another incompatible recipient, initiating a domino-paired kidney exchange. The chain ends with the donor of the last pair donating to a recipient on the waiting list or waiting for another suitable match, starting another sequence of paired donations later (non-simultaneous extended altruistic donor chain), thus becoming a bridge donor. This model is potentially associated with an incremental risk of donor reneging. The occurrence of broken chains has been reported to be as low as 1.5%, with the most common causes for broken chains being bridge donor medical issues (0.46%), donors electing not to proceed (0.34%) and broken chains resulting from the kidney being declined by the recipient surgeon (0.23%) (39).

The first deceased donor-initiated chain was reported by Furian, et al in 2019 (40). In the DECeased donor kidney paired exchange (DEC-K) program, the chain-initiating kidney, selected from the deceased donor pool, is allocated to a recipient with an incompatible living donor and, at the end of the domino-chain, the living donor of the last pair donates to a waiting list patient. The major advantage of the DEC-K program is the ability to offer transplantation to recipients of incompatible donor pairs, but it also benefits waiting list candidates by allocating chain-ending kidneys from a living donor to them, prioritizing sensitized patients and those who have waited a long time for immunological reasons.

List exchange is another form of KEP, proposed by Delmonico et al. (41), to prevent the issue of donor reneging. In this scheme, the donor of the incompatible pair donates before the recipient has received their compatible transplant from the deceased donor pool but, after donation, the paired recipient acquires priority over the WL candidates.

Other novel KEP schemes take place in the setting of "chronological incompatibility" and constitute the advanced donation programs where a living donor donates his/her kidney at his/her convenience to a recipient of an incompatible pair in need of transplant while his/her intended recipient will receive the reciprocal compatible kidney later on, when he/she actually needs a transplant (42).

ABO or HLA compatible pairs may also be included in a KEP, in order to increase the pool and provide benefits (such as better age or HLA matching) for the compatible recipient. A recent report from the National Kidney Registry linked to data from the Scientific Registry of Transplant Recipients identified 154 compatible pairs involved in kidney exchange programs, seeking to improve their HLA matching through an exchange. These patients obtained a transplant from younger donors, with higher estimated glomerular filtration rate and body mass index and a better score on the living kidney donor profile index as compared with their original donor (43).

Another strategy to improve results is combining exchange programs with desensitization. ABO incompatible transplantation in the absence of DSA provides excellent transplantation results, so ABO incompatible living donors against whom recipients have lower anti-blood group antibody titers can be included in a KEP. This strategy has been successfully applied in the Australian program and at the John Hopkins Institute (44,45).

Trans-organ paired exchange represents the most innovative concept of KEP. It might be used, for example, when a living kidney donor who is not eligible for renal donation but can donate his/her liver to a liver recipient of a pair whose donor is ruled out from liver donation but is suitable for kidney donation. Torres, et al published the first case of trans-organ exchange, attracting many criticisms related to the surgical risk of donation that is very different for different organs (46).

KEP Versus Desensitization

In 2005, Segev, et al. (47) showed, by a simulation based on UNOS data, the superiority of KEP over desensitization, guaranteeing better graft outcomes and higher transplantation rates for HLAi pairs. The authors clearly stated that KEP should be the preferred treatment for patients who have HLA incompatibilities with their willing donors.

However, despite the implementation of KEP strategies, in the United States, patients with a PRA of 99.9% remain the most disadvantaged transplant candidates with prolonged waiting times and high waiting list mortality (48). In fact, patients with a cPRA >80% were less likely to receive a living-donor kidney transplant (6.5%) compared with candidates with a cPRA <80% (26.7%), and in the 99% cPRA group, only 3.4% of all transplants were from a kidney paired donor, and only 1.3% in 100% cPRA candidates. This is why some transplantation centers still promote desensitization as a valid and needed approach to increase the probability of transplantation in highly sensitized patients (49). Others have proposed KEP only in cases of failed desensitization procedures, as a kind of "rescue" therapy (50).

Recommendations

- Access to the donor pool should be increased through greater use of:

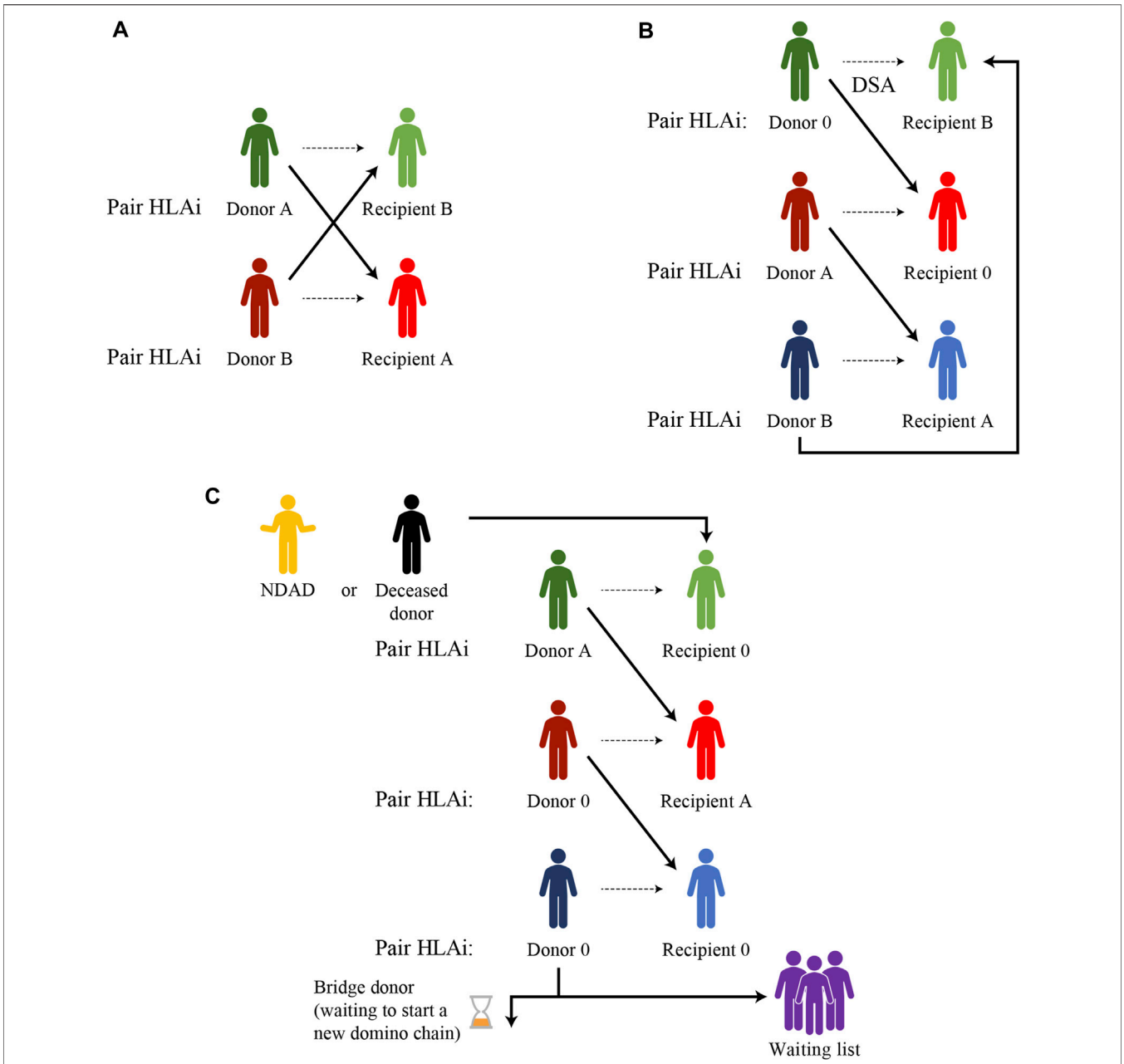

FIGURE 1 | Examples of kidney paired donation exchanges **(A)** Two-way exchange **(B)** Three-way exchange **(C)** Domino-chain ending with a donation to a wait-list patient or a bridge donor and starting from a non-directed altruistic donor (NDAD), a non-simultaneous extended altruistic donor (NEAD), or a deceased donor (Dec-K program).

  - Increased access to and harmonization of kidney exchange programs with greater and standardized sharing of outcomes (1C)
  - Inclusion of unspecified kidney donations (if these are performed) in kidney exchange programs (1C)
  - Inclusion of compatible pairs and deceased donor organs in kidney exchange programs (1C)
- Entry into a kidney exchange program is the preferred initial option over desensitization given the better transplant outcomes and cost-effectiveness, unless there is a need for desensitization, there is clinical urgency or a low chance of a transplant (1C).

DESENSITIZATION STRATEGIES IN KIDNEY TRANSPLANTATION

If the strategies listed above have not yielded, or are unlikely to yield, a transplant, desensitization may be considered. There are several ways to desensitize HLA-immunized patients.

In a randomized trial (51), it was shown that IVIgs alone allowed more patients to be transplanted, but the overall benefit was still quite limited. It is relatively simple to decrease the global level of IVIgs through plasma exchange or by immune-adsorption—an equivalent method. The number of plasma exchanges necessary to lower the IgG level is about five and the gain of increasing the number of plasma exchanges beyond that is small (44).

Rituximab (anti-CD20) can be used to desensitize patients prior to transplantation. This drug aims to decrease the rebound effect linked to decreased levels of immunoglobulins in the plasma. Efficacy is monitored using the expression of CD19 on B cells. Currently, the two methods used to desensitize patients are either a combination of anti-CD20 antibodies and high-dose IVIgs (2 g/kg over 2–4 days) (52), or a combination of 3–5 sessions of plasma exchange followed after each session by an infusion of low-dose IVIgs (0.1 g/kg) to avoid rebound (44). New anti-CD20 monoclonal antibodies (such as ocrelizumab or obinutuzumab) may be more efficient, as well as anti-CD19 antibodies.

It is possible to decrease the synthesis of proteins (DSAs) using proteasome inhibitors such as the first-generation drug, bortezomib. This drug was tested in a study with such a complex design (including the testing of many other drugs) that it is difficult to clearly see its role in desensitization (53). Second generation drugs such as carfilzomib or ixazomib may be more efficient.

A logical approach to desensitization is to block the activity of complement in order to decrease the effect of antibodies such as DSAs. The anti-C5 monoclonal antibody, eculizumab, was the first to be tested in this indication. A randomized study was designed for living donor recipients and compared the use of eculizumab for 3 months post-transplantation with a control group who received desensitization (38). Unfortunately, the results were rather disappointing, with no significant difference found between the two groups. One explanation of these results is the difficulties in defining ABMR and probably more importantly, the use of anti-C5 in patients with DSAs not fixing the complement (54). In contrast, in a study in sensitized patients being transplanted with an organ from a deceased donor, it was possible to get a low incidence of ABMR using eculizumab. However, there were no controls in this study, so the overall results are not clear-cut, but it remains a logical approach that may be used in selected groups of patients. Other complement blockers (such as a C1-inhibitor) are the subject of current clinical trials (55).

Another approach, which is not strictly desensitization, is the use of a cysteine protease (IG endopeptidase, Ides, Imlifidase and Idefirix®). Imlifidase is currently the only approved therapy for use in the EU for desensitization treatment of highly sensitized adult kidney transplant patients with a positive crossmatch against an available deceased donor. It cleaves all IgGs, both intra- and extra-vascularly, without regard to their specificity, with an immediate action that lasts around 5–7 days; this drug cannot be re-dosed due to immunogenicity (56). It is important to stress that there is an anti-HLA antibodies rebound when the activity of the drug disappears, rebound that explains the frequency of ABMR. Imlifidase has been used in HLAi hyper-immunized patients with good and safe results and at 3 years, crossmatch positive patients who were converted to negative with imlifidase to enable transplantation had ABMR with a frequency equivalent to other desensitization methods. Three years after imlifidase-enabled desensitization and transplantation, the death-censored allograft survival was 84%, patient survival 90%, and mean eGFR was 55 ml/min/1.73 m^2 (49 ml/min/1.73 m^2 for those with ABMR and 61 ml/min/m^2 for those without ABMR) (57).

An additional desensitization strategy is the manipulation of the cytokines involved in B cell activation. In this indication, tocilizumab, an anti-IL6 receptor monoclonal antibody has been giving promising results in a randomized trial, used in addition to current desensitization protocols (58). Antibodies to anti-IL6 have been studied in a randomized clinical trial showing promising efficacy regarding decreased DSA, less eGFR decline as well as changes in biopsies features but also a careful evaluation of safety data (diverticular complications) (59). Belimumab, an anti-BAFF monoclonal antibody, might be a useful adjunct to standard care immunosuppression in renal transplantation patients, as it shows no major increased risk of infection and potential beneficial effects on humoral alloimmunity (60).

Recommendations

- The most efficacious desensitization strategy is to start with rounds of plasma exchanges/immunoadsorption together with IVIG or B-cell depletion with anti-CD20 monoclonal antibodies (1C).

Areas for Further Research

- As yet to be defined protocols including proteasome inhibitors and other anti-plasmocyte antibodies with costimulation blockade, B-cell immunomodulation targeting IL-6 as well as cleavage of IgG donor-specific antibodies with imlifidase are highly promising new strategies that deserve further investigation.

OUTCOMES AFTER HLA INCOMPATIBLE TRANSPLANTATION

Results from HLAi are often compared with those from compatible transplants, but many HLAi patients will never have the option of a compatible transplant, as the chance for the most highly sensitized to receive a deceased donor kidney, or matching in a KEP is essentially nil (48,61). It is important, therefore, when considering outcomes, to also include patients who remain on dialysis and who are waiting for an organ offer as comparators.

We have therefore considered the following:

- A comparison of mortality rates between HLAi and those who remain without a transplant
- A comparison of morbidity between HLAi and those who remain without a transplant
- A comparison of quality of life between HLAi and those who remain without a transplant

TABLE 2 | Mortality in HLAi transplant recipients versus those not transplanted and remaining on the waiting list.

	Country	Time (years)	Patient survival, %		*p*-value
			HLAi transplant	No transplant, but on waiting list	
(44)	United States	8	80.6% *n* = 211	30.5% *n* = 1,050	$p < 0.001$[a]
(62)	United States	8	76.5% *n* = 1,025	43.9% *n* = 5,125	$p < 0.001$[a]
(61)	United Kingdom	7	78.3% *n* = 213	76.9% *n* = 852	p = NS[b]
(64)	Korea	7	96.3% *n* = 189[c]	88.2% *n* = 930	$p < 0.001$

[a]*Kaplan Meier.*
[b]*Kaplan Meier and log rank test.*
[c]*Includes cross-match negative recipients.*
NS, not significantly different.

Mortality

There are only four studies comparing mortality in those who have undergone HLAi with those who remain on the waiting list, and these are detailed in **Table 2**. The study by Montgomery (44) compared outcomes from a single center with those in patients taken from the United Network for Organ Sharing (UNOS) database. There was a clear survival advantage for those who underwent HLAi compared with remaining on the waiting list.

However, it might have been possible that the survival benefit shown for HLAi was due to the approach in this (expert) center, so in 2016, a study by Orandi (62) considered HLAi in 1,025 patients from 22 centers in the United States (these included 185 DSA positive, crossmatch negative patients). The results were strikingly similar.

The results from these studies have been partly contradicted by a UK registry study, which found no difference in survival when comparing 213 HLAi patients with 852 well-matched controls who remained on the waiting list (61). It is unclear why findings differ between the United States and Europe, but one explanation may be a generally lower historical survival rate on dialysis in the United States (63).

More recently, a study from Korea compared 131 patients, from two hospitals, with a positive CDC or flow crossmatch (and 44 with DSA but a negative crossmatch) with a group of matched controls of those who were waiting for a transplant ($n = 3,701$), or who received a deceased donor transplant ($n = 907$). They found that patient survival was significantly better for those undergoing an HLAi transplant, compared with either control group (64).

It remains unclear whether there is a survival advantage from an HLAi transplant, compared with remaining on the waiting list; nevertheless, no survival disadvantage for HLAi was found.

Morbidity

There are no studies that compare morbidity in those undergoing HLAi with those who remain on the waiting list. This is an important gap in our knowledge, particularly given the statements above regarding survival. There is one study by Orandi (65), which compared hospital readmissions in 379 HLAi transplants with matched controls who remained on the waiting list, using registry data from the United States. Those who underwent HLAi, unsurprisingly, had a higher readmission rate in the first month (RR 5.86; 95% CI 4.96–6.92; $p < 0.001$), but interestingly, had lower rates of hospitalization subsequently (at 3 years: RR 0.74; 95% CI 0.66–0.84; $p < 0.001$).

A report by Kim (66) compared 56 HLAi (positive T cell flow cytometric crossmatches were excluded) with 274 compatible transplants, providing data on infectious complications, which may help in considering the risk. Urinary tract infections (41% vs. 7.7%), cytomegalovirus viraemia (54% vs. 14%) and pneumocystis jiroveci pneumonia (PJP) (5% vs. 0%) were all significantly higher in the HLAi group ($p < 0.001$). Another study that compared 27 HLAi patients with 69 ABOi patients, found no significant difference in viral, bacterial or fungal infections between the two groups, although of note, 6% of the ABOi group had PJP, compared with none of the HLAi group (67).

Quality of Life

We were unable to find any studies that compared quality of life in those undergoing HLAi, with those remaining on the waiting list and hoping for a compatible transplant.

Recommendations

Areas for Further Research

- We recommend that data be collected prospectively for sensitized patients, in order to compare the effect of an HLA incompatible transplant with remaining on the waiting list. This data should include mortality, morbidity and quality of life.

STRATEGIES FOR ACCESS TO KIDNEY TRANSPLANTATION FOR HIGHLY SENSITIZED PATIENTS

Some patients have cellular memory without current circulating antibodies detectable in the peripheral blood. There are currently no clinically validated and available tools that accurately assess such cellular memory responses. It is therefore difficult to propose well-substantiated recommendations for this type of risk.

Among the most successful transplant policies are 1) sliding scales or priority points programs; 2) an allocation system based on AM HLA antigens rather than the avoidance of unacceptable ones and 3) achieving HLA compatibility using living donor transplant options, such as ABO incompatible transplantation or KEP.

HLA immune responses are driven both by alloreactive T and B lymphocytes. However, while alloreactive T cells are key in allograft rejection, there is a lack of sensitive and validated immune tools that can be implemented clinically to mitigate these effects (68,69). Currently, immune-risk stratification in kidney transplant candidates is focused on the humoral effector pathway through the detection of serum anti-HLA antibodies directed against donor antigens, but interpretation of SAB data may be affected by antibody titer, prozone effect, or competition of shared epitopes on different beads, as well as irrelevant antibody reactivity against denatured HLA molecules (70–72). The ability of DSA identified by SAB to bind donor cells *ex vivo* in FCM is a good predictor of subsequent ABMR lesions and graft loss in 50% and 30% of recipients, respectively (73–76). Importantly, by accepting every SAB signal, a high number of patients would be defined as highly sensitized, with the consequently lower chance of receiving an organ offer through regular allocation systems—likely reducing a patient's chance by up to five-fold (76). Therefore, an individualized risk-assessment of previous sensitizing events, adding a thorough epitope analysis and most importantly, the likelihood of receiving an HLA compatible transplant in their respective region, should be considered.

A European working group endorsed by the ESOT, ENGAGE, has put forward an initiative proposing an integrative consensus of the most consistent evidence to stratify kidney transplant candidates into five distinct risk categories with the aim of conferring the best chance of successful transplantation. These risk categories take into account an individual patient's past immunological clinical background, integrated with an assessment of serological alloimmune memory using CDC-crossmatch, FCM crossmatch and SAB assays (1) (**Figure 2**).

The use of a sliding scale priority points system for allocation of deceased donor organs can increase the transplant rate for highly sensitized transplant candidates. In the United States, those with a cPRA ≥98% receive a higher sliding scale priority point score, in which ABO incompatible (A2/A2B to B organ) offers are also permitted due to their lower immunogenicity (77–79). Remarkably, kidney transplant rates among these patients dramatically increased when the scale was introduced, from 2.5% to 13.4% (80). A similar scheme exists in Spain, with a national sliding scale priority program using an ABO identical deceased organ donor allocation system (PATHI) (81). However, these programs have only significantly helped access to transplantation for those transplant candidates with a cPRA<100% (80,82,83). For those with 100% cPRA, sliding priority points schemes do not seem to increase their chance of receiving a kidney transplant, or even an organ offer, especially when stratifying the levels of sensitization into decimals (99.95%–100%) (84) (**Figure 3**).

KEP are discussed earlier but some important points with respect to risk stratification are:

- National demographics: the incidence of blood groups and HLA types varies across different countries, and will therefore affect the chances within a KEP
- The size of the pool: the larger the pool the greater the chances of a match, although there is probably a maximum size beyond which there is no incremental advantage
- Recipient characteristics: for example, those who are very highly sensitized (e.g., cPRA/cRF 100%) will have a low or even negligible chance in a KEP, for the same reasons that they will have a low chance of receiving a deceased donor transplant
- KEP algorithm: each KEP will have its own algorithm, which will affect the chances an individual has for a match in the scheme. This should be considered when entering a patient into the scheme.

The easiest way to address these factors is to access an online calculator which incorporates the factors into a probability of a match, ideally with confidence intervals. An example from the UK scheme is given at https://www.odt.nhs.uk/living-donation/tools-and-resources and at https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/calculators/, which addresses the likelihood of a deceased donor transplant for sensitized patients.

Finally, an important point to consider is that entry into a KEP should not be considered as a definitive solution. Figures from the UK KEP show that the incremental chance of a match after 6 or 7 "runs" is low (**Figure 4**), and thus, at this stage, if there are alternatives, such as a direct antibody incompatible transplant, these should be considered.

The Eurotransplant AM program fully prioritizes the allocation of compatible donor kidneys to highly sensitized patients (>85% cPRA), focusing on finding acceptable matches rather than to prohibit matches (29). The main advantage of the AM over prioritization schemes is that it entails better matching and thus may lead to better long-term outcomes. Unfortunately, it does not seem to increase access to transplantation for those very highly sensitized patients (>99% cPRA). Nevertheless, a considerable number of patients have already been transplanted within the AM program, both first and repeat transplantations (**Figure 5**). Interestingly, kidney transplant failure is significantly lower in the highly sensitized patients included in the AM program, compared with highly sensitized patients not included in the AM program. Furthermore, death-censored graft survival rate is similar to the rate in non-sensitized patients and is related to a lower chance of rejection in the highly sensitized patients included in the AM program (85).

Recommendations

- To define the humoral risk in kidney transplantation, the use of the ENGAGE 5 strata system is recommended (1C).
- Prioritization policies should be linked across countries for equity of access (1C).
- The Eurotransplant Acceptable Mismatch program should be expanded to other European countries (that do not have this type of matching) to improve donor/recipient matching (1C).

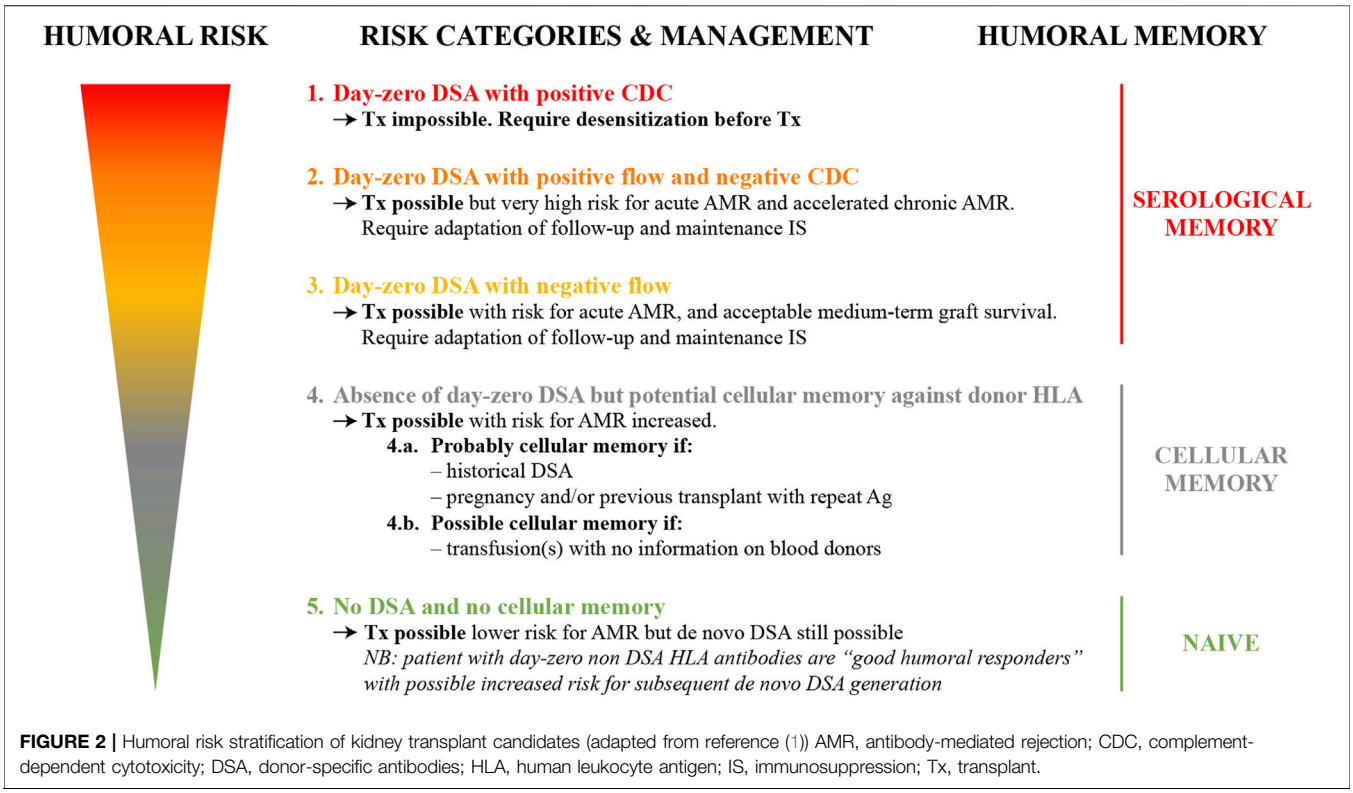

FIGURE 2 | Humoral risk stratification of kidney transplant candidates (adapted from reference (1)) AMR, antibody-mediated rejection; CDC, complement-dependent cytotoxicity; DSA, donor-specific antibodies; HLA, human leukocyte antigen; IS, immunosuppression; Tx, transplant.

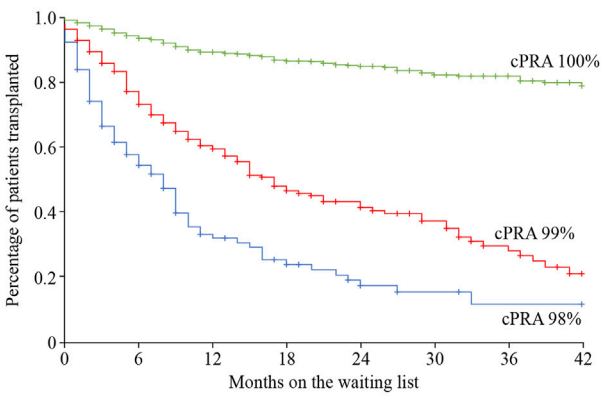

FIGURE 3 | Time on the wait list and percentage of patients receiving a kidney transplant relative to patient cPRA in the priority program for highly sensitized kidney transplant patients in Spain. Image reproduced with thanks and with permission from the Spanish priority allocation programme (PATHI) from the Spanish National Transplant Organization (www-ONT.es). cPRA, calculated percentage of actual organ donors who express one or more unacceptable antigens.

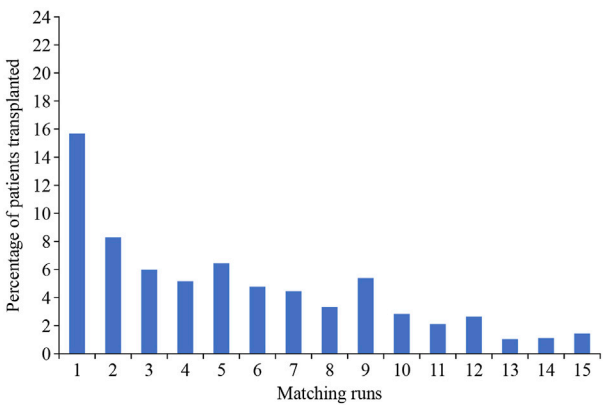

FIGURE 4 | Correlation of the chance of a transplant relative to the number of matching runs (UK figures from National Health Service Organ Donation and Transplantation Clinical website: https://www.odt.nhs.uk).

there are no organ offers for a patient in a kidney exchange program (1C).

- All kidney exchange programs should develop calculators to help assess the probability of an organ match (1C).
- Therapeutic options (including HLA- or ABO-incompatible transplantation) should be reconsidered if

Areas for Further Research

- Work to develop schemes to help patients with very high cPRA or cRF who may not be transplanted in kidney paired donations or under deceased donor priority schemes should continue.

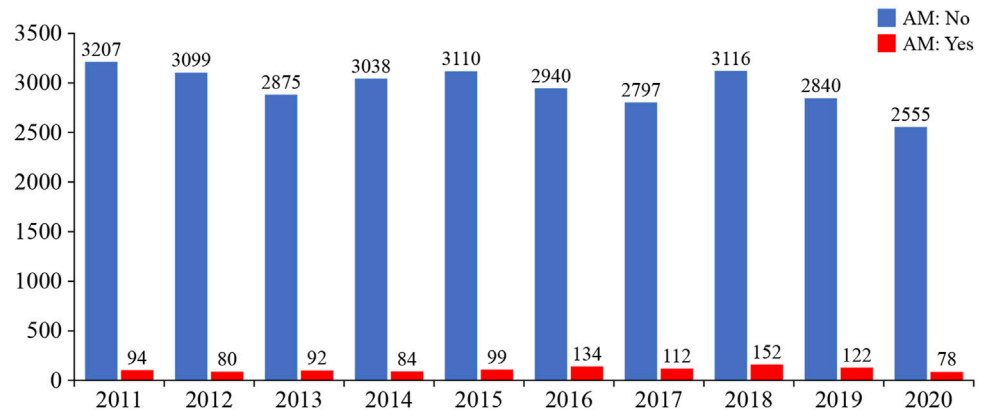

FIGURE 5 | Relative numbers of kidney transplantations achieved by Eurotransplant and by the Acceptable Mismatch (AM) program (image reproduced with permission from Eurotransplant, www.eurotransplant.org. https://statistics.eurotransplant.org; accessed May 2021).

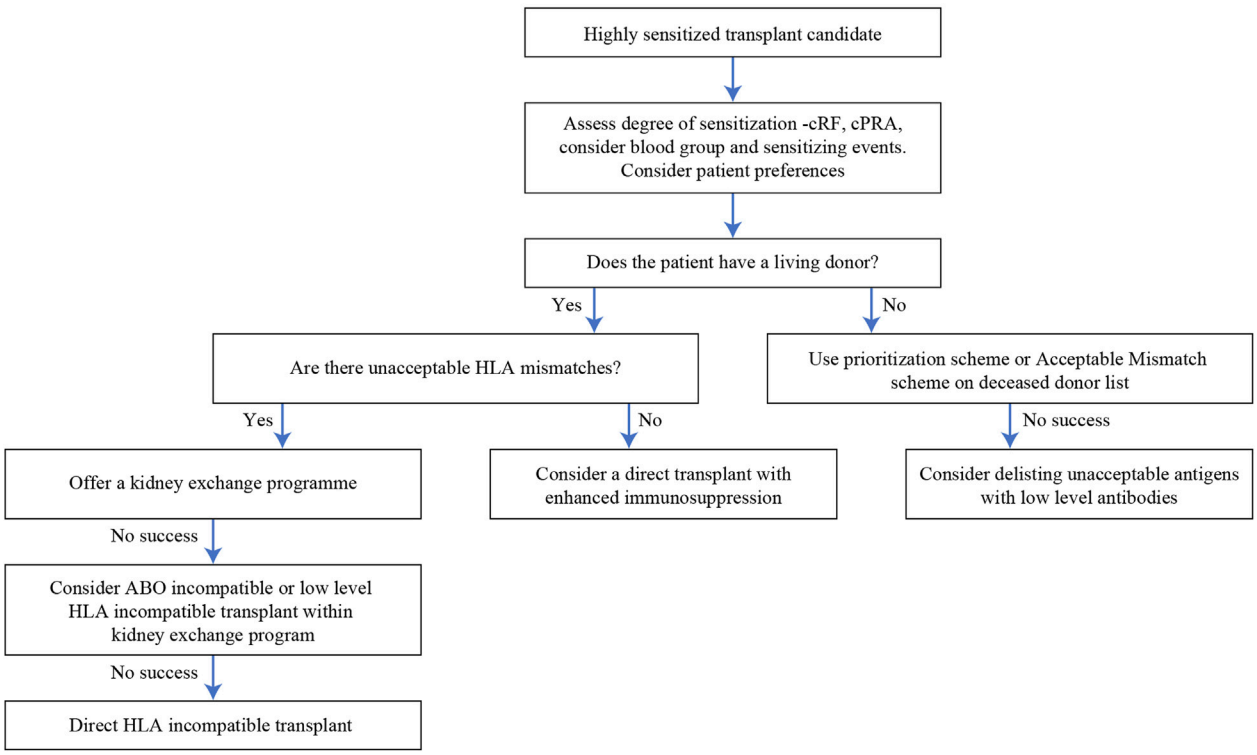

FIGURE 6 | Algorithm of options for a highly sensitized transplant candidate.

- The role of induction immunosuppression in relation to sensitization and its role in long-term outcomes should be further explored.
- Whether better risk stratification, thorough immunological evaluation and avoidance of HLA-DSA can improve outcomes should be determined.

AN INTEGRATED APPROACH TOWARDS SENSITIZED PATIENTS

We have given a suggested algorithm for approaching patients with HLA antibodies in **Figure 6**, since we believe that the options described above are not necessarily independent of each other but

can be integrated in a clinical decision. This will not be applicable in all settings, since it will depend on the availability of the various modalities, but we hope it will prove to be a useful framework. Two points are worth emphasizing—firstly, that for individual patients, the risks of the various options (including no transplant) should be assessed and conveyed using the limited data that is available. Secondly, flexibility is important; a patient should not be left in a KSS indefinitely if other options are available, or if new treatments appear.

AUTHOR CONTRIBUTIONS

The members of WS06 of ESOT provided input and critical review of this article (OB, FC, LF, SG, CL, LP, and MN). NM: drafted manuscript and chaired group

FUNDING

The authors declare that this study received funding from Hansa Biopharma. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication. Medical writing support was provided by Linda Edmondson and Rebecca Mant, independent medical writers, funded by the European Society of Organ Transplantation.

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.

ACKNOWLEDGMENTS

Support of the working group is gratefully acknowledged from European Society of Organ Transplantation: Giovanna Rossi, Ariane Brusselmans, Chloe Xilinas and Devi Mey. Thanks to the Centre for Evidence in Transplantation, University of Oxford, United Kingdom for bibliographic searches and support and to Fiona Loud for participation. The authors gratefully acknowledge the kind assistance of Professor Baris Akin (Demiroglu Bilim University Florence Nightingale Hospital, Istambul, Turkey), Professor John Boletus (National and Kapodistrian University of Athens, Greece), Professor Peter Conlon (Beaumont Hospital, Dublin, Ireland), Dr. Caterina Di Bella (University Hospital of Padua, Italy), Associate Professor Piotr Domagala (Medical University of Warsaw, Poland), Frank Dor (Imperial College NHS Healthcare Trust, London, United Kingdom), Dr. Farsad-Alexander Eskandary (Medical University Vienna, Austria), Professor Fadi Haidar (HUG, Switzerland), Assistant Professor Nataša Katalinić (University of Rijeka, Croatia), CL (Necker Hospital, Paris, France), Dr. Gabriel Oniscu (Edinburgh Transplant Centre, United Kingdom), Professor Vassilios Papalois (Hammersmith Hospital, Imperial College, London, United Kingdom), Professor Søren Schwartz Sørensen (Copenhagen University Hospital, Denmark), Dr. Maria Simonenko (Almazov National Medical Research Centre, St. Petersburg, Russia); Professor Ondrej Viklicky (Transplant Center, Prague, Czechia), Professor Stela Zivcić-Cosi (University Hospital Center Rijeka, Croatia), Assistant Professor Renata Žunec (University Hospital Center, Zagreb, Croatia) for providing information on current practice in each of their countries for **Table 1**. This work was previously presented as part of the review process at the European Society of Organ Transplantation Workstream 06 Expert Working Group meeting on 28th August 2021 in Milan, Italy.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2022.10511/full#supplementary-material

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ESOT | Transplant International

REVIEW
published: 25 August 2022
doi: 10.3389/ti.2022.10482

Deceased Donor Characteristics and Kidney Transplant Outcomes

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Kidney transplantation is the therapy of choice for people living with kidney failure who are suitable for surgery. However, the disparity between supply versus demand for organs means many either die or are removed from the waiting-list before receiving a kidney allograft. Reducing unnecessary discard of deceased donor kidneys is important to maximize utilization of a scarce and valuable resource but requires nuanced decision-making. Accepting kidneys from deceased donors with heterogenous characteristics for waitlisted kidney transplant candidates, often in the context of time-pressured decision-making, requires an understanding of the association between donor characteristics and kidney transplant outcomes. Deceased donor clinical factors can impact patient and/or kidney allograft survival but risk-versus-benefit deliberation must be balanced against the morbidity and mortality associated with remaining on the waiting-list. In this article, the association between deceased kidney donor characteristics and post kidney transplant outcomes for the recipient are reviewed. While translating this evidence to individual kidney transplant candidates is a challenge, emerging strategies to improve this process will be discussed. Fundamentally, tools and guidelines to inform decision-making when considering deceased donor kidney offers will be valuable to both professionals and patients.

Keywords: mortality, kidney transplant, graft loss, deceased donor, discard, kidney failure

INTRODUCTION

Kidney transplantation is the treatment modality of choice for kidney failure patients deemed fit enough for surgery. While successful kidney transplantation lowers both cardiovascular (1) and all-cause mortality (2,3), and provides better quality of life and cost-effectiveness in most scenarios (4), kidney transplant failure and return to dialysis is associated with heightened risk for mortality over-and-above transplant-naïve waitlisted dialysis patients (see **Figure 1**) (5,6). Therefore, personalizing use of deceased donors for individual waitlisted kidney transplant candidates at the most appropriate time is challenging (see **Figure 2**) (7).

These factors partly explain unnecessary kidney discards. Mohan et al. observed 17.3% of procured kidneys in the United States between 2000–2015 were discarded, despite partner kidneys of unilaterally discarded kidneys experiencing 1-year death-censored graft survival rates >90% (8). Over 80% of kidney discard rates can be explained by the broadening donor pool and unexplained residual factors (9). Organ discard rates in European countries are lower than the United States (10), although donor characteristics differ (e.g., more opioid-related deaths in the United States) (11). If deceased donor kidney acceptance in the United States mirrored the French model (discard rate 17.9% versus 9.1% respectively, $p < 0.001$), then utilization of discarded kidneys

OPEN ACCESS

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***Received:** 01 March 2022*
***Accepted:** 25 July 2022*
***Published:** 25 August 2022*

Citation:
Sharif A (2022) Deceased Donor Characteristics and Kidney Transplant Outcomes. Transpl Int 35:10482. doi: 10.3389/ti.2022.10482

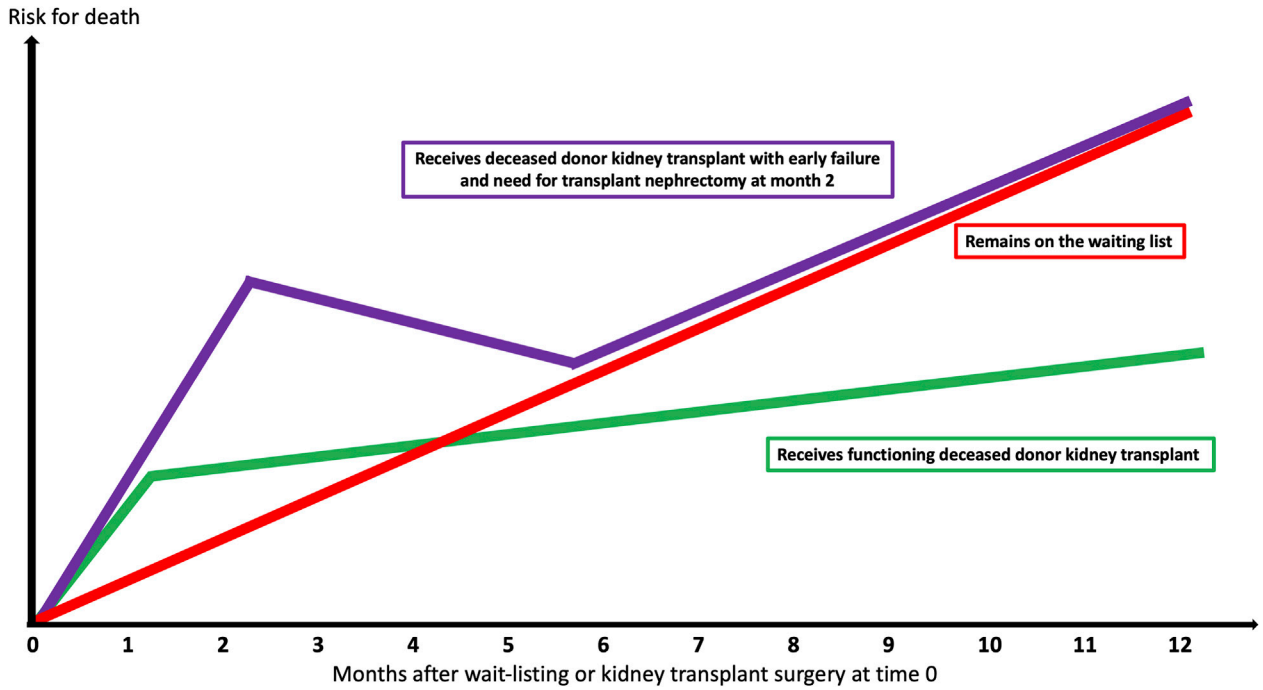

FIGURE 1 | Survival probabilities based upon deceased donor kidney transplant success, failure, and remaining on the waiting-list.

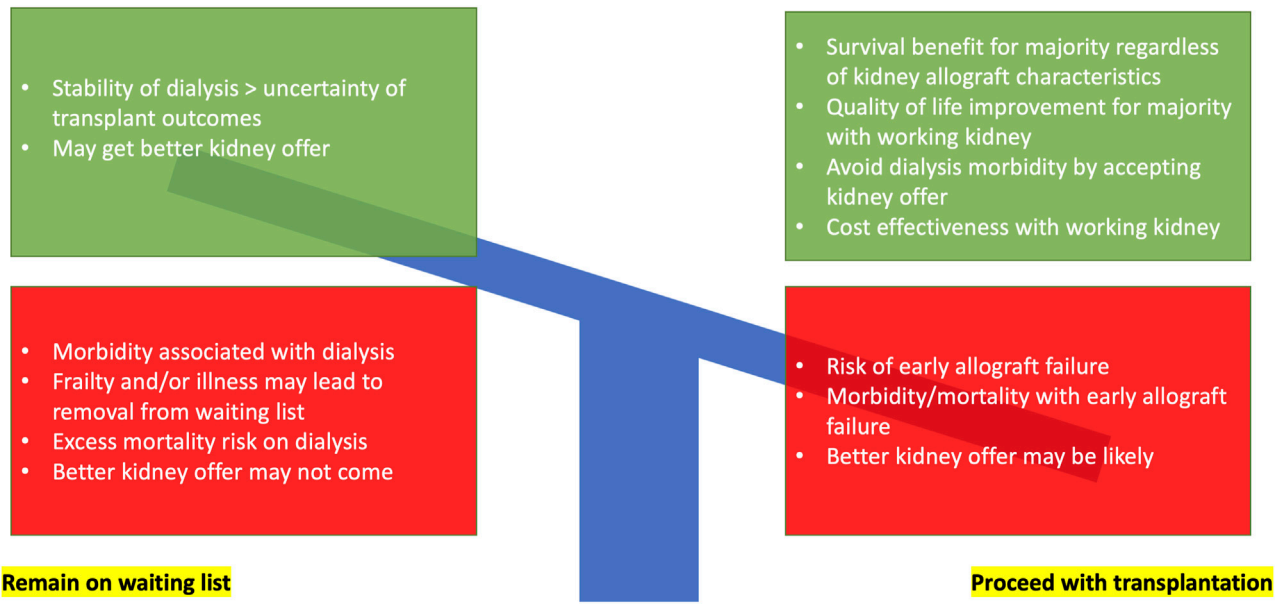

FIGURE 2 | Decision-making for waitlisted kidney failure individuals with a deceased donor kidney offer balancing risk, benefit, and uncertainty.

(n = 17,435) could generate 132,445 allograft life-years (12). 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 (13). Apart from clinical benefits, transplantation using kidneys of any quality is cost-effective versus remaining on the waiting-list (14).

In view of increasing marginality of kidneys procured from deceased donors (15,16), which contributes to sub-optimal organ

utilization, informed decision-making to accept kidney offers for individual kidney transplant candidates must be the objective. While organ allocation systems continue to evolve (17), which impact upon utilization, the aim of this review is to summarize published evidence regarding kidney transplant outcomes associated with deceased kidney donor characteristics. Translating such data into decision-making pathways is a clinical challenge and emerging ways to foster better organ utilization are discussed.

DONOR CLINICAL FACTORS

Expanded Criteria Donor

An ECD is one who, at the time of death, is aged ≥60 years or aged 50–59 years with any two the following three criteria: 1) cause of death is cerebrovascular accident, 2) pre-existing history of systemic hypertension, and 3) terminal serum creatinine >1.5 mg/dl. The criteria for defining ECD was based on the presence of variables that historically increased the risk for graft failure by 70% compared with a standard criteria donor (SCD) kidney (18).

Previous systematic reviews suggested ECD kidneys should not be offered to younger (aged <40 years) kidney transplant candidates or those undergoing re-transplantation (19). ECD kidneys may be better prioritized for older recipients by ignoring immunology-based allocation. Using this strategy, the Eurotransplant Senior program have shown favorable 5-year outcomes using ECD kidneys in older recipients (20).

However, recent analyses support broadening access with careful risk stratification. Querard et al. conducted a systematic review and meta-analysis of 32 studies comparing survival outcomes between SCD and ECD kidneys (21). Pooled 5-year patient survival probabilities were 78.4% versus 86.4% in ECD versus SCD recipients respectively. A significant difference in mortality was observed comparing North American and European studies, with 5-year pooled patient survival closer in European studies (ECD versus SCD; 85.3% versus 90.3% respectively) than in North American studies (ECD versus SCD, 73.4% versus 83.6% respectively). The corresponding pooled RR was estimated at 1.50 (95% CI 0.50–3.43) for the European studies versus 1.62 (95% CI 1.18–2.22) for the North American studies. Similar effect sizes were seen with regards to death-censored graft survival.

ECD kidney allograft survival may be improved in the absence of circulating donor-specific antibody ($p < 0.001$) and CIT <12 h ($p = 0.030$) according to a French study (22). Optimal utilization of ECD kidneys may also be stratified by recipient age, with studies suggesting recipients aged ≥60 years (23) or ≥65 years (24) be prioritized. However, while a 1.75-fold (95% CI 1.53–2.00, $p < 0.0001$) increased risk for graft failure using ECD versus SCD kidneys was observed in one study, population-average effect using propensity scores with 10-year follow-up highlighted a minimal absolute effect of only 8 months (95% CI 2–14 months) quicker time to graft failure attributed to ECD kidneys (24). 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.

Donation After Cardiac Death

DCD refers to a donor who does not meet the criteria for donation after brain death (DBD) but in whom cardiac standstill or cessation of cardiac function occurred before organs were procured, with cessation of cardiac function initiated deliberately (controlled) or occurring spontaneously (uncontrolled) (18).

Data from the United Kingdom, examining outcomes in adult recipients receiving a deceased donor kidney transplant between 2000–2007, compared survival outcomes between 8,289 DBD kidneys and 845 DCD kidneys (25). Despite increased rates of delayed graft function (DGF) after DCD kidney transplantation, first-time recipients of DCD kidneys ($n = 739$) or DBD kidneys ($n = 6{,}759$) showed no difference in 5-year graft survival (HR 1.01, 95% CI 0.83–1.19, $p = 0.97$). Increasing donor or recipient age, repeat transplantation, and CIT >12 h were associated with worse graft survival for recipients of DCD kidneys. Subsequent analyzes demonstrate equivalent 5-year patient survival or 10-year death-censored graft survival comparing DCD versus DBD kidneys (26). Prolonged CIT (>24 h versus <12 h) was associated with poorer graft survival for DCD versus DBD kidneys in cohorts from the United Kingdom and United States (27). The rate of primary nonfunction for both DCD and DBD kidneys was low (3.1 and 2.5% respectively) and not significantly different (risk-adjusted OR 1.18, 95% CI 0.9–1.5, $p = 0.21$) (28). These reassuring long-term outcomes suggest DCD kidneys of any age should be actively considered for all kidney transplant candidates, if logistics and resources can facilitate timely surgery to avoid prolonged CIT.

Studies report heterogeneous outcomes for ECD-DCD kidneys. Locke et al., exploring data from the United States between 1993–2005, observed donor age was associated with increased graft failure risk, although graft survival was similar between ECD-DBD and >50-year old DCD kidneys (29). Singh et al., analyzing data from the United States including 562 ECD-DCD kidneys, showed slightly increased risk for graft loss in recipients receiving DCD versus non-DCD kidneys, which was not significantly modified by ECD status (30). Across a number of studies, ECD-DCD kidneys report acceptable 3-year death-censored graft survival rates between 70%–90%, which are inferior to SCD-DCD kidneys but not ECD-DBD kidneys (26-32). However, Montero et al. demonstrate how important selecting the most appropriate donor-recipient combination is in a recently published risk modelling study (33). In their multi-center cohort study, mortality risk for the highest risk-stratification group receiving ECD-DCD kidneys was significant. Although survival was better post-transplantation compared to remaining waitlisted, it raises a level of caution in decision making when dealing with donor-recipient extremes. Therefore, use of ECD-DCD kidneys is acceptable for select waitlisted kidney transplant candidates when carefully balanced against their mortality risk without transplantation and quality of life considerations.

Kidney Donor Risk Index

The KDRI is a risk quantification score developed in 2009 by Rao et al. using data from the United States between 1995–2005 containing 14 donor- or transplant-specific variables (34). A recent re-evaluation using more contemporary United States data reported the original KDRI remains robust for discrimination and predictive accuracy for graft failure (35). KDRI has been implemented into allocation policy within the United States, with low KDRI (i.e., better quality) kidneys preferentially allocated to kidney transplant candidates with the greatest expected longevity (36).

A pan European study including 24,177 adult kidney transplant recipients demonstrated an increase in KDRI by 1.3% annually, from 1.31 (IQR 1.08–1.63) in 2005 to 1.47 (IQR 1.16–1.90) in 2015, driven by increased donor age, hypertension, and use of DCD kidneys (16). No difference was observed in 5-year patient or allograft survival outcomes, with survival probabilities improving over time for the highest KDRI kidneys. Within any given KDRI interval, although ECD kidneys have higher rates of discard and graft failure risk, the ECD categorization does not confer additional risk of discard or graft failure compared with SCD kidneys within the same KDRI interval (37).

However, caution should be exercised with the KDRI. It contains components which can increase the risk quantification score but now demonstrate comparable outcomes (e.g., DCD). Translatability of the KDRI to population cohorts outside the United States may not be valid (38,39). Due to disparate survival outcomes observed for kidney failure patients treated with dialysis (40,41) versus kidney transplantation (42) in the United States versus elsewhere, and different utilization of deceased donors (e.g., greater use of older and DCD kidneys in the United Kingdom versus the United States for example) (43), generalizability may be invalid.

Donor Age

Donor age has the strongest independent association with long-term kidney transplant outcomes (44). These accepted deleterious effects justify donor age being a component of the KDRI risk score but also the fundamental stratification for ECD classification. Donor age is one of the most frequent explanations for organ discard (8), despite an increasing proportion of deceased organs over time being procured from older donors (16). While many studies dichotomize at an arbitrary cut-off donor age of 60 years, deleterious effects for kidney transplant recipients may start earlier. Keith et al. analyzed data from the United States between 1990 and 1997 and observed adjusted 10-year patient survival starts to drop with deceased donor ages 36–40 years (45). There is a strong interaction between donor and recipient age, with additive detrimental effect on allograft survival with a combination of older kidneys into older recipients (46), although many allocation systems prioritize on this like-for-like basis.

Some centers consider dual versus single kidney transplants using older kidneys. However, when using donors aged ≥60 years, no graft survival advantage at 5-year was observed comparing dual versus single kidney transplantation in an analysis from the United Kingdom between 2005–2017 (adjusted HR 0.81, 95% CI 0.59–1.12). However, dual kidney transplantation did result in slightly higher 1-year estimated glomerular filtration rate [eGFR] (40 versus 36 ml/min/1.73 m^2 respectively, $p < 0.001$) (47).

Donor Ethnicity

Non-white ethnicity demonstrates conflicting associations with kidney transplantation outcomes. Pisavadia et al., exploring data from the United Kingdom between 2003–2015, observed higher risk for graft loss with south Asian (HR 1.38, 95% CI 1.12–1.70, $p = 0.003$) and Black (HR 1.66, 95% CI 1.30–2.11, $p < 0.001$) donated kidneys independent of recipient ethnicity, with no survival advantage from donor-recipient ethnicity matching (48). Locke et al., exploring data from the United States between 1993–2006, suggested DCD kidneys from Black donors, but not DBD kidneys, were associated with better patient and graft survival for Black recipients (49). This contrasts with evidence from registry data that kidneys donated by ethnic minorities (especially Black individuals) are associated with poorer graft survival for any kidney transplant recipient (50,51).

However, using ethnicity for risk stratification of deceased donors is questionable. Ethnicity is not a reliable proxy for genetic difference between individuals (52). While incorporating ethnicity into clinical decision-making can be considered a form of personalized medicine, it may not add additional value. For example, Chong et al., in an analysis of data from the United States between 2000–2017, demonstrated removal of donor ethnicity from KDRI calculations makes negligible difference to patient and kidney allograft survival, strongly advocating for removal of donor ethnicity as a risk factor (53).

Donor Body Mass Index

In a population cohort study from the United Kingdom, Arshad et al. observed an independent association between donor BMI and delayed graft function (54), with risk increased in recipients of kidneys from overweight (Odds Ratio [OR] 1.12, 95% CI 1.00–1.23, $p = 0.022$), obese (OR 1.23, 95% CI 1.08–1.39, $p < 0.001$), and morbidly obese (OR 1.38, 95% CI 1.16–1.63, $p < 0.001$) donors when compared to normal donor BMI group. However, donor BMI did not influence long-term patient or graft survival. This is corroborated with data from the United States. In a study of 6,932 recipients of DCD kidneys in the United States, Ortiz et al. reported donors with a BMI between 30.0–34.9 kg/m^2 incurred 1.77-fold increased odds of developing DGF, with similar odds for DGF in donors with a BMI between 35.0–39.9 kg/m^2 (OR 1.78, $p < 0.001$) (55). However, only DCD kidneys from donors with a BMI >45.0 kg/m^2 were associated with an increased risk of death-censored graft failure (adjusted HR 1.84, 95% CI 1.23–2.74, $p < 0.001$) relative to a normal donor BMI category.

Donor Size

The influence of donor-to-recipient size matching has shown conflicting results. Arshad et al., exploring data from the United Kingdom between 2003–2015, showed no association between donor-to-recipient size match difference and risk for

DGF or death-censored graft survival (56). Donor-to-recipient difference in body weight was associated with higher 12-month creatinine in large recipients receiving small donor kidneys. Increased mortality was observed in recipients receiving larger kidneys (HR 1·21, 95% CI 1.05–1.40 $p = 0.009$), which conflicts with other population-cohort studies that show inferior long-term patient and graft survival associated with larger recipients receiving smaller donor kidneys (57-59). Some show negative effects of size mismatch (large kidney into small recipient) only in the context of ECD kidneys (58) or male recipients of female kidneys (59).

Donor Acute Kidney Injury

The relationship between donor AKI and kidney transplant outcomes has been reviewed by Koyawala and Parikh (60). In total, 37 studies were identified comparing transplant outcomes between kidneys with versus without donor AKI. Donor AKI was associated with DGF, with prolonged nights in hospitals and additional attributed costs. In a separate meta-analysis of 14 cohort studies exploring 15,345 donors, Zheng et al. estimate the relative risk of DGF to be 1.76 (95% CI 1.52–2.04) for recipients of kidneys with versus without donor AKI (61).

No association is seen between donor AKI and risk for rejection after 6 months or 1 year, either in a review of published studies (60) or meta-analysis of empirical data (RR 0.87, 95% CI 0.66–1.15) (61). No association was seen between donor AKI and graft function (60).

From a graft survival perspective, donor AKI was not associated with graft failure in 25/29 studies (60). However, some studies provide more granular insight. Botha et al. analyzed 11,219 transplanted kidneys in the United Kingdom, comprising 1,869 (17%) with AKI (62). While 1-year graft survival difference was statistically significant comparing AKI versus non-AKI donor kidneys, the numerical difference was clinically insignificant (89% versus 91% respectively, $p = 0.02$). DGF rates increased with severity of AKI (no AKI = 28%, AKI stage 1 = 35%, AKI stage 2 = 43%, AKI stage 3 = 55%, $p < 0.005$). Primary nonfunction rates were higher with donor AKI stage 3 versus no AKI kidneys (9% versus 4%, $p = 0.04$) and graft function was lower among donor AKI kidneys (OR 1.25, 95% CI 1.08–1.31, $p < 0.005$). This study differed from other cohorts due to its higher sample size, with a larger proportion of donor kidneys with severe AKI and donation after circulatory death, meaning this study may be better powered to observe differences in outcomes among donor kidneys with higher levels of injury. Other studies observed higher rates of graft failure only among a sub-select of studies using ECD donor kidneys with AKI (63,64).

Donor AKI is more acceptable with high versus low quality kidneys. Single center outcomes using donors with both AKI (comparing advanced stages 2–3 versus 0–1) and high KDPI (≥85%) demonstrated more DGF (71% versus 37% respectively, $p < 0.001$), more primary nonfunction (5.3% versus 0.6% respectively, $p = 0.02$), no difference in eGFR in ml/min/1.73^2 (44 versus 46 respectively, $p = 0.42$) and lower 1-year death-censored graft failure 14.5% versus 3.5% for AKI 2-3 versus AKI 0-1 high KDPI kidneys respectively (HR 2.40, 95% CI 1.24–4.63, $p = 0.01$) (65).

Donor Diabetes

Cohen et al. studied survival outcomes for kidney transplant patients receiving diabetic versus non-diabetic kidney allografts in the United States between 1994–2013 (66). Recipients of diabetic donor kidneys had higher rates of all-cause allograft failure (HR 1.21, 95% CI 1.16–1.26) and death (HR 1.19, 95% CI 1.13–1.24) compared to receiving non-diabetic donor kidneys. Allograft survival was worse for younger (≤45 years of age) versus older recipients of diabetic donor kidneys, but no difference was observed in patient survival. Due to a significant interaction between donor and recipient diabetes status (with diabetic recipients receiving diabetic donor kidneys having the worst patient and allograft survival), paired analyzes of mate-kidneys from the same donor were undertaken where one recipient was diabetic and the other non-diabetic. In this analysis, diabetic recipients had significantly higher risk of allograft failure (HR 1.27, 95% CI 1.05–1.53) and death (HR 1.53, 95% CI 1.22–1.93) compared to non-diabetic recipients. Diabetic recipients of non-diabetic donor kidneys and non-diabetic recipients of diabetic donor kidneys had similar rates of all-cause allograft survival.

The critical question is whether waitlisted patients should accept diabetic donor kidneys versus waiting for better kidneys. Cohen et al. compared survival benefits of kidney transplantation using diabetic donor kidneys versus remaining on the waiting-list in the United States between 1994–2015 (67). They observed recipients of diabetic donor kidneys had lower mortality compared with remaining on the waiting-list and/or transplantation later with a non-diabetic donor kidney (adjusted HR 0.91, 95% CI 0.84–0.98). Although recipients of non-diabetic donor kidneys with high KDPI scores had lower mortality risk (adjusted HR 0.86, 95% CI 0.81–0.91), recipients of diabetic donor kidneys with similar high KDPI scores showed no survival difference (adjusted HR 1.09, 95% CI 0.97–1.22). Younger waitlisted patients (aged <40 years) had no survival benefit from transplantation with diabetic donor kidneys, while diabetic patients with longer waiting-list times attained the greatest survival benefit.

Donor Hypertension

Donor hypertension is increasing in prevalence and observed in nearly a third of deceased donors (16). Altheaby et al., in a systematic review and meta-analysis, identified 15 studies published between 1963–2014 exploring the association between donor hypertension and kidney transplant outcomes (68). Pooled risk ratios (RR) demonstrate donor hypertension is associated with kidney allograft failure (RR 1.31, 95% CI 1.06–1.63, $p = 0.014$) but not mortality (RR 0.996, 95% CI 0.652–1.519, $p = 0.984$).

Donor Smoking

Donor smoking and kidney transplant outcome associations are unclear. Lin et al. explored data from the United States between 1994–1999 and observed smoking history among deceased

kidney donors was associated with increased transplant recipient risk for death and graft loss (69). However, Gillott et al. explored data from the United Kingdom between 2001–2013 and observed no association between donor smoking and allograft survival for kidney transplant recipients, although an association with mortality was observed (adjusted HR 1.16, 95% CI 1.03–1.29, $p = 0.011$) (70).

Donor Cause of Death

Death by cerebrovascular accident remains the commonest cause of death, varying little across Europe between 2005–2015 (16), and contributes to ECD classification for donors aged ≥50 years. Few studies have explored the impact of cause of donor death and recipient outcomes, although cause of death that can result in disease transmission has been of greater concern.

Donor-Derived Disease Transmission

Risk for donor-derived disease transmission (defined as either infection or malignancy) leading to morbidity or mortality occurred in only 0.96% of all solid organ transplantation in the United States (71). Increased risk for disease transmission (IRD) kidneys tend to be better quality (defined as lower KDPI scores) and associated with survival benefits. For example, Bowring et al. analyzed data in the United States between 2010–2014 and demonstrated: 1) recipients who declined IRD kidneys and subsequently received non-IRD kidneys accepted a higher median KDPI (21 versus 52 respectively); and 2) after a short risk period in the first 30 days following IRD acceptance (adjusted HR 2.06, 95% CI 1.22–3.49, $p = 0.008$) (absolute mortality 0.8% versus 0.4%), those who accepted IRDs had lower risk of death 1–6 months (adjusted HR 0.67, 95% CI 0.50–0.90, $p = 0.006$) and beyond 6 months (adjusted HR 0.52, 95% CI 0.46–0.58, $p < 0.001$) (72).

However, most cases of donor-disease transmission will occur in clinically covert donors. For example, in a systematic review of published literature, donors with a history of cancer or an ongoing malignancy contributed to disease transmission in only 17.1% ($n = 32$) of cases (73). Using data from the United Kingdom, it is estimated the risk of transmitting cancer from a donor not known to have a malignancy is very low at 1 in 2,000 (0.05%) (74).

Donor Increased Risk Behavior

Increased risk behavior (IRB) among deceased donors can be classed as intravenous drug use (IVDU), imprisonment, or high-risk sexual behavior. Trotter et al, analyzing data from the United Kingdom between 2003–2015, studied the outcomes associated with use of IRB deceased donor kidneys (75). Donors with IRB provided 1,091 organs for transplantation (including 624 kidneys) and transplant outcomes were similar in recipients of organs from donors with versus without IRB. Only three cases of unexpected hepatitis C virus transmission were identified, all from an active IVDU donor who was hepatitis C virus seronegative at time of donation but was found to be viremic on retrospective testing. National registry data and single center studies from the United States have shown excellent outcomes and minimal risk associated with using deceased donor kidneys from IVDU individuals (76-79). High decline rates observed with IRB kidneys (75,76) suggest a valuable but underutilized resource due to a subjective perception of heightened risk for kidney transplant recipients not supported by objective evidence.

DONOR HISTOPATHOLOGY

The benefit of obtaining donor histopathology to guide kidney utilization is unclear. In a systematic review of published evidence, Wang et al. combined empirical evidence from 47 studies (80). In these retrospective studies exploring heterogenous histopathological criteria, no semi-quantitative scoring system was conclusively associated with post-transplant outcomes including DGF, grant function, and/or graft failure. This may relate to weak inter-observer correlation and variability between pathologists, which could be improved using a dedicated pool of specialist pathologists (81). Preimplantation biopsy analysis may be useful in a subset of deceased donor kidneys where chronic injury is prevalent like ECD kidneys. Based upon this rationale, the PreImplantation Trial of Histopathology In renal Allografts (PITHIA) study is an open, multicenter, stepped-wedge cluster randomized study, that involved all UK adult kidney transplant centres (82). Using a pool of dedicated pathologists, it will explore whether a national, 24-h, digital histopathology service improves organ utilization from deceased donors aged 60 years and over. The results from this national study are awaited but should provide clarity regarding the value of pre-implantation donor histopathology.

DECISION CHALLENGES

Translating this evidence to nuanced decision-making is the big challenge. No guidelines or recommendations exist to support this process, which is difficult considering the nature of available data. For example, most deceased donors will have a combination rather than individual clinical factors (see **Figure 3**). This requires individualized considerations of population-level data which are not amenable to simple flowcharts. Organ utilization has behavioral components, from both patients and professionals, that will influence decision-making, and it is important every kidney transplant candidate receives the same opportunities (83). Therefore, consensus recommendations to support decision-making may be welcomed by the transplant community.

However, this is a challenge due to the multi-factorial factors that influence post-transplant outcomes. Kerr et al., exploring data from the United States, quantified the magnitude of paired deceased donor effects when transplanted into different recipients (84). In analyses adjusted for KDPI, Kerr et al. demonstrated moderate donor effects for DGF and minimal donor effects for 1- and

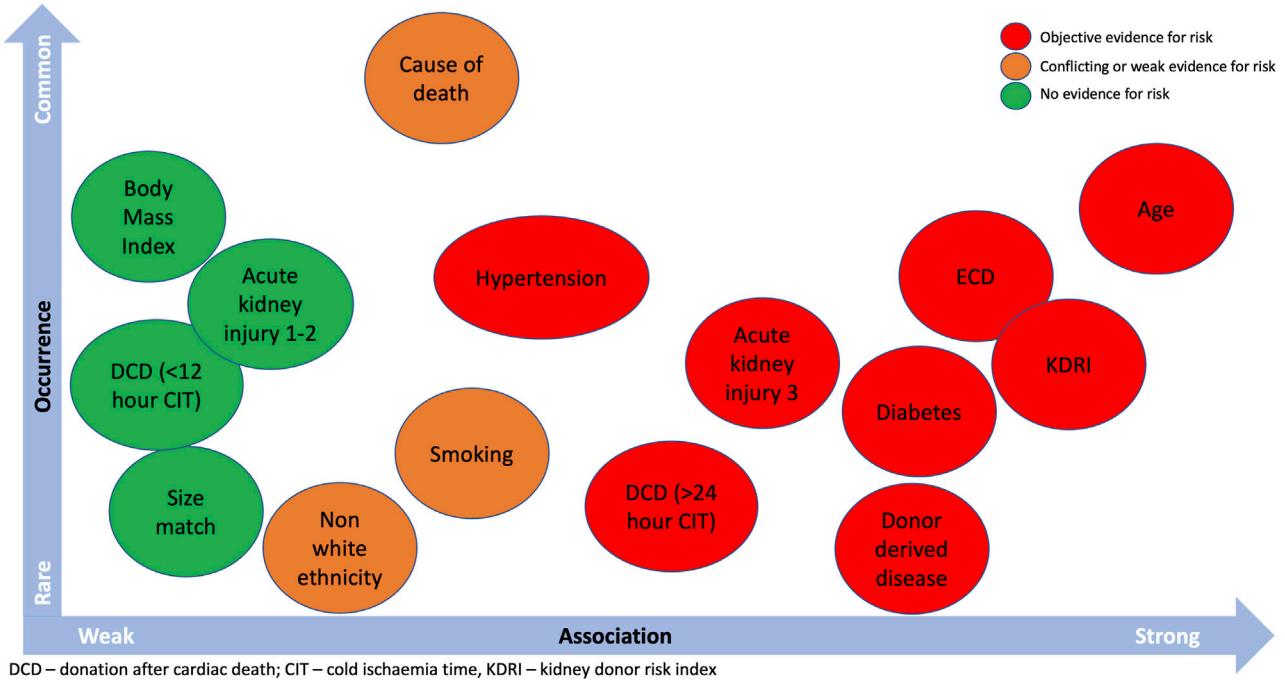

FIGURE 3 | Donor characteristics that can influence kidney allograft outcomes and the probability of occurrence.

3-year graft failure, with 4%–8% excess absolute risk over baseline for a graft if the mate kidney failed. Therefore, it is important to appreciate that post kidney transplant outcomes are influenced by a complex interplay of factors that include, but are not exclusive to, donor characteristics.

Developing and validating novel strategies and/or techniques to improve the process is therefore necessary. Various tools to aid decision-making are currently available or under investigation. These include donor risk scores in the setting of DCD kidneys (85), donor-recipient characteristics (86), donor-specific features (87), monitoring of perfusion parameters and assessment of tissue viability function *ex situ* (88), molecular diagnostics (89), and machine learning and artificial intelligence (AI) algorithms (90-92). The latter remains in its infancy, with tremendous potential to augment the decision-making regarding transplantation (93), but requires more granular data, generalizability, and validation across different population cohorts to enter mainstream use. Such AI tools must provide survival probabilities for kidney transplant candidates to proceed with an individual organ offer versus remaining on the waiting-list to allow a meaningful decision to be made about transplantation. While some risk communication tools are available (http://www.transplantmodels.com or https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/risk-communication-tools/for the US and UK respectively), they lack the machine learning capability or enhanced AI to provide more personalized risk probabilities.

CONCLUSION

Complex deceased donor kidney offers, with time-pressured decision-making, can lead to unnecessary decline and/or discard of acceptable kidneys. By outlining donor clinical factors associated with post kidney transplant outcomes, the aim of this review is to support clinical decision-making. However, donor characteristics are only one component of a complex interplay that influence post-transplant outcomes. While any kidney allograft may not be better than no kidney allograft in every clinical scenario, the objective evidence would argue most kidney allografts are better than being denied the opportunity of kidney transplantation if deemed suitable for waitlisting.

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

AS is the local Clinical Lead for Utilisation (CLU) supported by NHS Blood and Transplant. AS has participated in the Stakeholder Forum for the Organ Utilisation Group set up by the Department of Health and Social Care. Both organisations have had no role in the writing of this manuscript.

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SYSTEMATIC REVIEW AND META-ANALYSIS
published: 05 August 2022
doi: 10.3389/ti.2022.10565

Follow-Up of Offspring Born to Parents With a Solid Organ Transplantation: A Systematic Review

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Pregnancy after solid organ transplantation (SOT) has potential risks for the offspring. Most existing research focused on short-term pregnancy outcomes. The aim of this systematic review was to evaluate available data concerning longer term outcomes (>1 year) of these children. A systematic literature search, following PRISMA guidelines, of PubMed and Embase was performed from the earliest date of inception through to 6th April 2022. Publications on all types of (combined) SOT were eligible for inclusion. In total, 53 articles were included. The majority assessed offspring after kidney (78% of offspring) or liver transplantation (17% of offspring). 33 studies included offspring aged >4 years and five offspring aged >18 years. One study was included on fathers with SOT. The majority of the 1,664 included children after maternal SOT had normal intellectual, psychomotor, and behavioral development. Although prematurity and low birth weight were commonly present, regular growth after 1 year of age was described. No studies reported opportunistic or chronic infections or abnormal response to vaccinations. In general, pregnancy after SOT appears to have reassuring longer term outcomes for the offspring. However, existing information is predominantly limited to studies with young children. Longer prospective studies with follow-up into adulthood of these children are warranted.

Keywords: transplantation, long-term, offspring, follow-up, pregnancy

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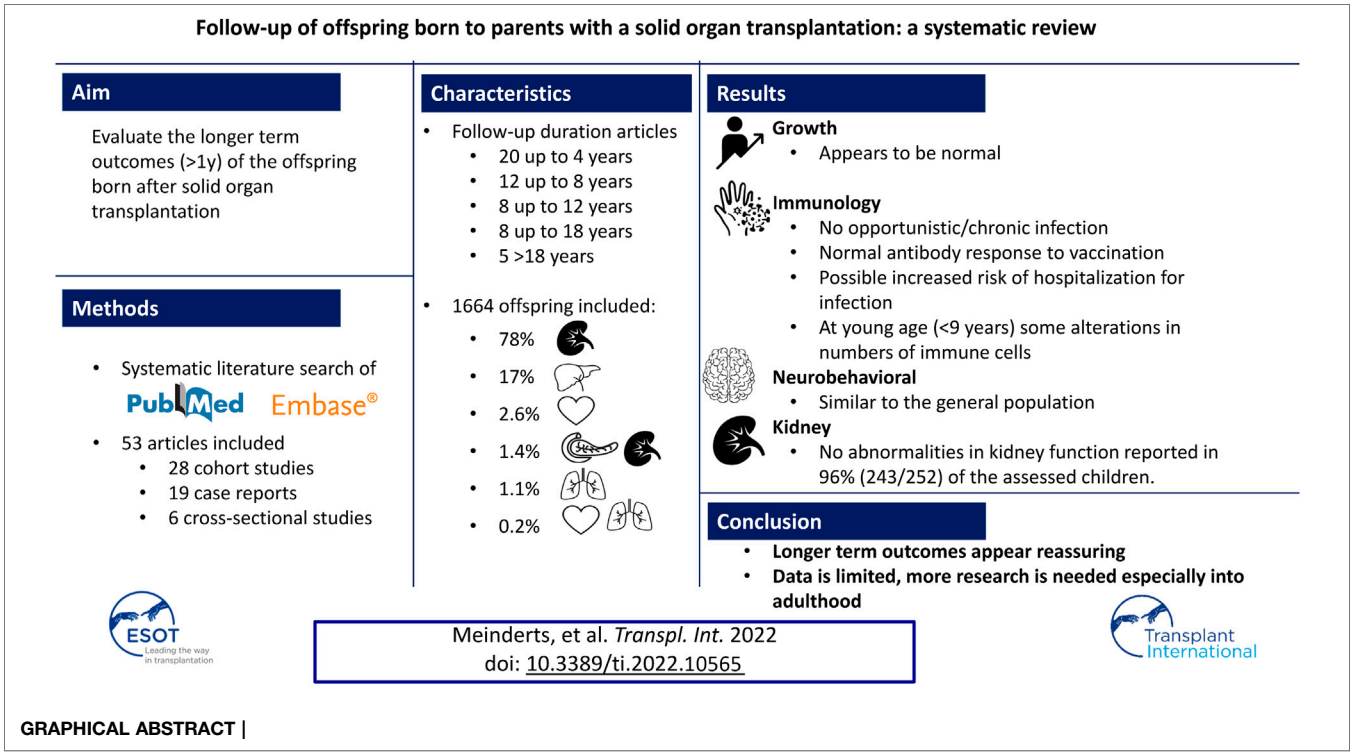
***Received:** 12 April 2022*
***Accepted:** 06 July 2022*
***Published:** 05 August 2022*

Citation:
Meinderts JR, Prins JR, Berger SP and De Jong MFC (2022) Follow-Up of Offspring Born to Parents With a Solid Organ Transplantation: A Systematic Review. Transpl Int 35:10565. doi: 10.3389/ti.2022.10565

Abbreviations: HTx, heart transplantation; IQ, intelligence quotient; JBI, Joanna Briggs Institute; KTR, kidney transplant recipient; KTx, kidney transplantation; LBW, low birth weight; LiTx, liver transplantation; LuTx, lung transplantation; MMF, mycophenolate mofetil; NOS, Newcastle Ottawa Scale; PRISMA, preferred reporting items for systematic review and meta-analyses; SOT, solid organ transplantation.



GRAPHICAL ABSTRACT |

INTRODUCTION

Solid organ transplantations (SOT) are increasingly performed worldwide. Pregnancy numbers after SOT have increased. Over 3,200 pregnancies after maternal SOT have been described in the Transplant Pregnancy Registry International (TPRI) database (1). SOT pregnancies are associated with increased incidence of prematurity and low birth weight (LBW) (1–3). All pregnancies after SOT are classified as high risk (1), but risk differs per SOT. The most severe risk is seen after heart and lung transplantation (HTx, LuTx) (1). However, after kidney and liver transplantation (KTx, LiTx), live birth rate and miscarriage rates are reported to be similar to the general population (3–5), and the majority of offspring in SOT pregnancies are reported as healthy at birth (1–4). Most data on the offspring only focused on perinatal outcomes such as prematurity, birth weight, congenital abnormalities, congenital infections, and APGAR scores. A recent overview on post-transplant pregnancy by Klein et al. emphasized the lack of available data on the long-term health of the offspring (6). To the best of our knowledge, no systematic review on longer term outcomes after birth of the offspring born after SOT exists. Therefore, the aim of this systematic review is to evaluate the available data concerning longer term outcomes (>1 year) of children of SOT patients.

MATERIALS AND METHODS

Data Sources and Searches

A systematic literature search, made in consultation with an information specialist, of PubMed and Embase was performed, from the earliest date of inception through to 6th April 2022. A protocol for the systematic review was prepared locally but not submitted or registered online. The following key terms and their synonyms were used: organ transplantation (with all SOT transplants: heart, lung, kidney, liver, pancreas and small bowel separately mentioned), pregnancy, child. A reproducible search strategy is provided in **Supplementary Table S1**.

Study Selection

All pregnancies with either a mother or father with a SOT (heart, lung, kidney, liver, pancreas, or small bowel) as well as combined SOT in their history were eligible for inclusion. Articles were included if >1-year follow-up data of the offspring was described. In overlapping articles, the most recent article was included. Articles not written in English, conference abstracts, (systematic) reviews, and meta-analysis were excluded.

Initial selection based on title and abstract was performed by two researchers (JRM and MFC) independently. All disagreements were discussed and, if there was doubt, the study was included for full-text screening, performed by the same two researchers. All discrepancies during full-text screening were resolved by consensus by the same two researchers. All citations of eligible articles and relevant review articles were consulted for **Supplementary References**. Two articles were identified that were not found in the primary search. The PRISMA (preferred reporting items for systematic review and meta-analyses) flowchart (7) was used to document the number of articles included and excluded, including the rationale for exclusion (**Figure 1**).

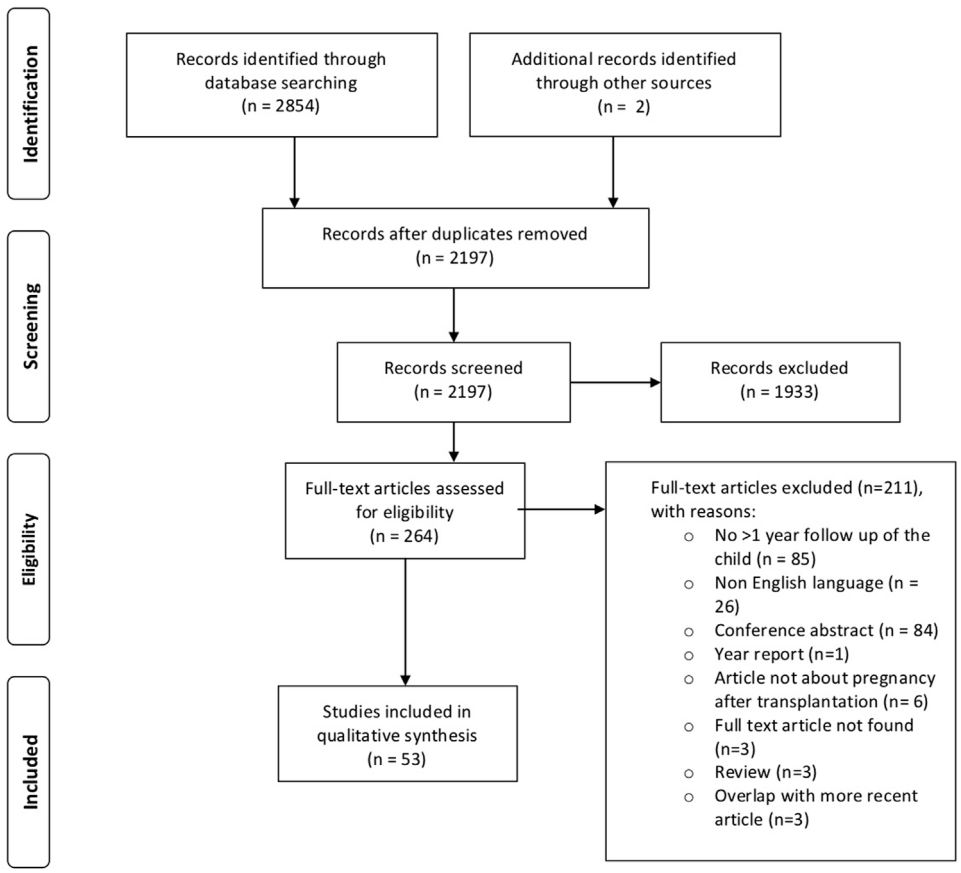


FIGURE 1 | PRISMA flow diagram study inclusion.

Data Extraction

Data extraction was carried out by one researcher (JRM). A second researcher (MFC) independently performed a full-text check for accuracy and completeness. All discrepancies were resolved by consensus of the authors. For each included study the following data was extracted and summarized in two tables: first author, country, study type, follow-up period, number of live births, transplanted organ, immunosuppressive regimen, mean/median birth weight, mean/median gestational age, method of assessment, and the longer-term outcomes. All longer-term outcomes were evaluated, with specific attention for growth, immunological, neurocognitive, and behavioral follow-up and kidney function. Data on intra uterine fetal deaths and miscarriages were not included. Authors of primary studies were not contacted to provide missing data. Biased appraisal of the articles was performed by two researchers (JRM and JRP) (**Supplementary Tables S2A,S2B**). For prospective and retrospective cohort studies we used the Newcastle Ottawa Scale (NOS) for cohort studies (8). For cross-sectional studies and case reports we used the applicable Joanna Briggs Institute (JBI) critical appraisal checklists (9).

Definitions

The following definitions were used: preterm: <37 weeks of gestation, LBW: <2,500 g, and catch-up growth: rapid growth in children following a period of reduced growth (10).

RESULTS

The systematic search yielded 2,854 articles. 657 were duplicates (**Figure 1**). After full text screening ($n = 264$), $n = 53$ articles were selected (**Tables 1**, **2**; **Supplementary Tables S2A,S2B**), yielding 19 case reports, 18 retrospective, 10 prospective, and six cross-sectional cohort studies. In 16 studies a comparison with a control group was made, whereby the control group was matched in 12 studies. In 13 articles, pregnancies after multiple SOT types were assessed, leading to 36 articles assessing offspring born after KTx, 16 after LiTx, three after combined pancreas-kidney transplantation, seven after HTx, one after LuTx, and one after combined heart-lung transplantation. No article about offspring born after small bowel transplantation was found.

TABLE 1 | Included studies, cohort studies.

Author (Year), country	Transplanted organ, number of children	Follow-up age children	Outcome measures
Devresse (2022), Belgium (13)	Kidney: 43 infants (2 twins) from 32 women (57 pregnancies), 48% female	Median follow-up 17 years (range 7–25)	• Questionnaire sent to 43 children or their parents if < 18 years. 21 responded. Questions on current situation (weight, height, familial status, and treatment), medical history (hypertension, diabetes, and depression), addictions (smoking, etc.) and education
Egerup (2021), Denmark (49)	Kidney: 124 infants Control: 1,231 infants	Median follow-up 14.5 years [IQR 7.1–22.8] Median follow-up control group 14.1 years IQR 6.6–25.4]	• Administrative codes of diagnosis and antibiotic prescriptions identified in national registries
Borek-Dziecioł (2020), Poland (58)	Kidney: 40 infants Control: 40 infants	Newborns, infants, and children over 1 year of age were examined. Not described at what age	• Renal parameters: urea, creatinine, potassium, and sodium concentration were analyzed
Dębska-Slizien (2020), Poland (26)	Kidney: 25 infants	Median follow-up 9 years (range 0.5–30 years)	• No specific long-term outcomes described
Bachmann (2019), Germany (40)	Kidney: 30 infants Combined kidney-pancreas: 2 infants	Follow-up at birth, 12 and 24 months 65.6% of the children had a complete dataset at 24 months	• Physical and psychomotor development examination by a pediatrician, collected from the patient file (weight, length, and head circumference) • Questionnaire filled in by the mother about the child (physical examination, anthropometric measures, medical, and paramedical history)
Morales-Buenrostro (2019), Mexico (50)	Kidney: 50 infants Control: 50 infants	Children >4 years were included. Most children were aged between 6 and 16 years (n = 32 in the study group and n = 37 in the control group)	• Interview with the mother and the child • Intellectual performance: IQ scores (age-specific test: WPPSI, WISC-IV, WAIS-III)
Schreiber-Zamora (2019), Poland (1) (51)	Kidney: 36 infants Control: 36 infants	Follow-up at one time-point, median 3.12 years	• Age-specific neurological examination including ultrasound
Schreiber-Zamora (2019), Poland (2) (42)	Liver: 35 infants Kidney: 26 infants Control: 64 infants	Follow-up Tx group: 6 children 1–12 months, 15 children 1–3 years, 25 children 3–6 years, 15 children >6 years Follow-up control group: 7 children 1–12 months, 16 children 1–3 years, 24 3–6 years, 17 children >6 years	• Measurement of BMI as a one-time measurement
Turkyilmaz (2018), Turkey (14)	Liver: 8 infants	Mean follow-up 3.2 years ± 2.4 years, range 1–7 years	• Retrospective analyses of patient records, no specific long term outcome measurements described
Kociszewska-Najman (2018), Poland (52)	Liver: 42 infants Kidney: 38 infants Control: 78 infants	1 assessment per child (n = 31 < 30 months, n = 47 > 30 months)	• Psychological examination performed by qualified clinical psychologists. Results expressed in IQ (age specific tests: Psyche Cattell Infant Intelligence Scale, Terman-Merril Intelligence Scale, Scales of Raven's Progressive Matrices)
Ono (2015), Brazil (44)	Kidney: 28 infants (1 twin) Control group 1: 40 infants Control group 2: 28 infants	Immunological follow-up at birth and at 8 months of age. General follow-up by the pediatrician every month during the first 6 months, every 3 months until 2 years of age	• Blood sample collection at birth from the umbilical cord and at 8 months from a peripheral vein. Immuno-phenotypic studies were done with fresh blood. Each sample was stained with fluorochrome-conjugated monoclonal antibodies • Factors associated with hospital admission were analyzed by univariate logistic regression
Czaplinska (2014), Poland (60)	Liver: 51 infants Control: 51 infants	Neonates, infants, and children >1 year of age were examined. Not described at what age	• Analysis of liver parameters: alanine transaminase (ALT) and aspartate transaminase (AST) and two kidney parameters (urea and creatinine)
Norrman (2014), Sweden (61)	Kidney Group 1: 7 infants (1 twin) Group 2: 199 infants Control Group 3: 665 infants Group 4: 3,980 infants	Group 1: mean age at follow-up: 9.7 ± 4.2 years Group 2: mean age of follow-up: 14.7 ± 9.4 years	• Retrospective analyses of 5 registries: National Quality Register of Assisted Reproduction, the National Register in IVF, the Swedish Medical Birth Register, the National Patient Register, and the Swedish Cause of Death Register
Drozdowska-Szymczak (2014), Poland (48)	Kidney: 39 infants Control: 39 infants	Follow-up at 1 time-point, range: 1 day-15 years (n = 26 > 10 months) and in the control group 1 day till 14 years	• Serum IgG and IgM measurements at 1 time-point with agglutination immunoassays
Kociszewska-Najman (2013), Poland (62)	Liver: 37 infants Kidney: 45 infants Control: 66 infants	Follow-up: neonatal (1–4 weeks of age), babyhood (2–12 months), early kindergarten (1–3 years), later kindergarten (4–6 years) and school years (>6 years). Not all children at all follow-up moments tested. Most children tested in the late kindergarten stage	• Retrospective analyses of the parameters in the neonatal period of the child • Prospective ophthalmological examinations by a pediatric ophthalmologist

(Continued on following page)

TABLE 1 | (*Continued*) Included studies, cohort studies.

Author (Year), country	Transplanted organ, number of children	Follow-up age children	Outcome measures
Shaner (2012), United States (16) Nulman (2010), Canada (30)	Lung: 18 infants (1 triplet) Kidney: 39 infants Control: 38 infants	Follow-up mean: 7.0 years (± 5.37), range: 1.25 till 17.36 years Mean follow-up 8.06 years, range: 3 years 7 months till 15 years 9 months	• NTPR registry and retrospective questionnaires, no specific long-term outcomes described • Physical examination of the child (weight, length, and head circumference) • Psychological examination of mother and child conducted by a trained psychologic assistant under supervision of a registered psychologist • Child: IQ: WPPSI-R, Visuomotor abilities: VMI-4 and the WRAVMA.
Al-Khader (2004), Saudi-Arabia (12)	Kidney: 110 infants (3 twins)	Follow-up of 41 infants, mean follow-up: 52 months (range: 13–83 months)	• Retrospective analyses of medical records including laboratory measurements, no details on the method of follow-up mentioned
Miniero (2004), Italy (18)	Kidney: 52 infants Liver: 7 infants Heart: 8 infants (1 twin)	Follow-up ranging from 2 months till 13 years	• Retrospective questionnaires, patient record data, and interviews in person or by telephone (growth, vaccinations, allergic reactions, diseases, laboratory tests, and last measured height and weight)
Bar (2003), Israel (63)	Kidney: 48 infants Control: 48 infants	Follow-up 2–7 years	• Retrospective analyses of medical records (short-term outcomes e.g., caesarean delivery, hospitalization, stillbirths) • Blinded periodical examination up to 7 years (maternal renal function, infant status, presence of severe handicap)
Sgro (2002), Canada (31)	Kidney: 32 infants Control: 88 infants	Follow-up mean 3.1 year (range 3 months till 11 years)	• Retrospective analyses of medical records • Pediatric follow-up visit: physical examination including growth parameters, neurodevelopmental assessment (Denver Developmental Screening test)
Giudice (2000), France (32)	Kidney: 10 infants (1 twin) Pancreas-kidney: 1 infant Heart: 2 infants Liver: 1 infant	Follow-up of 12 children at 2.6 ± 1.8 years (range 1.0–6.9 years)	• Renal function tests (blood pressure, inulin clearance, paraminohippuric acid clearance, microalbuminuria, electrolyte reabsorption rate, renal ultrasound including renal size) • Retrospective neonatal history • Complete physical examination at the time of the renal function study
Willis (2000), United Kingdom (33)	Kidney: 48 infants (1 triplet)	Median follow-up: 5.2 years (range 9 months–18 years)	• Surveys, semi-structured interviews, medical records, and physical examination carried out by a researcher (blood pressure, developmental milestones, scholastic and educational achievements, urine sample, ultrasound examination of the urinary tract)
Stanley (1999), United States (56)	Kidney: 175 infants (52% girls)	Range of the child's age at interview: 4 months-12 years, mean age: 4.4 years	• Assessment of developmental status (≤5 years: Child Development Review system, >5 years: prior developmental or present educational morbidity reported by the mother)
McGrory (1998), United States (19)	Combined pancreas -kidney and 1 pancreas followed by kidney: 20 infants	Follow-up ranging from 1 month to 8 years	• Data collected from a questionnaire, medical records, and telephone interviews. No specific long-term outcome measurements
Wu (1998), Germany (34)	Liver: 23 infants (1 twin)	Follow-up range 1–99 months 5 children <1 year at last follow-up	• Data obtained via medical records and questionnaires evaluated by the pediatrician (height and weight, psychological development, neurological development)
Jain (1997), United States (35)	Liver: 27 infants (long-term follow-up n = 25)	Multiple, frequency and timing not specified, follow-up moments. Median follow-up of 39 months (range 10–76 months)	• Prospectively collected data by patients, obstetricians, and the physicians. Weight for age percentiles calculated from the National Center for Health Statistics percentiles
Wong (1995), New-Zealand (55)	Kidney: 11 infants	Follow-up ranging from 15 months to 18 years	• Retrospective information from medical records (clinical and laboratory data, physical growth, physical examination, school performance, work achievement, social behavior, developmental milestones tested with the Denver developmental screening test)

(Continued on following page)

TABLE 1 | (*Continued*) Included studies, cohort studies.

Author (Year), country	Transplanted organ, number of children	Follow-up age children	Outcome measures
Pilarski (1994), Canada (45)	Kidney: 11 infants Liver: 1 infant	1 follow-up per infant. Follow-up time ranging from 5 months till 9 years (1 child <1 year at follow-up)	• Immunological assessment of blood samples
Pahl (1993), United States (43)	Kidney: 26 infants	Mean follow-up: 5 years, range: 1 week - 18 years (5 children <1 year)	• Analyses of medical records (mother and child if present), interviews with the physician, interviews of the mothers by telephone or email (childhood development of their child (ren))
Shaheen (1993), Saudi Arabia (59)	Kidney: 26 infants	Mean follow-up 39 months (range 6–72 months)	• Basic tests of kidney function and integrity on 22 children • Serum cyclosporine was measured in whole blood using radioimmunoassays
Wagoner (1993), United States (25)	Heart: 28 infants Heart and lung: 3 infants	Mean follow-up 3.4 years (range 3 months till 6.5 years)	• Questionnaires study: no specific long-term outcome measurements described
Rasmussen (1981), Sweden (47)	Kidney: 5 infants	Follow-up ranging from 4.5 to 9 years. Follow-up frequency between 2 and 4 times	• Somatic and psychomotor evaluation at regular intervals • Immunological follow-up from peripheral blood at multiple time points: % rosette-forming PBM's, proliferative responses of PBM to phythemagglutinin and pokeweed mitogen, counting the PBMs with surface immunoglobulins using fluoresceinated anti-light chain antisera, quantitative immunoglobulin levels for IgG, IgA and IgM, serum testing for antibodies against hepatitis B, polio virus, Haemophilus influenza, and *Escherichia coli*. Serum aspartate transferase and alanine transferase in HBsAg-positive children • Chromosomal analyses performed in 4 children
Korsch (1980), United States (11)	Fathers with a kidney Tx: 4 infants (0 girls) from 3 fathers Mothers with a kidney Tx: 6 infants (2 girls) in 5 women	Follow-up: ranging from 4 months to 6 years and 8 months (father KT: 4 months, 10 months, 11 months, 2 years 7 months and mother KT: 7 months, 1 year, 1 year 10 months, 2 years 4 months, 3 years 2 months, 6 years 8 months)	• Patient records, physical examination by a pediatrician • Developmental evaluations on nine of the children by a specialist in assessing child development (age specific: Stanford-Binet test, Gesell Developmental Schedules, and Bayley Scales of Infant Development) • A semi-structured interview by a social work assistant trained in sociologic research methods on the parents' attitudes about their child's development

One study on children from fathers with SOT was found (11). The majority of the studies (n = 33 (62%)) reported results on children with a follow-up of >4 years. Of these, twelve reported on children aged up to 8 years and eight on children aged up to 12 years. Follow-up on children aged up to 18 years was reported in eight studies and in five studies, children above the age of 18 were included (**Tables 1**, **2**). Paragraphs 3.1–3.6 describe the offspring born to mothers with a SOT; paragraph 3.7 describes the offspring born to a father with a SOT.

Characteristics of Included Patients

A total of 1,664 live births were recorded, of which 78% (n = 1,290) were born after KTx, 17% (n = 287) after LiTx, 2.6% (n = 43) after HTx, 1.4% (n = 23) after combined pancreas-kidney transplantation, 1.1% (n = 18) after LuTx, and 0.2% (n = 3) after combined heart-lung transplantation. In pregnancies of which the complete immunosuppressive regimen was known, 78% of the women used corticosteroids, 49% cyclosporine, 41% azathioprine, and 30% tacrolimus. In 51 pregnancies with a live birth mycophenolate mofetil (MMF) was used for at least part of gestation, in five pregnancies rapamycin, and in one pregnancy everolimus. Two studies did not specify if MMF and/or rapamycin was stopped during pregnancy (12, 13). No congenital abnormalities were mentioned in these live-born children. Details on gestational age and birth weight can be found in **Supplementary Tables S2A,S2B**. In 15 articles (n = 191 children, 12%) "normal development," "no problems," or "doing well" was mentioned without conducting specific tests or parameters (14–28).

Growth

Specific results on growth were described in 16 articles (11, 29–43), of which 6 are case reports (29, 36–39, 41). Overall these results indicate that growth development in the offspring of SOT patients is normal. Of the 234 children born after KTx, 219 (94%) had weight and length development comparable to the general population (11, 30–33, 37–40, 42, 43). Sgro et al. reported a significantly higher weight for age and a significantly lower

TABLE 2 | Included studies, case reports.

Author (Year), country	Transplanted organ, number of children	Follow-up age children	Outcome measures
Rao (2019), Australia (41)	Kidney: 1 infant	Follow-up 2 years	• The weight of the infant was followed up for 2 years
Mahmoud (2017), Kuwait (15)	Kidney: 4 infants (1 triplet)	Follow-up at birth, discharge, 12 months and 24 months	• No specific outcome measurements described
Kociszewska-Najman (2012), Poland (29)	Liver: 2 infants	1 infant: follow-up visit at 7 months 1 child follow-up visit at 21 months	• Length, weight, head circumference, blood pressure, laboratory tests, abdominal ultrasound, and echocardiogram • Neurodevelopmental and socio-emotional assessment • Mental ability tested with the Cattell Infant Intelligence scale
Nicovani (2009), Chile (27)	Kidney: 3 infants (triplet)	4 years follow-up	• No specific long term outcome measures described
Xia (2008), China (17)	Liver: 1 infant	Follow-up 4 years, every 3–6 months	• Routine follow-up visits, patient self-examination of the baby's growth and development
Scott (2002), United States (28)	Kidney: 5 infants (3 girls) (1 mother)	Follow-up at one time-point, age of the offspring: 23, 21, 18, 17, 15 years	• No outcome measurements described
Morini (1998), Italy (20)	Heart: 1 infant	Follow-up 14 months	• No specific long-term outcome measurements
Roll (1997), Germany (36)	Liver: 1 infant	Follow-up of 2 years and 6 months	• No specific long-term outcome measurements
Eskandar (1996), Canada (21)	Heart: 2 infants	Follow-up of >2 years in both children	• No specific long-term outcome measurements
Morita (1996), Japan (37)	Kidney: 8 infants	Mean follow-up: 4.1 years (range: 1 year till 11 years)	• 1-time point of evaluation. No specific method of assessment mentioned
Liljestrand (1993), Sweden (64)	Heart: 1 infant	Follow-up 18 months	• Specific long-term outcome measurements not described • At 12 months: detailed evaluation at a regional specialized center in pediatric cardiology
Baarsma (1992), Netherlands (46)	Liver: 1 infant	Follow-up 2-year, not clear how many follow-up moments	• Immunological assessment of blood samples and functional assessment of the immune system
Grow (1991), United States (54)	Liver: 2 infants (twins)	Neurodevelopmental follow-up of 25 months	• Unspecified neurodevelopmental follow-up
Scantlebury (1990), United States (53)	Liver: 20 infants (1 twin)	Follow-up ranging from 9 months till 12 years ($n = 16 >$ 1 year)	• No specific long-term outcome measurements described
Key (1989), United States (22)	Heart: 1 infant	Follow-up of 3 years	• No specific long-term outcome measurements described
Preieto (1989), Spain (23)	Kidney: 4 infants (2 sets of twins)	1 twin follow-up at 22 months and 1 twin at 8 months	• No specific long-term outcome measurements described
Boner (1981), Israel (24)	Kidney: 2 infants (twins)	Follow-up of 6 years	• No specific long-term outcome measurements for the physical and psychological assessment described • Cell mediated immunity examination at 8–10 months with blood samples: lymphocytic transformation measurement with phytohemaglutinin, estimation of the secretion of macrophage migration inhibition factor, PPD skin test, delayed hypersensitivity skin tests
Berant (1976), Israel (38)	Kidney: 1 infant	Multiple follow-up visits: at birth, 3 months, 5 months and 2 years	• Immunological evaluation with blood samples • At birth: chest x-ray for the thymic shadow • Lymphocytic transformation by phytohemagglutinin at birth and 2 years
Price (1976), United Kingdom (39)	Kidney: 2 infants Control: 54 infants	1 child follow-up of 32 months and 1 child follow-up of 24 months. Not specified how many follow up moments	• No specific long-term outcome measurements described, developmental tests not specified • Blood lymphocyte, cortisol levels, and chromosome analyses measured at multiple timepoints

length for age at a mean follow-up of 3.1 years (range 3 months-11 years) in the KTx offspring group compared to the control group (31). Schreiber-Zamora et al. reported no significant differences in the prevalence of overweight and underweight when comparing offspring of KTx recipients (KTR) with offspring of LiTx recipients and a control group. In the transplant group 16.4% had obesity and in the control group 6.3% did ($p = 0.072$). The theoretical incidence of obesity in the general population (5%) was significantly lower than the incidence in the LiTx (17.1%), the KTx offspring (15.4%), and the overall transplant group (16.4%) ($p < 0.001$, $p = 0.02$, $p < 0.001$ respectively). Prenatal exposure to tacrolimus was associated with a 2.8-fold increased risk for developing a higher body mass index at later follow-up (42).

Catch-up growth was reported in three case reports with three children from KTR and one child from a LiTx recipient (36, 38, 39). Willis et al. also reported impressive catch-up growth in 21 children born with a birth weight <10th percentile (33). In five articles the growth of 86 infants born after LiTx was evaluated; even though birth weight was low, subsequent height and weight development was within the normal range (29, 34–36, 42).

Immunological Follow-Up

Ten studies focused on immunological follow-up of the offspring (18, 29, 38, 39, 44–49), of which four were case reports (29, 38, 39, 46). In none of the included studies were opportunistic or chronic infections reported. Antibody response to vaccination was normal and no side-effects of vaccination were observed (18, 38, 45, 46). Two studies reported a significantly higher number of children hospitalized due to infectious disease in the KTx offspring group compared to a control group (44, 49). Ono et al. reported that 28.6% of the KTx group compared to 7.5% of the unmatched control group was hospitalized ($p = 0.046$) (44). All hospitalized children were exposed to tacrolimus during pregnancy. Egerup et al. matched a KTx offspring group aged 0–5 years with a control group in a 1:10 ratio. 41.9% of the KTx offspring compared to 24.8% of the control group were hospitalized due to infectious disease (risk ratio 1.67). The average number of antibiotic prescriptions filled between age 1–5 years was significantly higher in the KTx compared to the controls. However, this difference was not observed in the group as a whole (age 0–5 years) and not for group <1 year (**Supplementray Table S2A**) (49).

Serum levels of IgA, IgM, and IgG within the normal range were reported (29, 38, 47, 48). Moreover, Drozdowska et al. found no differences in IgG and IgM concentrations between 39 children of KTR and 39 age-matched controls (age one day-15 years) (48). At birth low numbers of total lymphocytes and specific lymphocyte subsets were reported in three studies, but in 28 of these 31 children normal lymphocyte counts were found at a maximum follow-up of 2 years (39, 44, 46). Ono et al. reported a significantly lower percentage of transitional B cells ($CD19^+CD10^+$) and a higher expression of CD154 on $CD4^+$ T cells in children exposed to tacrolimus compared to children exposed to cyclosporine ($p = 0.029$ and $p = 0.009$ respectively) (44). Pilarski et al. reported that in an offspring group ($n = 10$, range 5 months-9 years) compared to a control group, cyclosporine-exposed children had significantly higher numbers of CD45RA + R0- T cells and azathioprine-exposed children had significantly higher numbers of CD45RA-R0+ T cells, suggesting that cyclosporine exposure delayed T cell development and azathioprine exposure accelerated T cell development (45). Moreover, children exposed to cyclosporine had a lower and to azathioprine a higher expression of CD29 T cells compared to the control group (45).

In summary, normal response to vaccination and no opportunistic infection were reported but, especially at young age, the results show some alterations in numbers of immune cells in the transplant offspring group and two studies indicate an increased risk of hospitalization for infection.

Neurobehavioral and Cognitive Follow-Up

Sixteen articles conducted specific tests on neurobehavioral development or cognition (11, 13, 29–31, 33, 37, 45, 47, 50–56), of which three are case reports (29, 53, 54). The studies show that neurological development is similar to the general population. Five articles described intelligence quotient (IQ) scores (11, 29, 30, 50, 52). No significant differences regarding global intellectual performance were found when comparing the transplant offspring with the general population or matched control groups at infant, toddler, pre-school, and school age (11, 30, 50). However, Morales-Buenrostro et al. reported that visuospatial working memory might be affected in preschool children born after KTx ($p = 0.007$) (50). No significant differences in IQ scores were found between children only exposed to cyclosporine and children exposed to both cyclosporine and azathioprine (30). Subgroup analyses with mothers taking MMF prior to their awareness of being pregnant did not show statistical differences in full scale IQ (50). Kocisezwska-Najman et al. found no differences in the distribution of IQ between children born to LiTx and KTx recipients, though children of KTR had significantly higher percentages of preterm birth and LBW (risk factors for lower IQ) (57) compared to offspring of LiTx recipients (52). Devresse et al. reported that 8/21 (38%) children had a grade repetition, which is lower than their country's general population (60%) (13).

In 296 children neurodevelopmental follow-up was performed without comparison to a control group (31, 33, 37, 47, 53–55). In 87% no developmental problems were reported and in 13% developmental delays, such as the need for educational support or neurological abnormalities such as cerebral palsy, slightly delayed psychomotor development, and intellectual disability, were reported.

Kidney Function

Eight studies mentioned specific results on kidney function (12, 13, 26, 32, 33, 58–60). No abnormalities in kidney function were reported in 96% (243/252) of the assessed children. Al-Khader et al. reported no signs of glomerular or tubular defects and no hypertension or proteinuria in 41 children born from KTR at a mean follow-up of 52 months (12). In 95% of these pregnancies a calcineurin inhibitor (CNI, 73% cyclosporine, 22% tacrolimus) was used. Giudice et al. also reported no renal abnormalities in 12 children born from KTR at a mean follow-up of 2.6 years (32). In all these pregnancies cyclosporine was used during pregnancy. Willis et al. reported 4/40 (10%) children with urinary tract abnormalities on ultrasound: one ureteropelvic junction obstruction, one unilateral scar, and two unilateral renal dysplasia (two female siblings). These two female siblings also had abnormalities on urine analyses. 50% of the mothers used cyclosporine during pregnancy. The reported 10% is significantly more than the general population (2.9%, $p = 0.036$) (33). Dębska-Slizien et al. reported one child with symptoms of glomerulonephritis out of 22 children born to KTR (26). Borek-Dziecioł et al assessed kidney function parameters (urea, creatinine, potassium, and sodium concentrations) in 40 infants (newborns and children aged >1 year, age not

specified) born to mothers with a KTx and 40 control infants matched to gestational age. They did not find any significant differences between the KTx and the control group, nor did they find any differences between the immunosuppressive regimens use by the mothers (58). Shaheen et al. analyzed basic kidney function parameters in the blood of offspring born to KTR as well (median age 39 months, range 6–72 months) and did not find problems in renal functioning or integrity (59). Devresse et al. analyzed questionnaires of 21 children born after KTx aged 7–25 years. None of the children reported taking any chronic medication and no one reported a history of chronic kidney disease, renal stones, gross hematuria, or pathological urine dipstick at school medicine (13). Czaplinska et al. assessed liver function (AST, ALT) and kidney function (creatinine and urea) in 51 infants born to mothers with a LiTx (newborns and children aged >1 year, age not specified). They did not find significant differences between the LiTx group and the control group matched to gestational age and time period of birth, except for significantly lower ALT levels in the LiTx group (60).

Other Findings

One study with a relatively large sample size (n = 199 live births) reported significantly more cases of acute bronchitis, systemic lupus erythematosus, and hyperactivity disorders in the KTx offspring compared to the matched control group (p = 0.007, p = 0.025, p = 0.038 resp.) (61). The same study reported a significantly higher number of hospitalizations in the transplant offspring group compared to the control group (65.8% vs. 45.6%, $p < 0.001$), without specifying the reason for admission (61). One study focused on ophthalmological follow-up in children aged 1 week till >6 years (not further specified); no differences in pathological findings between the offspring of LiTx, KTx and the control group were found (62).

Bar et al. reported no significant difference in the rate of severe disability in the long-term; there were 8% (n = 3) in the transplant offspring group (two cases of cerebral palsy due to extreme prematurity and one deaf child, probably due to a cytomegalovirus infection) and 2.4% (n = 1) in the primary renal disease group (63). In one case report and one retrospective cohort study, two cases of hepatoblastoma at young age (2.5 years and 18 months) were reported: one child of a LiTx recipient and one child of a KTR (36, 43). One child born to a mother with a HTx had a serious, probably hereditary, cardiac insufficiency (64).

Fathers With a History of a Transplantation

One article (11), described longer term follow-up of children born to fathers with a history of a SOT (11). Four children born to three fathers with a KTx were described. At follow-up (age 4 months, 10 months, 11 months and 2 years 7 months) no abnormalities were found on physical examination except for one child with sickle cell trait. The height percentiles were 25th, 25th, 55th, and 75th percentile and the weight percentiles were 10th, 45th, 75th, and 95th. On the Bayley Scales Mental Development Index the offspring scored within the range of normal (82, 83, 105, and 120).

DISCUSSION

To the best of our knowledge this is the first systematic review evaluating the available data regarding longer term (>1 year) outcomes of children of SOT patients. In general, we found that pregnancy after SOT appears to have reassuring longer term outcomes. Most children had normal physical and neurobehavioral development, despite frequent preterm birth and/or LBW.

The included studies reported high percentages of preterm birth and LBW in infants of mothers with a SOT. Precise numbers of preterm birth and LBW could not be calculated since some of the articles only mentioned mean or median gestational age and birth weight without giving the number of children fulfilling the definitions. In general, women who get pregnant after SOT are a selected population of patients who do well after transplantation. In this selected population, in line with our results on perinatal outcomes, previous research reported high preterm birth rates of 32% after LiTx (65) and 43% after KTx (3). Preterm birth and LBW are associated with poor growth in the first 2 years of life, as well as lower motor and cognitive scores compared to term infants (57). Interestingly, this is not in line with the data on offspring of mothers with SOT presented in this systematic review. Length and weight development was within the normal range in almost all children, including in children that were born preterm and/or with LBW, suggesting that the effects of transplantation and immunosuppressive medication on these outcomes are transient. A possible explanation for this difference is that the underlying mechanism leading to preterm birth and LBW is different in SOT recipients compared to the general population. Placentation is affected by the history of a SOT and especially by KTx, and the vascular remodeling in pregnancy is likely to be affected by immunosuppressive medication (66). Of the immunosuppressive medication, fetal exposure to CNIs especially is concerning, since approximately 70% of maternal tacrolimus and 37%–64% of maternal cyclosporine concentrations reach the fetus. Corticosteroids freely cross the placenta but 90% is metabolized to inactive forms in the placenta and azathioprine cannot be converted to its active form in the human fetal liver (6). However, the rate of obstetric complications such as preterm birth and LBW is similar in post-transplantation pregnancies on different immunosuppressive regimens, suggesting that immunosuppressive medication is not the only factor affecting the risk of complications (6).

The included studies show that results of neurological and cognitive assessment are similar to the general population. The results of our systematic review are in line with the TPRI that also suggests that cognitive and physical development of the children (>1,500 children) is comparable to the general population although their data is subject to reporting bias because of collection via voluntary patient questionnaires (1).

On immunological follow-up some abnormalities were seen. Low numbers of lymphocytes shortly after birth are reported in studies included in this review (39, 44, 46) and in other studies with a follow-up of <1 year (67, 68). However, lymphocyte numbers normalized at longer follow-up. Some differences in levels of subtypes of immune cells between immunosuppressive

medications were observed. The relevance of these findings is arguable since no differences in immunological complications between the different immunosuppressive regimens were reported. Moreover, in none of the 1,664 children were opportunistic or chronic infections reported. Three studies reported a significantly higher number of hospitalizations in children born to transplanted mothers, including a higher number of antibiotic prescriptions in one study (44, 49, 61). A possible explanation for the increased rate of hospitalization in the transplant offspring is increased alertness to possible problems by their mothers and/or doctors. It is likely that the upbringing of children is influenced by the SOT of the mother. For example, maternal anxiety about her own and the child's health may lead to increased care seeking behavior (11). Besides, some of the complications such as the reported kidney abnormalities may be due to hereditary risk and are not necessarily linked to the transplantation itself.

Several limitations of this systematic review must be acknowledged. A main limitation is the large proportion of case reports and retrospective studies that may be subjected to publication bias. However, of the included studies 16/53 had a control group (58% of the offspring, n = 960). Furthermore, most data presented here focused on childhood outcomes. Only five studies included offspring aged >18 years in their study group. Another limitation is that the majority of births (78%) presented here are after KTx. Therefore, it is difficult to draw conclusions about differences between the types of SOT. Future research should focus on the long-term follow-up of offspring born after SOT at multiple time points and preferably into adult age, since it could be hypothesized that *in utero* exposure to immunosuppressive medication could lead to vascular damage which in turn leads to organ damage later in life. It seems plausible that immunosuppressive medication, which has nephrotoxic side-effects in the transplant population, affects the development of the kidneys in the offspring. Fortunately, the existing studies described here are reassuring. However, the majority of the offspring were evaluated at a relatively young age. It would be possible that there are already small (non-significant) health problems in these children that become apparent at an older age. Future research should assess if problems at later age arise. This would be in line with findings in antenatal exposure to cyclosporine in rabbits whereby nephrological abnormalities and systemic hypertension occur, worsening with advanced age (69).

In conclusion, this systematic review shows that the majority of offspring of SOT patients are healthy and develop well. These findings are encouraging for patients considering pregnancy after SOT and should be discussed in preconception counseling. However, this systematic review also shows that existing information is scarce and predominantly limited to small studies with young children. Larger and longer prospective studies with long-term follow-up into adulthood of these children are necessary to optimize pregnancy counselling of SOT patients.

AUTHOR CONTRIBUTIONS

JM: Study design, data collection, data analysis, bias appraisal and manuscript writing. JP: Bias appraisal, manuscript writing and critical review. SB: Manuscript writing and critical review. MJ: Study design, data collection, data analysis and manuscript writing.

CONFLICT OF INTEREST

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

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2022.10565/full#supplementary-material

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ORIGINAL RESEARCH
published: 12 August 2022
doi: 10.3389/ti.2022.10528

Real-World Treatment Patterns of Antiviral Prophylaxis for Cytomegalovirus Among Adult Kidney Transplant Recipients: A Linked USRDS-Medicare Database Study

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Limited data exist on cytomegalovirus (CMV) antiviral treatment patterns among kidney transplant recipients (KTRs). Using United States Renal Database System registry data and Medicare claims (1 January 2011–31 December 2017), we examined CMV antiviral use in 22,878 KTRs who received their first KT from 2011 to 2016. Three-quarters of KTRs started CMV prophylaxis (85.8% of high-, 82.4% of intermediate-, and 32.1% of low-risk KTRs). Median time to prophylaxis discontinuation was 98, 65, and 61 days for high-, intermediate-, and low-risk KTRs, respectively. Factors associated with receiving CMV prophylaxis were high-risk status, diabetes, receipt of a well-functioning kidney graft, greater time on dialysis before KT, panel reactive antibodies ≥80%, and use of antithymocyte globulin, alemtuzumab, and tacrolimus. KTRs were more likely to discontinue CMV prophylaxis if they developed leukopenia/neutropenia, had cardiovascular disease, or received their kidney from a deceased donor. These findings suggest that adherence to the recommended duration of CMV-prophylaxis for high and intermediate-risk patients is suboptimal, and CMV prophylaxis is overused in low-risk patients.

Keywords: kidney transplantation, antiviral, cytomegalovirus, prophylaxis, pharmacoepidemiology

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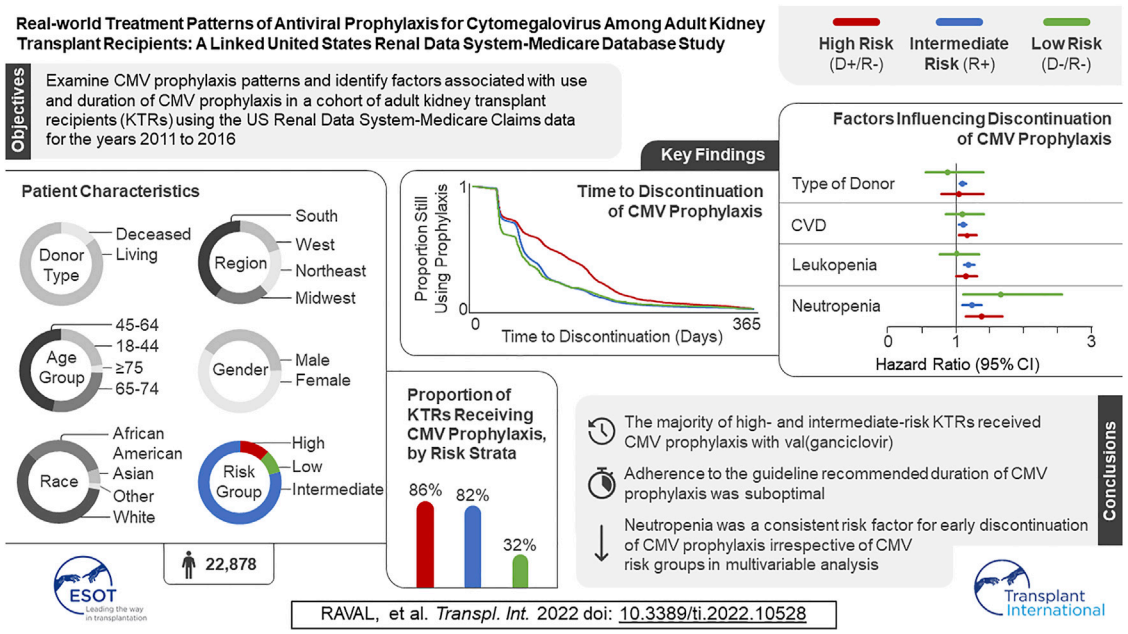
***Received:** 23 March 2022*
***Accepted:** 03 June 2022*
***Published:** 12 August 2022*

Citation:
Raval AD, Ganz ML, Fraeman K, Lorden AL, Saravanan S, Tang Y and Santos CAQ (2022) Real-World Treatment Patterns of Antiviral Prophylaxis for Cytomegalovirus Among Adult Kidney Transplant Recipients: A Linked USRDS-Medicare Database Study. Transpl Int 35:10528. doi: 10.3389/ti.2022.10528

INTRODUCTION

Cytomegalovirus (CMV) is the most common opportunistic infection in kidney transplant recipients (KTRs) (1, 2). In the absence of prevention, 20%–60% of KTRs develop CMV infection/disease. CMV infection and its manifestations increase the risk of rejection, graft loss, and mortality (1, 3). Previous research has shown that the use of CMV antiviral agents, including (val)ganciclovir, is associated with a reduced risk of CMV infection/disease (3–7). Prophylactic use of these antivirals not only lowers the risk of CMV infection/disease, but also mitigates the negative impact of CMV on graft and survival outcomes (3-7). However, currently available CMV antiviral agents may lead to adverse



GRAPHICAL ABSTRACT |

outcomes such as myelosuppression from (val)ganciclovir or nephrotoxicity from foscarnet, which may require modifications to antiviral or immunosuppressive therapy regimens that can also adversely affect graft and survival outcomes (3, 5, 7, 8).

CMV serostatus is a key determinant of CMV infection/disease risk. CMV seronegative KTRs (R–) who received a graft from a CMV seropositive donor (D+) are at the greatest risk for CMV infection/disease, followed by CMV seropositive (R+) KTRs regardless of donor serostatus (D±), who are at intermediate risk, and CMV seronegative KTRs who receive a graft from a CMV seronegative donor (D–/R–), who are at lowest risk of CMV infection/disease (9). CMV prevention is prioritized for high-risk KTRs, leading to a recommended 200 days of prophylaxis, while efficacy and safety are balanced for intermediate-risk KTRs, leading to a recommended duration of 100 days. CMV prophylaxis is not recommended for low-risk KTRs. The standard valganciclovir daily dose of 900 mg can be lowered to 450 mg to reduce the risk of myelosuppression if antiviral toxicities are a concern, but this strategy may be suboptimal (10).

While preemptive therapy can be substituted for prophylaxis if the KTR has the logistical support necessary for monitoring, a recent systematic review of post-transplant CMV preventive strategies for nearly 70,000 KTRs found that prophylaxis was the most common approach for high-risk transplants, preemptive therapy was the most common approach for intermediate-risk transplants, and ganciclovir or valganciclovir were identified as the most commonly used medications regardless of CMV risk (3). However, the majority of reported studies are limited to examining a single center, or are outdated due to updated guidelines supporting a longer duration of CMV prophylaxis consistent with results from the IMPACT clinical trial (11). Additionally, few studies have published CMV prophylaxis patterns among KTRs using large-scale national-level databases in the United States (US), leaving a gap in real-world evidence regarding the characteristics and determinants of CMV prophylaxis patterns among adult KTRs. Therefore, we conducted this study to determine patterns of CMV prophylaxis use and identify factors associated with use and duration of CMV prophylaxis.

MATERIALS AND METHODS

Data Source

We used files from the US Renal Data System (USRDS) linked to Medicare claims between 1 January 2011 and 31 December 2017 (12). The USRDS is a national registry that collects treatment and outcomes data from individuals with chronic kidney disease and end-stage renal disease (ESRD) in the US. The USRDS-Medicare database is considered the most complete source of information on the use of healthcare services by KTRs in the US, because ESRD is a qualifying condition for Medicare coverage and the registry includes all individuals who require maintenance dialysis. The USRDS standard analysis files contain data on person-level clinical and demographic characteristics, kidney transplant (KT) information from the United Network of Organ Sharing (UNOS), and death. The standard USRDS files can be linked to Medicare Institutional (Part A), Physician/Supplier (Part B), and Prescription Drug (Part D) claims. This study was approved by the New England Institutional Review Board on 9 September 2020 (study number 1289813) and was conducted in accordance with the International Society for Pharmacoepidemiology Guidelines for Good

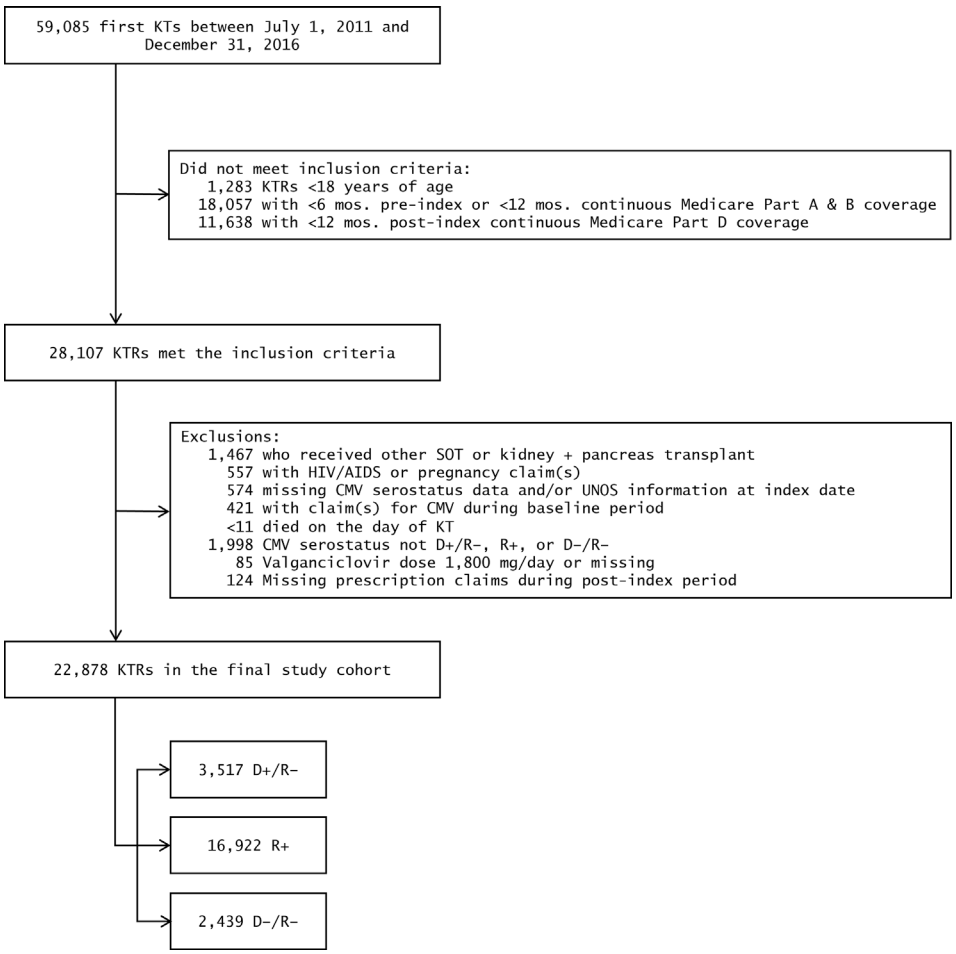


FIGURE 1 | Study Sample Selection. Abbreviations: AIDS, acquired immunodeficiency syndrome; CMV, cytomegalovirus; D+, seropositive donor; D–, seronegative donor; HIV, human immunodeficiency virus; KT, kidney transplant; KTRs, kidney transplant recipients; mos., months; R+, seropositive recipient; R–, seronegative recipient; SOT, solid organ transplant.

Pharmacoepidemiology Practices, Revision 3, the principles of the Declaration of Helsinki, and all applicable federal, state, and local laws, rules, and regulations.

Study Design and Sample

We performed a retrospective, observational cohort analysis of individuals who were at least 18 years of age at the time of their first KT that occurred between 1 June 2011 and 31 December 2016. The claims-derived date of their first KT was used as the KTRs' index dates. Included KTRs had to have at least one medical procedure claim for KT in the Medicare claims data within 15 days of the registry-based date of the KT; at least 6 months of continuous Medicare Parts A, B, and D coverage prior to their index date; and at least 12 months of continuous Medicare Parts A, B, and D coverage post-index date or continuous Medicare Part A, Part B, and Part D up to date of death if death occurred within 1 year of transplant. KT was identified by the International Classification of Diseases, Clinical Modification diagnosis codes 55.69 (ninth revision) and 0TY00Z0, 0TY00Z1, 0TY00Z2, 0TY10Z0, 0TY10Z1, and 0TY10Z2 (10th revision) in the Medicare Claims data. Once all KTRs who met inclusion criteria were identified, exclusion criteria were applied to identify our final cohort (**Figure 1**). Exclusion criteria included evidence of HIV/AIDS or pregnancy in claims data, missing CMV or UNOS information at index date, claim for CMV during the baseline period, died on day of KT, CMV serostatus missing, and valganciclovir dose missing or exceeded 1,800 mg/day.

Definitions of CMV Prophylaxis and Duration

We defined CMV prophylactic therapy as use of ganciclovir or valganciclovir within 28 days after the KT index date. CMV antiviral therapies were identified in Part D Medicare claims using National Drug Codes for ganciclovir and valganciclovir, or Parts A or B Medicare claims using Healthcare Common Procedure Coding System (HCPCS) or Current Procedural Terminology (CPT) codes for administration of those agents. To calculate duration of CMV prophylaxis, we first identified the fill date and the days' supply and then estimated the run-out date for

TABLE 1 | Baseline demographic, clinical, and medication-related characteristics of adult KTRs.

Characteristic	Overall (N = 22,878)	High Risk (D+/R–) (N = 3,517)	Intermediate Risk (R+) (N = 16,922)	Low Risk (D–/R–) (N = 2,439)	P-value[a]
Mean age in years (SD)	53.8 (13.9)	52.5 (14.2)	54.5 (13.7)	51.3 (14.6)	<0.01
Age category in years, N (%)					
18–44	6,167 (27.0%)	1,053 (29.9%)	4,269 (25.2%)	845 (34.6%)	<0.01
45–64	10,753 (47.0%)	1,628 (46.3%)	8,072 (47.7%)	1,053 (43.2%)	
65–74	5,366 (23.5%)	749 (21.3%)	4,129 (24.4%)	488 (20.0%)	
≥75	592 (2.6%)	87 (2.5%)	452 (2.7%)	53 (2.2%)	
Gender, N (%)					
Male	13,552 (59.2%)	2,452 (69.7%)	9,445 (55.8%)	1,655 (67.9%)	<0.01
Female	9,326 (40.8%)	1,065 (30.3%)	7,477 (44.2%)	784 (32.1%)	
Race, N (%)					
White	13,471 (58.9%)	2,429 (69.1%)	9,338 (55.2%)	1,704 (69.9%)	<0.01
African American	7,528 (32.9%)	1,003 (28.5%)	5,856 (34.6%)	669 (27.4%)	
Asian	1,321 (5.8%)	45 (1.3%)	1,239 (7.3%)	37 (1.5%)	
Other[b]	558 (2.4%)	40 (1.1%)	489 (2.9%)	29 (1.2%)	
Hispanic ethnicity, N (%)					
Yes	4,832 (21.1%)	410 (11.7%)	4,191 (24.8%)	231 (9.5%)	<0.01
No	17,851 (78.0%)	3,077 (87.5%)	12,583 (74.4%)	2,191 (89.8%)	
Unknown	195 (0.9%)	30 (0.9%)	148 (0.9%)	17 (0.7%)	
Geographic region, N (%)					
Northeast	4,168 (18.2%)	726 (20.6%)	2,863 (16.9%)	579 (23.7%)	<0.01
Midwest	4,874 (21.3%)	815 (23.2%)	3,403 (20.1%)	656 (26.9%)	
South	9,223 (40.3%)	1,419 (40.3%)	6,971 (41.2%)	833 (34.2%)	
West	4,549 (19.9%)	552 (15.7%)	3,641 (21.5%)	356 (14.6%)	
Other US territories	64 (0.3%)	<11	44 (0.3%)	15 (0.6%)	
Primary diagnosis leading to ESRD, N (%)					
Diabetes mellitus, Type 2	6,481 (28.3%)	890 (25.3%)	5,063 (29.9%)	528 (21.6%)	<0.01
Hypertensive nephrosclerosis	6,267 (27.4%)	885 (25.2%)	4,736 (28.0%)	646 (26.5%)	
Polycystic kidney disease	1,405 (6.1%)	244 (6.9%)	978 (5.8%)	183 (7.5%)	
Focal glomerular sclerosis	1,244 (5.4%)	211 (6.0%)	880 (5.2%)	153 (6.3%)	
Systemic lupus erythematosus	815 (3.6%)	108 (3.1%)	638 (3.8%)	69 (2.8%)	
IGA Nephropathy	737 (3.2%)	108 (3.1%)	519 (3.1%)	110 (4.5%)	
Diabetes mellitus, Type 1	732 (3.2%)	138 (3.9%)	482 (2.8%)	112 (4.6%)	
Malignant hypertension	282 (1.2%)	50 (1.4%)	207 (1.2%)	25 (1.0%)	
Wegener's granulomatosis	127 (0.6%)	25 (0.7%)	78 (0.5%)	24 (1.0%)	
Goodpasture's syndrome	69 (0.3%)	14 (0.4%)	47 (0.3%)	<11	
Other Disease	4,719 (20.6%)	844 (24.0%)	3,294 (19.5%)	581 (23.8%)	
Charlson Comorbidity Index, N (%)					
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.01
1–2	1,658 (7.2%)	293 (8.3%)	1,132 (6.7%)	233 (9.6%)	
3–4	9,958 (43.5%)	1,553 (44.2%)	7,260 (42.9%)	1,145 (46.9%)	
≥5	11,262 (49.2%)	1,671 (47.5%)	8,530 (50.4%)	1,061 (43.5%)	
Comorbid health conditions, N (%)					
Congestive heart failure	18,183 (79.5%)	2,750 (78.2%)	13,573 (80.2%)	1,860 (76.3%)	<0.01
Diabetes	10,549 (46.1%)	1,536 (43.7%)	8,045 (47.5%)	968 (39.7%)	<0.01
Diabetes without chronic complication	10,150 (44.4%)	1,480 (42.1%)	7,752 (45.8%)	918 (37.6%)	<0.01
Diabetes with chronic complication	9,397 (41.1%)	1,352 (38.4%)	7,191 (42.5%)	854 (35.0%)	<0.01
Chronic pulmonary disease	3,885 (17.0%)	608 (17.3%)	2,861 (16.9%)	416 (17.1%)	0.86
Peripheral vascular disease	3,025 (13.2%)	467 (13.3%)	2,253 (13.3%)	305 (12.5%)	0.54
Rheumatologic disease	2,952 (12.9%)	425 (12.1%)	2,246 (13.3%)	281 (11.5%)	0.02
Mild liver disease	2,465 (10.8%)	377 (10.7%)	1,830 (10.8%)	258 (10.6%)	0.93
Moderate or severe liver disease	1,688 (7.4%)	278 (7.9%)	1,221 (7.2%)	189 (7.7%)	0.28
Myocardial infarction	1,606 (7.0%)	231 (6.6%)	1,192 (7.0%)	183 (7.5%)	0.37
Dementia	50 (0.2%)	<11	37 (0.2%)	<11	0.77
Mean time on dialysis prior to KT (SD), years	4.7 (3.3)	4.7 (3.1)	4.7 (3.3)	4.6 (3.1)	0.42
Mean wait time (SD), years	2.5 (2.1)	2.7 (2.1)	2.5 (2.2)	2.5 (2.0)	<0.01
PRA, N (%)					
0%	15,056 (65.8%)	2,485 (70.7%)	10,869 (64.2%)	1,702 (69.8%)	<0.01
1%–19%	1,932 (8.4%)	308 (8.8%)	1,413 (8.4%)	211 (8.7%)	
20%–79%	3,437 (15.0%)	478 (13.6%)	2,607 (15.4%)	352 (14.4%)	
80%–100%	2,238 (9.8%)	236 (6.7%)	1,840 (10.9%)	162 (6.6%)	
Missing	215 (0.9%)	<11	193 (1.1%)	12 (0.5%)	

(Continued on following page)

TABLE 1 | (*Continued*) Baseline demographic, clinical, and medication-related characteristics of adult KTRs.

Characteristic	Overall (N = 22,878)	High Risk (D+/R–) (N = 3,517)	Intermediate Risk (R+) (N = 16,922)	Low Risk (D–/R–) (N = 2,439)	P-value[a]
HLA A B donor-recipient match, N (%)					
0	4,907 (21.4%)	746 (21.2%)	3,653 (21.6%)	508 (20.8%)	<0.01
1	7,704 (33.7%)	1,266 (36.0%)	5,636 (33.3%)	802 (32.9%)	
2	5,100 (22.3%)	816 (23.2%)	3,659 (21.6%)	625 (25.6%)	
≥3	4,855 (21.2%)	629 (17.9%)	3,751 (22.2%)	475 (19.5%)	
Missing	312 (1.4%)	60 (1.7%)	223 (1.3%)	29 (1.2%)	
Hepatitis C seropositive, N (%)	1,262 (5.5%)	161 (4.6%)	987 (5.8%)	114 (4.7%)	<0.02
Epstein-Barr virus antibody positive, N (%)	18,769 (82.0%)	2,729 (77.6%)	14,088 (83.3%)	1,952 (80.0%)	<0.01
Calendar year of transplant, N (%)					
2011	1,970 (8.6%)	318 (9.0%)	1,477 (8.7%)	175 (7.2%)	<0.01
2012	3,923 (17.1%)	607 (17.3%)	2,930 (17.3%)	386 (15.8%)	
2013	4,066 (17.8%)	601 (17.1%)	3,076 (18.2%)	389 (15.9%)	
2014	3,991 (17.4%)	616 (17.5%)	2,982 (17.6%)	393 (16.1%)	
2015	4,377 (19.1%)	685 (19.5%)	3,155 (18.6%)	537 (22.0%)	
2016	4,551 (19.9%)	690 (19.6%)	3,302 (19.5%)	559 (22.9%)	
Used immunosuppressive agents, N (%)	22,619 (98.9%)	3,480 (98.9%)	16,723 (98.8%)	2,416 (99.1%)	0.53
Induction immunosuppressive therapy, N (%)					
ATG	12,264 (54.2%)	1,821 (52.3%)	9,082 (54.3%)	1,361 (56.3%)	<0.02
Basiliximab	5,090 (22.5%)	762 (21.9%)	3,864 (23.1%)	464 (19.2%)	<0.01
Alemtuzumab	3,660 (16.2%)	599 (17.2%)	2,676 (16.0%)	385 (15.9%)	0.2
Rituximab	186 (0.8%)	17 (0.5%)	158 (0.9%)	11 (0.5%)	<0.01
Muromonab-CD3	21 (0.1%)	<11	11 (0.1%)	<11	0.04
Daclizumab	<11	0 (0.0%)	<11	0 (0.0%)	NA
Cyclophosphamide	<11	0 (0.0%)	0 (0.0%)	<11	NA
Maintenance immunosuppressive therapy, N (%)					
Prednisone or methylprednisolone	21,779 (96.3%)	3,337 (95.9%)	16,117 (96.4%)	2,325 (96.2%)	0.38
MMF	21,776 (96.3%)	3,336 (95.9%)	16,136 (96.5%)	2,304 (95.4%)	<0.01
Tacrolimus	21,436 (94.8%)	3,283 (94.3%)	15,862 (94.9%)	2,291 (94.8%)	0.46
Belatacept	556 (2.5%)	84 (2.4%)	423 (2.5%)	49 (2.0%)	0.33
Cyclosporine	472 (2.1%)	73 (2.1%)	354 (2.1%)	45 (1.9%)	0.72
Sirolimus	256 (1.1%)	45 (1.3%)	169 (1.0%)	42 (1.7%)	<0.01
Everolimus	208 (0.9%)	36 (1.0%)	141 (0.8%)	31 (1.3%)	0.08
Leflunomide	<11	<11	<11	<11	0.87
AZA	77 (0.3%)	14 (0.4%)	54 (0.3%)	<11	0.73
Other	385 (1.7%)	57 (1.6%)	300 (1.8%)	28 (1.2%)	0.08
Donor type, N (%)					
Deceased	19,703 (86.1%)	3,462 (98.4%)	13,895 (82.1%)	2,346 (96.2%)	<0.01
Living	3,175 (13.9%)	55 (1.6%)	3,027 (17.9%)	93 (3.8%)	
Mean cold ischemia time in hours (SD)	15.5 (9.8)	16.9 (8.8)	15.1 (10.1)	16.2 (8.7)	<0.01
Cold ischemia time in hours category, N (%)					
<24 h	18,597 (81.3%)	2,838 (80.7%)	13,751 (81.3%)	2,008 (82.3%)	<0.01
≥24 h	3,949 (17.3%)	660 (18.8%)	2,893 (17.1%)	396 (16.2%)	
Missing	332 (1.5%)	19 (0.5%)	278 (1.6%)	35 (1.4%)	
Mean donor creatinine in mg/dL (SD)	1.1 (1.0)	1.2 (1.1)	1.1 (0.9)	1.2 (1.0)	<0.01
Donor creatinine in mg/dL category, N (%)					
≤1.5 mg/dl	19,270 (84.2%)	2,891 (82.2%)	14,363 (84.9%)	2,016 (82.7%)	<0.01
>1.5 mg/dl	3,598 (15.7%)	626 (17.8%)	2,549 (15.1%)	423 (17.3%)	
Missing	<11	0 (0.0%)	<11	0 (0.0%)	

Abbreviations: ATG, antithymocyte globulin; AZA, azathioprine; D, donor; D+, seropositive donor; D–, seronegative donor; ESRD, end-stage renal disease; HLA, human leukocyte antigen; IGA, immunoglobulin A; KT, kidney transplant; MMF, mycophenolate mofetil; NA, not applicable; PRA, panel-reactive antibody; R, recipient; R+, seropositive recipient; R–, seronegative recipient; SD, standard deviation; US, United States.

[a]*p-values are compared across patients by type of prophylaxis using t-tests or analysis of variance (ANOVA) for continuous variables or chi-square tests for categorical variables.*

[b]*Other includes American Indian, Alaska Native, Native Hawaiian, Pacific Islander, multiracial, other, and unknown.*

each CMV antiviral prescription. We defined the index prescription as the first CMV antiviral medication within 28 days after the KT. Fill gaps were then calculated, where a fill gap was the difference between run-out date and the next fill date for the CMV prophylactic antiviral being used. Finally, we defined the last prophylaxis prescription by the first occurrence of a fill gap of ≥15 days after the index prescription. Duration was the difference between the last prophylaxis prescription run-out date and the index prescription fill date.

Valganciclovir Daily Dose

We estimated the total daily dose (TDD) for each identified valganciclovir prescription by multiplying the strength of the

prescription by the number of tablets dispensed, divided by the number of days supplied (e.g., 60 tablets of valganciclovir 450 mg dispensed for 30 days equals a TDD of 900 mg). Once calculated for each prescription, an average TDD for CMV prophylaxis was calculated for each KTR and used to classify KTRs to a valganciclovir daily dose category (450 mg, 900 mg, or other).

Definitions of Leukopenia and Neutropenia

We created time-varying covariates to capture when KTRs developed leukopenia and/or neutropenia on or after their transplant dates. These time-varying covariates were defined using diagnosis codes present during hospitalizations and were equal to "no" until the date of their first relevant diagnosis code for each condition, after which point they were set equal to "yes."

Other KTR Characteristics

Demographic characteristics included age, gender, race (White, African American, other), ethnicity, and geographic region (Northeast, Midwest, South, West and other US territories). Clinical factors that may influence outcomes, which were used as covariates for adjusted analyses, included primary diagnosis leading to ESRD (diabetes of any type, hypertensive nephrosclerosis, polycystic kidney disease, focal glomerular sclerosis, other diseases), Charlson Comorbidity Index (CCI), other comorbid conditions (cardiovascular disease, chronic pulmonary disease, diabetes, liver disease, rheumatologic disease), donor type (deceased, living), cold ischemia time (≥24, <24 h), donor creatinine (≤1.5, >1.5 mg/dl), time on dialysis prior to KT (in months), human leukocyte antigens (HLA) A B match (≥3, <3), panel reactive antibodies (PRA; ≥80%, <80%), hepatitis C virus status, and Epstein Barr virus status. Two types of immunosuppressive therapies were considered. Induction agents included antithymocyte globulin (ATG), alemtuzumab, basiliximab, and other agents (daclizumab, muromonab-CD3, rituximab, and cyclophosphamide). Maintenance agents included mycophenolate mofetil (MMF), tacrolimus, azathioprine (AZA), everolimus, cyclosporine, prednisone and/or methylprednisolone, and other agents (sirolimus, leflunomide, belatacept, or any others identified as maintenance).

Statistical Analysis

Summary statistics were used to describe the KTRs and their CMV prophylaxis patterns. Comparisons between groups were performed using the F-test from analysis of variance and the chi-square test for continuous and categorical variables, respectively. All analyses were stratified by CMV risk associated with the donor/recipient serostatus. Results for cells containing fewer than 11 KTRs have been suppressed (i.e., reported as "<11") as required by the USRDS data use agreement. We generated Kaplan-Meier (KM) curves to visualize time to prophylaxis discontinuation and the log-rank test to assess differences between those curves. Multivariable logistic and Cox proportional hazard (PH) regression models were used to estimate the adjusted associations between KTRs' demographic and clinical characteristics and the probabilities of starting and discontinuing, respectively, their CMV prophylaxis. Regression models were estimated for all KTRs while adjusting for risk group and separately by risk group, and results were reported as odds and hazard ratios for the logistic and Cox PH models, respectively, along with 95% confidence intervals and two-sided *p*-values. The logistic and PH Cox regression models included the same core set of covariates, which was selected based on the literature; the PH Cox models also included two time-varying covariates capturing post-KT occurrence of leukopenia and neutropenia. When variables were missing values, we applied the following imputation strategies. For continuous variables such as time on dialysis and time on the transplant waiting list, we replaced the missing values with the risk-group-specific means. For categorical variables such as cold ischemia time, PRA, and HLA A B match, we replaced the missing values with the risk group-specific modal value. Missing values for categorical cold ischemia time and donor creatinine level were imputed after imputing the source continuous variables.

RESULTS

Baseline Characteristics

We identified 59,085 individuals who received their first KT from 2011 to 2016, of whom 22,878 satisfied all inclusion and exclusion criteria (**Figure 1**). **Table 1** summarizes the characteristics of our sample. Most (74.0%) KTRs were at intermediate risk of CMV infection, while 15.4% and 10.7% were at high and low risk, respectively. KTRs were, on average, 53.8 years of age at their initial KT. Most KTRs were male (59.2%) and White (58.9%); one-third was African American. Diabetes (28.3%), hypertensive nephrosclerosis (27.4%), polycystic kidney disease (6.1%), focal glomerular sclerosis (5.4%), and systemic lupus erythematosus (3.6%) were the five most frequent primary diseases leading to ESRD. Almost half (49.2%) of the KTRs had a CCI score ≥5, and a large proportion of KTRs also had congestive heart failure (79.5%). KTRs spent, on average, 4.7 years on dialysis prior to their KT and 2.5 years on the transplant waiting list. Large proportions of KTRs received their kidney graft from a deceased donor (86.1%) and were positive for Epstein-Barr virus (82.0%). Most donor kidneys experienced <24 h of cold ischemia time (81.3%) and were well-functioning (donor creatinine clearance ≤1.5 mg/dl). Approximately 21% had HLA A B donor-recipient match scores ≥3, and 9.8% of KTRs had PRA ≥80%. ATG was the most commonly used induction immunosuppressive agent (54.2%), followed by basiliximab (22.5%) and alemtuzumab (16.2%). Almost all KTRs used prednisone and/or methylprednisolone (96.3%), MMF (96.3%), and tacrolimus (94.8%) as maintenance immunosuppressive agents. High-risk KTRs were more likely to have had PRA equal to zero and were less likely to have had three or more HLA A B matches than other KTRs. Intermediate-risk KTRs were slightly older and more likely to be female, African American or Asian, Hispanic, reside in the Northeast or West regions, have diabetes or hypertensive nephrosclerosis as the

TABLE 2 | Characteristics of CMV prophylaxis among adults undergoing first kidney transplant by serostatus.

Prophylaxis Information	Overall (N = 22,878)	High Risk (D+/R–) (N = 3,517)	Intermediate Risk (R+) (N = 16,922)	Low Risk (D–/R–) (N = 2,439)	*p*-value
All prophylaxis agents					
CMV prophylaxis					
No prophylaxis	5,135 (22.4%)	498 (14.2%)	2,980 (17.6%)	1,657 (67.9%)	<0.01
Prophylaxis	17,743 (77.6%)	3,019 (85.8%)	13,942 (82.4%)	782 (32.1%)	
Type of prophylaxis, N (%)					
Valganciclovir	17,739 (100.0%)	3,019 (100.0%)	13,939 (>99.9%)	781 (99.9%)	0.18
Index dose 450 mg	10,614 (59.8%)	1,437 (47.6%)	8,760 (62.8%)	417 (53.4%)	<0.01
Index dose 900 mg	5,719 (32.2%)	1,347 (44.6%)	4,084 (29.3%)	288 (36.9%)	<0.01
Other index dose	1,406 (7.9%)	235 (7.8%)	1,095 (7.9%)	76 (9.7%)	0.16
Ganciclovir	<11	0 (0.0%)	<11	<11	0.18
Mean time to initiate any CMV prophylaxis in days (SD)	4.3 (4.5)	4.6 (4.7)	4.2 (4.4)	4.3 (4.8)	<0.01
Mean duration of CMV prophylaxis in days (SD)	102.7 (70.7)	123.6 (85.9)	98.7 (65.9)	93.8 (73.2)	<0.01
Duration of CMV prophylaxis, N (%)					
≥72 days	11,317 (63.8%)	1,942 (64.3%)	8,957 (64.2%)	418 (53.5%)	<0.01
≥90 days	10,977 (61.9%)	1,910 (63.3%)	8,665 (62.2%)	402 (51.4%)	<0.01
≥100 days	6,413 (36.1%)	1,550 (51.3%)	4,621 (33.1%)	242 (30.9%)	<0.01
≥180 days	3,211 (18.1%)	1,010 (33.5%)	2,081 (14.9%)	120 (15.3%)	<0.01
≥200 days	1,656 (9.3%)	470 (15.6%)	1,120 (8.0%)	66 (8.4%)	<0.01
Valganciclovir 450 mg					
Mean time to initiate valganciclovir 450 mg prophylaxis in days (SD)	4.1 (4.3)	4.5 (4.7)	4.0 (4.2)	4.3 (4.6)	<0.01
Mean duration of valganciclovir 450 mg prophylaxis in days (SD)	110.4 (71.9)	139.6 (88.2)	105.9 (67.4)	104.2 (77.4)	<0.01
Duration of valganciclovir 450 mg prophylaxis, N (%)					
≥72 days	7,527 (70.9%)	1,046 (72.8%)	6,223 (71.0%)	258 (61.9%)	<0.01
≥90 days	7,359 (69.3%)	1,030 (71.7%)	6,077 (69.4%)	252 (60.4%)	<0.01
≥100 days	4,197 (39.5%)	853 (59.4%)	3,194 (36.5%)	150 (36.0%)	<0.01
≥180 days	2,194 (20.7%)	599 (41.7%)	1,520 (17.4%)	75 (18.0%)	<0.01
≥200 days	1,118 (10.5%)	279 (19.4%)	795 (9.1%)	44 (10.6%)	<0.01
Valganciclovir 900 mg					
Mean time to initiate valganciclovir 900 mg prophylaxis in days (SD)	4.1 (4.5)	4.3 (4.4)	4.0 (4.5)	3.7 (4.7)	0.09
Mean duration of valganciclovir 900 mg prophylaxis in days (SD)	82.6 (62.6)	101.6 (77.1)	77.4 (56.2)	68.2 (55.0)	<0.01
Duration of valganciclovir 900 mg prophylaxis, N (%)					
≥72 days	2,695 (47.1%)	710 (52.7%)	1,883 (46.1%)	102 (35.4%)	<0.01
≥90 days	2,642 (46.2%)	706 (52.4%)	1,836 (45.0%)	100 (34.7%)	<0.01
≥100 days	1,416 (24.8%)	540 (40.1%)	831 (20.3%)	45 (15.6%)	<0.01
≥180 days	679 (11.9%)	317 (23.5%)	344 (8.4%)	18 (6.3%)	<0.01
≥200 days	320 (5.6%)	132 (9.8%)	180 (4.4%)	<11	<0.01
Valganciclovir other dose					
Mean time to initiate valganciclovir other dose in days (SD)	6.7 (5.3)	7.2 (5.3)	6.6 (5.3)	6.4 (5.9)	0.29
Mean duration of valganciclovir other dose prophylaxis in days (SD)	126.6 (74.0)	152.5 (90.2)	120.4 (68.5)	135.3 (77.8)	<0.01
Duration of valganciclovir other dose prophylaxis, N (%)					
≥72 days	1,093 (77.7%)	186 (79.1%)	849 (77.5%)	58 (76.3%)	0.82
≥90 days	974 (69.3%)	174 (74.0%)	750 (68.5%)	50 (65.8%)	0.20
≥100 days	799 (56.8%)	157 (66.8%)	595 (54.3%)	47 (61.8%)	<0.01
≥180 days	338 (24.0%)	94 (40.0%)	217 (19.8%)	27 (35.5%)	<0.01
≥200 days	218 (15.5%)	59 (25.1%)	145 (13.2%)	14 (18.4%)	<0.01

Abbreviations: CMV, cytomegalovirus; D, donor; D+, seropositive donor; D–, seronegative donor; R, recipient; R+, seropositive recipient; R–, seronegative recipient; SD, standard deviation.

primary cause of ESRD, have a CCI score ≥5, and PRA ≥80% than KTRs in the other groups. Low-risk KTRs were more likely to reside in the South or West and received ATG, and they were less likely to have had comorbid diabetes and to have used basiliximab as an induction immunosuppressive agent than other KTRs.

Use and Factors Associated With the Use of CMV Antiviral Prophylaxis

Table 2 displays, and compares across risk groups, the CMV prophylaxis characteristics of KTRs who started CMV prophylaxis. Slightly over three-quarters (77.6%) of KTRs started CMV prophylaxis (85.8% of high-, 82.4% of intermediate-, and 32.1% of low-risk KTRs). Overall, 59.8% and 32.2% of KTRs who started CMV prophylaxis used valganciclovir 450 mg and 900 mg, respectively, while 7.9% used other doses of valganciclovir; <11 patients used ganciclovir. Overall, KTRs who started prophylaxis did so, on average, 4.3 days after receiving their KTs; time to starting prophylaxis did not vary substantially across risk groups (4.2–4.6 days).

Table 3 displays the results of the logistic regression models for use of CMV prophylaxis (descriptive statistics stratified by CMV prophylaxis status within risk group are available in

TABLE 3 | Logistic regression for probability of starting CMV prophylaxis among adults undergoing a first kidney transplant.

Predictors	Overall		High Risk (D+/R–)		Intermediate Risk (R+)		Low Risk (D–/R–)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
CMV serostatus (vs. D–/R–)							—	—
D+/R–	15.79 (13.82–18.04)	<0.01	—	—	—	—	—	—
R+	11.21 (10.13–12.41)	<0.01	—	—	—	—	—	—
Age 18–64 years (vs. age ≥65)	1.44 (1.33–1.56)	<0.01	1.43 (1.14–1.79)	<0.01	1.47 (1.34–1.61)	<0.01	1.28 (1.01–1.62)	0.04
Female gender (vs. male)	1.14 (1.06–1.23)	<0.01	1.00 (0.80–1.25)	1.00	1.14 (1.04–1.24)	<0.01	1.32 (1.08–1.62)	0.01
Race (vs. White)								
African American	1.17 (1.07–1.27)	<0.01	1.29 (1.00–1.67)	0.05	1.14 (1.03–1.26)	0.01	1.16 (0.94–1.45)	0.17
Other[a]	1.62 (1.40–1.87)	<0.01	3.43 (1.24–9.52)	0.02	1.49 (1.27–1.74)	<0.01	2.50 (1.48–4.21)	<0.01
Region (vs. Northeast)								
Midwest	0.53 (0.47–0.59)	<0.01	0.63 (0.47–0.85)	<0.01	0.43 (0.37–0.49)	<0.01	0.68 (0.53–0.89)	<0.01
South	0.78 (0.70–0.86)	<0.01	0.82 (0.62–1.08)	0.16	0.59 (0.51–0.68)	<0.01	1.53 (1.21–1.94)	<0.01
West and Other US territories	0.77 (0.68–0.87)	<0.01	1.10 (0.77–1.57)	0.60	0.64 (0.55–0.75)	<0.01	0.73 (0.53–0.99)	0.05
Primary disease leading to ESRD (vs. diabetes of any type)								
Hypertensive nephrosclerosis	1.08 (0.96–1.22)	0.20	0.91 (0.66–1.26)	0.57	1.22 (1.05–1.41)	0.01	0.77 (0.56–1.07)	0.12
Polycystic kidney disease	1.03 (0.87–1.23)	0.73	1.07 (0.67–1.72)	0.77	1.10 (0.89–1.36)	0.36	0.77 (0.50–1.19)	0.24
Focal glomerular sclerosis	1.09 (0.91–1.31)	0.34	1.52 (0.85–2.73)	0.16	1.15 (0.92–1.43)	0.23	0.73 (0.47–1.16)	0.18
Other	0.98 (0.87–1.11)	0.77	0.76 (0.56–1.04)	0.09	1.15 (0.99–1.32)	0.07	0.63 (0.46–0.87)	0.01
CCI ≥5 (vs. <5)	0.87 (0.77–0.98)	0.02	0.65 (0.46–0.90)	0.01	0.91 (0.79–1.05)	0.21	0.89 (0.66–1.21)	0.45
Comorbid health conditions								
Cardiovascular disease	0.97 (0.87–1.08)	0.57	1.03 (0.76–1.39)	0.87	0.88 (0.77–1.00)	0.05	1.33 (1.02–1.73)	0.04
Chronic pulmonary disease	0.93 (0.85–1.02)	0.14	1.12 (0.86–1.45)	0.41	0.86 (0.77–0.96)	0.01	1.12 (0.88–1.42)	0.37
Diabetes	1.21 (1.07–1.38)	<0.01	0.89 (0.63–1.25)	0.51	1.37 (1.17–1.60)	<0.01	0.98 (0.70–1.37)	0.90
Liver disease	0.98 (0.88–1.10)	0.77	0.86 (0.63–1.15)	0.31	0.96 (0.84–1.09)	0.53	1.16 (0.86–1.55)	0.33
Rheumatologic disease	1.02 (0.91–1.14)	0.73	1.24 (0.90–1.70)	0.19	1.03 (0.91–1.17)	0.64	0.86 (0.64–1.16)	0.32
Donor type deceased (vs. living)	0.95 (0.85–1.06)	0.33	0.68 (0.30–1.57)	0.37	0.91 (0.81–1.03)	0.14	1.32 (0.77–2.27)	0.31
Cold ischemia time <24 h (vs. ≥24 h)	0.90 (0.82–0.99)	0.04	1.19 (0.93–1.53)	0.16	0.85 (0.75–0.95)	0.01	0.91 (0.71–1.15)	0.42
Donor creatinine >1.5 mg/dl (vs. ≤1.5 mg/dl)	1.19 (1.07–1.31)	<0.01	1.18 (0.91–1.54)	0.21	1.16 (1.02–1.32)	0.02	1.15 (0.92–1.46)	0.22
Time on dialysis prior to KT in years	1.04 (1.03–1.06)	<0.01	1.06 (1.02–1.11)	<0.01	1.04 (1.03–1.06)	<0.01	1.02 (0.99–1.06)	0.16
Wait time in years	1.00 (0.98–1.02)	0.69	0.97 (0.92–1.02)	0.28	1.00 (0.97–1.02)	0.77	1.01 (0.97–1.06)	0.54
PRAs ≥80% (vs. <80%)	1.27 (1.11–1.46)	<0.01	1.13 (0.74–1.72)	0.58	1.31 (1.11–1.54)	<0.01	1.15 (0.80–1.65)	0.46
HLA A B donor-recipient match ≥3 (vs. <3)	0.96 (0.88–1.05)	0.33	1.08 (0.84–1.40)	0.55	0.95 (0.86–1.05)	0.32	0.92 (0.73–1.17)	0.51
Calendar year of KT 2011–2013 (vs. 2014–2016)	1.06 (0.98–1.14)	0.15	0.92 (0.75–1.13)	0.43	1.14 (1.04–1.25)	<0.01	0.84 (0.69–1.02)	0.07
Induction immunosuppressive therapy[b] (vs. absence of therapy)								
ATG	1.83 (1.66–2.01)	<0.01	1.17 (0.89–1.54)	0.26	2.08 (1.86–2.33)	<0.01	1.54 (1.18–2.02)	<0.01
Alemtuzumab	1.62 (1.43–1.84)	<0.01	0.94 (0.67–1.32)	0.73	1.80 (1.55–2.09)	<0.01	1.50 (1.08–2.07)	0.01
Basiliximab	0.80 (0.72–0.88)	<0.01	1.00 (0.75–1.35)	0.98	0.75 (0.67–0.85)	<0.01	0.88 (0.65–1.20)	0.44
Other immunosuppression	1.61 (1.05–2.47)	0.03	1.35 (0.39–4.72)	0.64	1.48 (0.91–2.43)	0.12	2.82 (0.98–8.12)	0.06
Maintenance immunosuppressive therapy[c] (vs. absence of therapy)								
MMF	1.14 (0.96–1.35)	0.14	0.68 (0.41–1.13)	0.14	1.42 (1.16–1.73)	<0.01	0.90 (0.58–1.41)	0.65
Tacrolimus	1.19 (1.00–1.41)	0.05	0.86 (0.54–1.39)	0.55	1.38 (1.13–1.69)	<0.01	0.70 (0.43–1.13)	0.14
AZA, everolimus, and/or cyclosporine	0.39 (0.32–0.48)	<0.01	0.52 (0.29–0.94)	0.03	0.37 (0.29–0.47)	<0.01	0.69 (0.36–1.32)	0.26

(Continued on following page)

TABLE 3 | (*Continued*) Logistic regression for probability of starting CMV prophylaxis among adults undergoing a first kidney transplant.

Predictors	Overall		High Risk (D+/R–)		Intermediate Risk (R+)		Low Risk (D–/R–)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Other immunosuppression	1.05 (0.89–1.24)	0.57	0.57 (0.37–0.89)	0.01	1.36 (1.11–1.67)	<0.01	0.55 (0.34–0.91)	0.02
Prednisone or methylprednisolone	0.61 (0.51–0.74)	<0.01	1.20 (0.78–1.86)	0.41	0.51 (0.40–0.64)	<0.01	0.50 (0.33–0.77)	<0.01

Abbreviations: ATG, antithymocyte globulin; AZA, azathioprine; CCI, Charlson Comorbidity index; CI, confidence interval; CMV, cytomegalovirus; D, donor; D+, seropositive donor; D–, seronegative donor; ESRD, end-stage renal disease; HLA, human leukocyte antigen; KT, kidney transplant; MMF, mycophenolate mofetil; OR, odds ratio; PRA, panel-reactive antibody; R, recipient; R+, seropositive recipient; R–, seronegative recipient; US, United States.

[a]*Other includes Asian, American Indian, Alaska Native, Native Hawaiian, Pacific Islander, multiracial, other, and unknown.*

[b]*Other immunosuppression therapies included daclizumab, muromonab-CD3, rituximab, and cyclophosphamide.*

[c]*Other immunosuppression maintenance therapies included sirolimus, leflunomide, belatacept, or any other.*

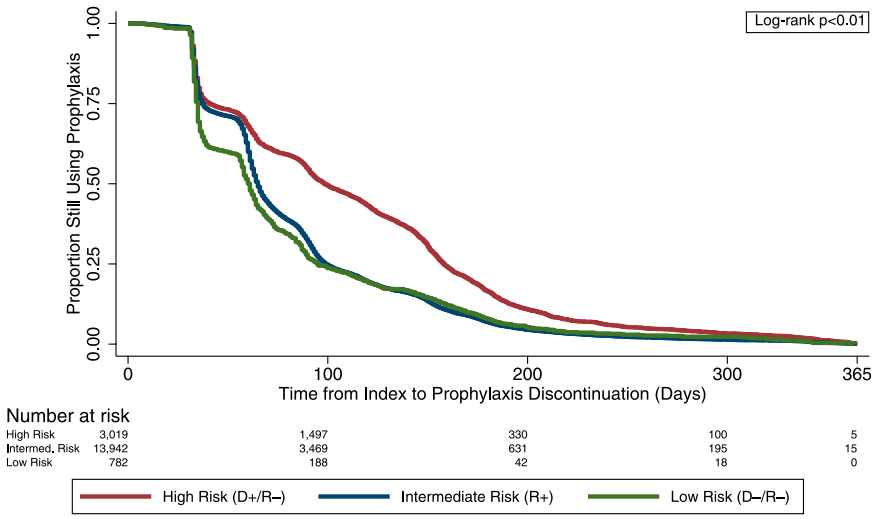


FIGURE 2 | KM Curves for Time to Prophylaxis Discontinuation, by Serostatus (CMV Risk Group). Abbreviations: D+, seropositive donor; D–, seronegative donor; R+, seropositive recipient; R–, seronegative recipient.

Supplemental Table S1). In general, CMV risk status was the factor most strongly associated with the use of CMV prophylaxis. KTRs who were younger, female, African American or of other races, as well as those with comorbid diabetes, whose donor creatinine levels were >1.5 mg/dl, who spent more time on dialysis prior to KT, had PRA ≥80%, and who used ATG, alemtuzumab, and tacrolimus were more likely to receive CMV prophylaxis (all and intermediate-risk KTRs). KTRs who resided in regions other than the Northeast, had CCI score ≥5, whose kidney graft experienced cold ischemia time <24 h, used basiliximab, AZA, everolimus, or cyclosporine, or prednisone and/or methylprednisolone were less likely to receive CMV prophylaxis (all and intermediate-risk KTRs). Additionally, high-risk KTRs who spent more time on dialysis prior to transplant were more likely to receive CMV prophylaxis; whereas those with a CCI score ≥5, and who used AZA, everolimus, or cyclosporine, or other maintenance immunosuppressive agents were less likely to receive CMV prophylaxis. Low-risk KTRs who were female, resided in the South, had comorbid cardiovascular disease, and used ATG and alemtuzumab as induction immunosuppressive agents were more likely to receive CMV prophylaxis.

Duration of Prophylaxis and Factors Associated With Risk of CMV Prophylaxis Discontinuation

Figure 2 displays the KM curves for time to prophylaxis discontinuation. The median time to prophylaxis discontinuation (i.e., prophylaxis duration), derived from the KM curves, for the high-risk group of KTRs was longer (98 days) than for intermediate- (65 days) and low-risk (61 days) KTRs. Regardless of the type of antiviral agent used, 15.6% of KTRs who used CMV prophylaxis did so for ≥200 days (19.4% and 9.8% of high-risk KTRs who used valganciclovir 450 mg and 900 mg, respectively, did so for ≥200 days) and slightly more than half (51.3%) of high-risk KTRs used CMV prophylaxis for ≥100 days (59.4% and 40.1% of high-risk KTRs who used valganciclovir 450 mg and 900 mg, respectively, did so for ≥100 days). One-third (33.1%) of intermediate-risk KTRs used CMV prophylaxis for ≥100 days

TABLE 4 | Cox proportional hazard regression for time to CMV prophylaxis discontinuation among adults undergoing a first kidney transplant.

Predictors	Overall		High Risk (D+/R–)		Intermediate Risk (R+)		Low Risk (D–/R–)	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
CMV serostatus (vs. D–/R–)								
D+/R–	0.69 (0.64–0.75)	<0.01	—	—	—	—	—	—
R+	0.97 (0.90–1.04)	0.44	—	—	—	—	—	—
Time-varying covariates (vs. no condition)								
Neutropenia	1.29 (1.17–1.43)	<0.01	1.38 (1.14–1.69)	<0.01	1.23 (1.09–1.39)	<0.01	1.67 (1.09–2.57)	0.02
Leukopenia	1.16 (1.09–1.23)	<0.01	1.14 (0.99–1.31)	0.08	1.18 (1.10–1.27)	<0.01	1.01 (0.76–1.35)	0.93
Age 18–64 (vs. age ≥65)	0.88 (0.85–0.91)	<0.01	0.83 (0.75–0.91)	<0.01	0.89 (0.85–0.92)	<0.01	0.80 (0.66–0.99)	0.04
Female (vs. Male)	0.97 (0.94–1.01)	0.12	0.97 (0.89–1.05)	0.46	0.98 (0.94–1.01)	0.19	1.00 (0.85–1.18)	0.98
Race (vs. White)								
African American	1.04 (1.01–1.08)	0.02	1.07 (0.98–1.17)	0.14	1.03 (0.99–1.08)	0.11	1.14 (0.96–1.35)	0.12
Other[a]	0.93 (0.88–0.98)	0.01	1.07 (0.85–1.34)	0.57	0.92 (0.87–0.97)	<0.01	1.12 (0.77–1.63)	0.55
Region (vs. Northeast)								
Midwest	1.15 (1.09–1.21)	<0.01	1.01 (0.90–1.13)	0.84	1.19 (1.13–1.26)	<0.01	1.13 (0.90–1.41)	0.30
South	1.33 (1.27–1.38)	<0.01	1.09 (0.99–1.21)	0.09	1.38 (1.32–1.45)	<0.01	1.46 (1.20–1.77)	<0.01
West and Other US territories	1.25 (1.19–1.31)	<0.01	1.09 (0.97–1.24)	0.15	1.29 (1.22–1.36)	<0.01	1.06 (0.81–1.40)	0.66
Primary disease leading to ESRD (vs. diabetes of any type)								
Hypertensive nephrosclerosis	0.99 (0.94–1.05)	0.81	0.97 (0.86–1.11)	0.69	0.99 (0.94–1.05)	0.75	1.05 (0.81–1.37)	0.70
Polycystic kidney disease	1.02 (0.94–1.10)	0.63	1.00 (0.84–1.20)	0.98	1.02 (0.94–1.12)	0.60	0.96 (0.67–1.36)	0.80
Focal glomerular sclerosis	1.03 (0.95–1.11)	0.49	0.96 (0.80–1.16)	0.69	1.06 (0.97–1.15)	0.22	0.90 (0.62–1.31)	0.59
Other	1.02 (0.97–1.07)	0.54	1.02 (0.90–1.16)	0.72	1.02 (0.96–1.08)	0.50	0.94 (0.72–1.23)	0.65
CCI ≥5 (vs. <5)	1.04 (0.99–1.09)	0.16	1.06 (0.94–1.20)	0.33	1.03 (0.97–1.09)	0.34	1.13 (0.86–1.48)	0.37
Comorbid health conditions (vs. absence of condition)								
Cardiovascular disease	1.11 (1.06–1.18)	<0.01	1.17 (1.03–1.32)	0.02	1.10 (1.03–1.17)	<0.01	1.10 (0.85–1.43)	0.46
Chronic pulmonary disease	1.02 (0.98–1.06)	0.37	1.02 (0.93–1.13)	0.64	1.02 (0.97–1.06)	0.49	1.10 (0.89–1.34)	0.37
Diabetes	0.94 (0.89–1.00)	0.04	1.00 (0.88–1.15)	0.97	0.93 (0.88–0.99)	0.03	0.92 (0.69–1.23)	0.58
Liver disease	0.92 (0.88–0.96)	<0.01	0.93 (0.83–1.05)	0.25	0.92 (0.87–0.97)	<0.01	0.90 (0.70–1.14)	0.37
Rheumatologic disease	1.02 (0.97–1.06)	0.52	1.09 (0.97–1.22)	0.16	1.00 (0.95–1.06)	0.90	0.90 (0.70–1.15)	0.39
Donor type deceased (vs. living)	1.09 (1.03–1.14)	<0.01	1.05 (0.78–1.42)	0.73	1.09 (1.04–1.15)	<0.01	0.88 (0.54–1.42)	0.60
Cold ischemia time <24 h (vs. ≥24 h)	0.98 (0.94–1.02)	0.23	0.96 (0.87–1.06)	0.42	0.98 (0.93–1.02)	0.33	0.99 (0.82–1.21)	0.95
Donor creatinine >1.5 mg/dl (vs. ≤1.5 mg/dl)	0.99 (0.95–1.03)	0.57	1.02 (0.93–1.13)	0.63	0.99 (0.94–1.03)	0.58	0.96 (0.80–1.17)	0.71
Time on dialysis prior to KT in years	0.99 (0.99–1.00)	<0.01	1.00 (0.99–1.02)	0.47	0.99 (0.98–1.00)	<0.01	0.99 (0.96–1.01)	0.30
Wait time in years	0.99 (0.98–1.00)	0.03	0.99 (0.97–1.00)	0.12	0.99 (0.98–1.00)	0.09	1.01 (0.97–1.05)	0.74
PRAs ≥80% (vs. <80%)	0.97 (0.92–1.02)	0.24	1.05 (0.90–1.22)	0.54	0.96 (0.91–1.02)	0.15	0.96 (0.72–1.27)	0.76
HLA A B donor-recipient match ≥3 (vs. <3)	0.96 (0.93–1.00)	0.06	1.01 (0.92–1.12)	0.77	0.95 (0.91–0.99)	0.02	1.08 (0.89–1.31)	0.44
Calendar year of transplant 2011–2013 (vs. 2014–2016)	0.51 (0.46–0.57)	<0.01	0.51 (0.40–0.66)	<0.01	0.50 (0.44–0.57)	<0.01	0.64 (0.36–1.16)	0.14
Induction immunosuppressive therapy[b] (vs. absence of therapy)								
ATG	0.97 (0.93–1.02)	0.22	0.98 (0.88–1.09)	0.69	0.97 (0.93–1.02)	0.27	0.98 (0.79–1.23)	0.88
Alemtuzumab	0.96 (0.91–1.02)	0.18	0.99 (0.87–1.13)	0.89	0.97 (0.91–1.03)	0.37	0.75 (0.58–0.97)	0.03
Basiliximab	0.98 (0.93–1.03)	0.40	1.01 (0.90–1.13)	0.87	0.98 (0.93–1.03)	0.39	0.93 (0.71–1.20)	0.56
Other immunosuppression	0.89 (0.77–1.03)	0.13	1.02 (0.66–1.57)	0.94	0.89 (0.76–1.05)	0.16	0.72 (0.35–1.50)	0.38
Maintenance immunosuppressive therapy[c] (vs. absence of therapy)								
MMF	0.95 (0.87–1.02)	0.16	0.93 (0.77–1.11)	0.42	0.94 (0.86–1.03)	0.18	1.10 (0.77–1.56)	0.61
Tacrolimus	0.86 (0.79–0.93)	<0.01	0.83 (0.70–1.00)	0.05	0.86 (0.79–0.94)	<0.01	0.95 (0.62–1.45)	0.80
AZA, everolimus, and/or cyclosporine	0.95 (0.84–1.06)	0.33	0.95 (0.74–1.21)	0.66	0.94 (0.82–1.07)	0.37	0.90 (0.54–1.53)	0.71
Other immunosuppression	0.98 (0.91–1.06)	0.66	1.00 (0.83–1.20)	0.99	0.98 (0.90–1.07)	0.70	0.89 (0.54–1.45)	0.63
Prednisone or methylprednisolone	1.00 (0.93–1.08)	0.98	1.02 (0.86–1.22)	0.79	1.01 (0.92–1.09)	0.89	0.79 (0.56–1.11)	0.18

Abbreviations: ATG, antithymocyte globulin; AZA, azathioprine; CCI, Charlson Comorbidity index; CI, confidence interval; CMV, cytomegalovirus; D, donor; D+, seropositive donor; D–, seronegative donor; ESRD, end-stage renal disease; HLA, human leukocyte antigen; HR, hazard ratio; KT, kidney transplant; MMF, mycophenolate mofetil; PRA, panel-reactive antibody; R, recipient; R+, seropositive recipient; R–, seronegative recipient; US, United States.

[a]*Other includes Asian, American Indian, Alaska Native, Native Hawaiian, Pacific Islander, multiracial, other, and unknown.*

[b]*Other immunosuppression therapies included daclizumab, muromonab-CD3, rituximab, and cyclophosphamide.*

[c]*Other immunosuppression maintenance therapies included sirolimus, leflunomide, belatacept, or any other.*

(36.5% and 20.3% of intermediate-risk KTRs who used valganciclovir 450 mg and 900 mg, respectively, did so for ≥100 days).

Table 4 displays the results of the PH Cox regression models for time to CMV prophylaxis discontinuation. We found that, regardless of risk group, KTRs who resided in the South and who developed neutropenia were more likely to discontinue CMV prophylaxis; all KTRs, as well as high- and intermediate-risk KTRs who developed leukopenia, were also more likely to discontinue. All KTRs, as well as intermediate-risk KTRs, who resided in regions other than the Northeast, had comorbid cardiovascular disease (plus high-risk KTRs), and received their kidney grafts from deceased donors were also more likely to discontinue CMV prophylaxis. High-risk (vs. low-risk) KTRs; KTRs who were younger; intermediate-risk (as well as all) KTRs with comorbid diabetes or liver disease or who had ≥3 HLA A B matches; high- and intermediate-risk (as well as all) KTRs who received tacrolimus; and low-risk KTRs who received basiliximab were less likely to discontinue CMV prophylaxis. Overall, KTRs who were African American were more likely to discontinue CMV prophylaxis, while intermediate-risk KTRs of other races were less likely to discontinue.

DISCUSSION

Based on a large cohort of adult KTRs who received their first KTs between July 2011 and December 2016, we found that most, but not all, high- and intermediate-risk KTRs used CMV prophylaxis. CMV prophylaxis was more common among high- (85.8%) than intermediate- (82.4%) and low-risk (32.1%) KTRs, with virtually all of those KTRs using valganciclovir and almost 60% of valganciclovir users using 450 mg per day. Furthermore, we found that the majority of KTRs used CMV prophylaxis for less than the guideline-recommended duration of 200 and 100 days for high- and intermediate-risk KTRs, respectively (4, 5, 7).

Compared with our current research, Santos *et al.* (2016) used USRDS-Medicare data for the period covering June 2006 to 2011 and found that 60% of KTRs used CMV prophylaxis (71%, 63%, and 34% of high-, intermediate- and low-risk KTRs, respectively) (13). In our study, we found, using more recent data from 2011 to 2017, that proportionately more KTRs—overall, high- and intermediate-risk KTRs—used prophylaxis, while low-risk KTRs continued to have the same proportion on prophylaxis. Overall, these findings reflect an improvement in adherence to guideline recommendations on the use of prophylaxis in high- and intermediate-risk KTRs, and a persistent overuse of prophylaxis in low-risk KTRs. Furthermore, we found that the mean duration of CMV prophylaxis was also longer in our study; however, still only approximately one in six high-risk KTRs completed 200 days of CMV prophylaxis and one in three intermediate-risk KTRs completed 100 days of CMV prophylaxis. These findings highlight premature discontinuation of CMV prophylaxis among high-and intermediate-risk KTRs.

To capture use of alternate treatments potentially still being used, the initial study definitions of CMV prophylaxis included treatment with valganciclovir, acyclovir, ganciclovir, valacyclovir, foscarnet, or cidofovir. Since current CMV treatment guidelines do not include the use of agents other than valganciclovir and ganciclovir, we utilized dose-based algorithms to identify alternative agents as CMV prophylaxis considering previous clinical guidelines and clinical expert inputs. Based on finding less than 0.5% of patients who received an alternative agent for CMV prophylaxis, we did not report findings due to lack of meaningful comparisons.

We also explored the impact of factors associated with the use and duration of CMV prophylaxis. In general, we found that characteristics thought or known to be risk factors for graft rejection and CMV infection/disease were key determinants for use, and longer duration, of CMV prophylaxis. The literature suggests that CMV serostatus (risk) and young age are risk factors for CMV (3, 6, 7). In addition, young age, high PRA, deceased donor, cold ischemia time >24 h, and HLA mismatch are also known risk factors for acute rejection requiring intensive immunosuppressive therapy (14). The use of certain T-cell depleting agents (ATG, alemtuzumab) (13, 15, 16) and high doses of immunosuppressive agents have been shown to be associated with increases in the risk of CMV (7). Additionally, younger age (17, 18), African American race, use of mammalian target of rapamycin inhibitors (19-24), and PRA ≥80% (25) are associated with decreased risk of CMV infection, and hence, decreased need for CMV prophylaxis. There is some evidence that basiliximab is negatively associated with CMV infection and the need for prophylaxis (17, 26). Our findings were mostly consistent in this regard. High-risk and younger (18–65 years) KTRs were the most likely to receive CMV prophylaxis and were the least likely to have discontinued CMV prophylaxis. Also consistent with previously published data, we found that KTRs who used basiliximab, AZA, everolimus, or cyclosporine, or other maintenance immunosuppressive agents, which included sirolimus (by high-risk KTRs), and whose kidney grafts spent <24 h in cold ischemia were less likely to have started prophylaxis. We also found that occurrence of myelosuppressive events was one of the factors, regardless of risk group, most strongly associated risk of CMV prophylaxis discontinuation. This finding is consistent with the prior studies highlighting valganciclovir discontinuation as a result of leukopenia and/or neutropenia. For example, Brar et al. (2021) recently reported that, among high-risk KTRs who received their KTs at a single institution, those who developed neutropenia were much more likely to have discontinued or reduced the dose of their prophylaxis as well as maintenance immunosuppressive therapies (27).

Retrospective database studies that use registry and claims data, such as ours, are inherently limited by the how recent the data are and by the specific types of information that are available, which are often obtained for purposes other than the study being designed. For our study, the data collected for surveillance and administrative purposes lacked clinical measures such as creatine levels or glomerular filtration rates (GFRs) collected at key points, such as initiation of CMV antiviral agents. The lack of clinical measures at precise times during treatment translated to limitations in understanding if the intended dose of valganciclovir for CMV prophylaxis was appropriate. Our methods used to impute TDD may not accurately reflect the intended dose of valganciclovir, as dose adjustments due to renal insufficiency or impairment were not available. We tested an alternative method to confirm intended dose by assuming centers would apply a uniform protocol for the use of CMV prophylaxis by CMV serostatus. However, the center level

analysis showed variation in the use of valganciclovir dose and did not inform intended dose. Therefore, it is possible that those with renal impairment (i.e., low GFR) may have used valganciclovir 450 mg, rather than the intended dose of 900 mg. These limitations within the data may have led to misclassification errors; however, since the majority of KTRs received a well-functioning kidney, this situation may apply to only a small fraction of KTRs.

To ensure use of valganciclovir or ganciclovir use was correctly assigned as CMV prophylaxis instead of pre-emptive therapy in our analysis, in addition to identifying individuals who initiated valganciclovir or ganciclovir within 28 post KT, we excluded individuals with a diagnosis of CMV infection during the baseline study period. Given the mean length of stay for the kidney transplantation procedure ranges from 4.5 to 5.5 days and the mean (SD) time to initiate either ganciclovir or valganciclovir was 4.3 (4.5) days in our study, these agents seem to be initiated at discharge without a prior diagnosis of CMV during the index transplant (28). Therefore, it was highly unlikely that these agents were used as pre-emptive therapy. Finally, because we only included Medicare Part D enrollees in our sample, our findings may not be generalizable to commercial insured or Medicare advantage enrollees and individuals who reside outside the United States.

However, despite these limitations, our study has many strengths. Our study used a large and detailed database containing KT registry data linked to Medicare claims that allowed us to analyze a broad number of donor and recipient clinical characteristics. Furthermore, we were able to accurately capture medication use patterns by limiting the sample to Medicare Part D-covered beneficiaries. Our findings contribute to the literature by documenting improvements in adherence to guideline recommendations for managing CMV in KTRs.

CONCLUSION

This study provides the most up-to-date information on national-level CMV prophylaxis among KTRs in the US. Most, but not all, high- and intermediate-risk KTRs received CMV prophylaxis, and virtually all KTRs who started prophylaxis used valganciclovir. However, our findings also highlight that adherence to the recommended duration of CMV prophylaxis is suboptimal. Furthermore, this is the first study of a very large sample of KTRs to confirm the association between development of leukopenia and neutropenia and subsequent risk of CMV prophylaxis discontinuation.

DATA AVAILABILITY STATEMENT

The data reported here have been supplied by the United States Renal Data System (USRDS). The USRDS-Medicare data are publicly available. For further information, visit https://usrds.org/for-researchers/standard-analysis-files.

ETHICS STATEMENT

This study was reviewed and approved by the WCG IRB, Puyallup, WA 98374 (IRB Study Number 1289813). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Substantial contributions to the conception or design of the work: AR, YT, MG, and CS. Acquisition, analysis, or interpretation of data for the work: MG, AL, KF, SS, AR, YT, and CS. Drafting the work or revising it critically for important intellectual content: AR, AL, MG, KF, YT, and CS. Final approval of the version to be published: AR, AL, MG, SS, KF, YT, and CS. All authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

AUTHOR DISCLAIMER

The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.

CONFLICT OF INTEREST

MG, KF, and AL are employed by Evidera. SS was employed by Evidera and AR and YT were employed by MSD while this study was conducted. MG is a minor shareholder of Thermo Fisher Scientific stock. CS received consulting fees from MSD for his work on this study.

This work was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, United States. The funder had the following involvement with the study: study design, data acquisition, interpretation of results, critical review of manuscript, and the decision to publish.

ACKNOWLEDGMENTS

Medical writing support was provided by Phillip S. Leventhal (Evidera).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2022.10528/full#supplementary-material

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ORIGINAL RESEARCH
published: 25 August 2022
doi: 10.3389/ti.2022.10489

Liver Transplant Recipient Characteristics Associated With Worse Post-Transplant Outcomes in Using Elderly Donors

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Advanced age of liver donor is a risk factor for graft loss after transplant. We sought to identify recipient characteristics associated with negative post-liver transplant (LT) outcomes in the context of elderly donors. Using 2014–2019 OPTN/UNOS data, LT recipients were classified by donor age: ≥70, 40–69, and <40 years. Recipient risk factors for one-year graft loss were identified and created a risk stratification system and validated it using 2020 OPTN/UNOS data set. At transplant, significant recipient risk factors for one-year graft loss were: previous liver transplant (adjusted hazard ratio [aHR] 4.37, 95%CI 1.98–9.65); mechanical ventilation (aHR 4.28, 95%CI 1.95–9.43); portal thrombus (aHR 1.87, 95%CI 1.26–2.77); serum sodium <125 mEq/L (aHR 2.88, 95%CI 1.34–6.20); and Karnofsky score 10–30% (aHR 2.03, 95%CI 1.13–3.65), 40–60% (aHR 1.65, 95%CI 1.08–2.51). Using those risk factors and multiplying HRs, recipients were divided into low-risk (n = 931) and high-risk (n = 294). Adjusted risk of one-year graft loss in the low-risk recipient group was similar to that of patients with younger donors; results were consistent using validation dataset. Our results show that a system of careful recipient selection can reduce the risks of graft loss associated with older donor age.

Keywords: liver transplantation, elderly donors, patient characteristics, posttransplant outcome, organ procurement and transplant network and united network for organ sharing

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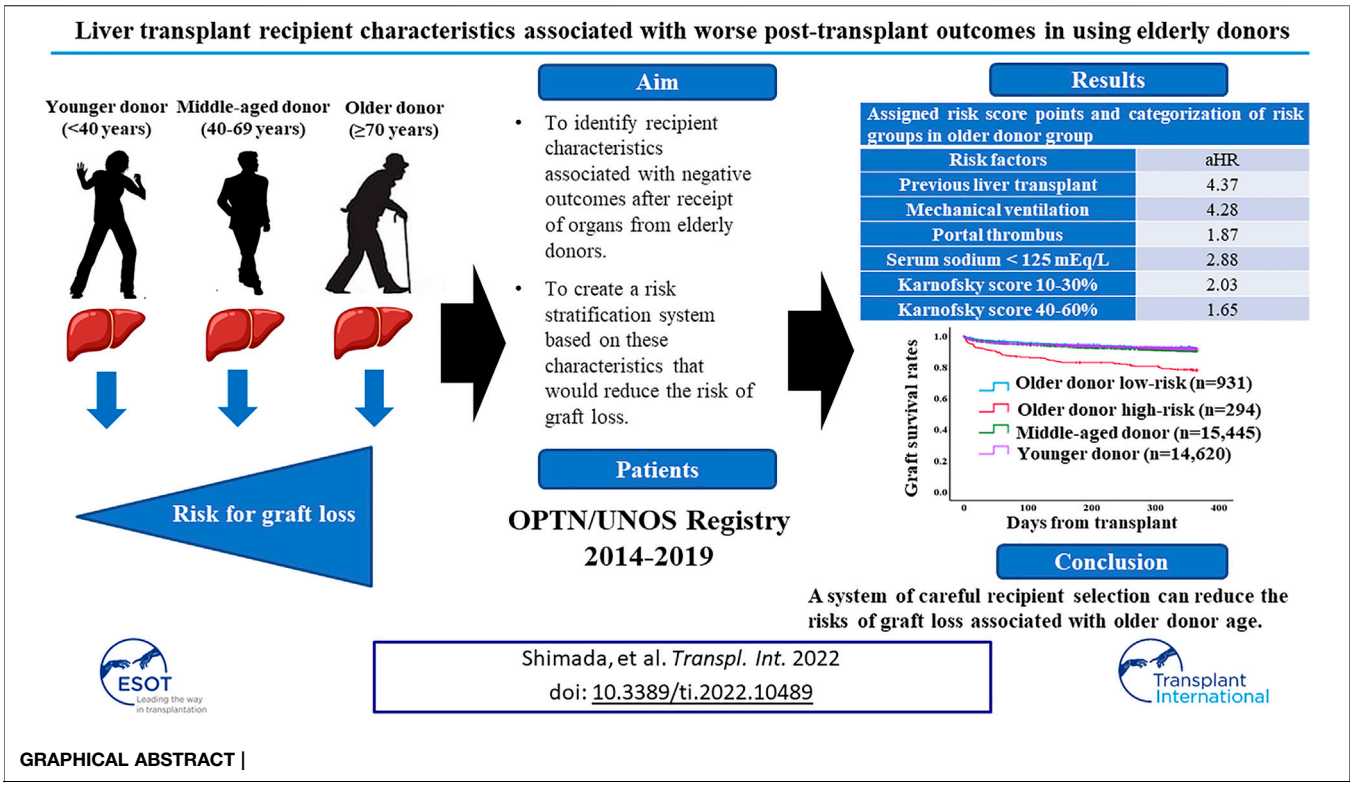
***Received:** 07 March 2022*
***Accepted:** 10 August 2022*
***Published:** 25 August 2022*

Citation:
Shimada S, Shamaa T, Ivanics T, Kitajima T, Collins K, Rizzari M, Yoshida A, Abouljoud M, Moonka D, Lu M and Nagai S (2022) Liver Transplant Recipient Characteristics Associated With Worse Post-Transplant Outcomes in Using Elderly Donors. Transpl Int 35:10489. doi: 10.3389/ti.2022.10489

Abbreviations: aHR, adjusted hazard ratio; BAR, balance of risk; BMI, body mass index; CVA, cerebrovascular accident; DCD, donation after circulatory death; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; IQR, interquartile range; LT, liver transplant; MELD, model for end-stage liver disease; OPTN, organ procurement and transplant network; ROC, receiver operating characteristic; STAR, standard transplant and research; UNOS, united network for organ sharing.



GRAPHICAL ABSTRACT |

INTRODUCTION

The need for donor livers currently exceeds the number of organs available for transplantation in the US [1]. For example, in 2019 there were 12,767 new registrations for liver transplantation (LT), but only 8,896 were performed [2]—underscoring the importance of expanding the donor pool. However, expanding the donor pool by using older donors may compromise post-LT outcomes. Higher donor age is a significant risk factor for graft loss and mortality after LT [3, 4] and for ischemia-reperfusion injury, with increased necrosis and apoptosis [5, 6]. Although a donor age of ≥70 years is considered the highest risk category [3], by 2030 the proportion of the US population older than 70 will have increased from 9% to almost 14% [7]. Within this context, optimizing the usage of grafts from older donors is essential.

Previous studies have investigated recipient risk factors for poor liver transplantation outcomes when using livers from older donors [8-10]; these include previous LT or abdominal surgery, active hepatitis C virus (HCV) infection, and hepatocellular carcinoma (HCC), as well as current hospitalization, need for pre-transplant dialysis, and registration as status 1 (risk of imminent demise) [8–10]. However, given the rising age of both donors and recipients, the introduction of highly effective direct-acting antiviral treatments for HCV, and changes in liver allocation policy, a more current appraisal of factors associated with successful outcomes after liver grafts with transplantation from elderly donors is necessary.

In this study, we hypothesized that using liver from older donors could be optimized by carefully considering the medical and surgical conditions of recipients. We sought to identify recipient characteristics associated with negative outcomes after receipt of organs from elderly donors and to create a risk stratification system based on these characteristics that would reduce the risk of graft loss. The primary endpoint was set for one-year graft loss which includes patient death.

PATIENTS AND METHODS

Study Population

This study used data from the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) Standard Transplant and Research (STAR) files for LT. The study period was set from 1 January 2014 to 31 December 2019, with 1 year of post-transplant observation for each patient. Study procedures were approved by the Henry Ford Health System Institutional Review Board; the requirement for written informed consent was waived due to the deidentified nature of the data. Patients who were 18 years or older at the time of transplant were eligible for this study. Patients who received a partial/split graft or combined organ transplant with thoracic organs, kidney, intestine, and/or pancreas or patients for whom donor age was unknown were excluded. Also, if patients who had one or more missing data which was evaluated in this study, those were excluded (**Figure 1**). To assess the impact of donor age on post-LT outcomes and to determine whether specific recipient

characteristics were associated with worse post-LT outcomes with liver grafts from older donors, the cohort was divided into three groups according to the donor age. Age categories were determined using the liver donor risk index [3]: older donor (≥70 years); middle-aged donor (40–69 years); and younger donor (<40 years).

Covariates

Binary variables included: recipient gender; recipient diabetes; primary liver disease etiologies including HCV infection; alcohol related disease, non-alcoholic steatohepatitis and other diseases, diagnosis of HCC; history of abdominal surgery; previous liver transplant; registration as status 1; dialysis requirement at transplant; mechanical ventilation at transplant; portal thrombosis at transplant; donation after circulatory death (DCD); donor diabetes; donor history of heavy alcohol use; donor history of hypertension; and donor history of myocardial infarction. In the risk factor analysis, model for end-stage liver disease (MELD) score or MELD-sodium score was not included. Instead, 4 parameters of MELD-sodium score (serum total bilirubin, creatinine, sodium, and INR) were separately included. MELD-sodium score was calculated using the following formula; MELD-sodium = MELD +1.32 x (137-serum sodium)—[0.033 x MELD x (137 - serum sodium)] [11]. Continuous variables were classified into multilevel categorical variables. Recipient data at time of transplant included: age (<50, 50–64, and ≥65 years); BMI (<18.5, 18.5–24.9, 25.0–29.9, and ≥30.0 kg/m^2) [12]; serum bilirubin (<2.0, [2.0–4.4, 4.5–11.9, and ≥12.0 mg/dl [total bilirubin of 2.0 mg/dl: based Child-Pugh score [13], 4.5 and 12 mg/dl were 33 and 66%tile in the cohort]); serum creatinine (<1.5, 1.5–1.7, 1.8–2.5, and ≥2.5 mg/dl [creatinine of 1.5 mg/dl is used for a diagnosis hepatorenal syndrome criteria in patients with cirrhosis] [14], 1.8 and 2.5 mg/dl were 33 and 66%tile in the cohort]), serum sodium (<125, 125–134, 135–145, and ≥146 mEq/L) [15]; and international normalized ratio (INR; <1.5, 1.5–1.7, 1.8–2.4, and ≥2.5 [INR ≥1.5; a factor of acute liver failure] [16], 1.8 and 2.5 were 33 and 66%tile in the cohort]). Organ related variables included donor age at transplantation (<40, 40–69, and ≥70 years old) and cold ischemia time (<6.0, 6.0–7.9, and ≥8 h [6 h was median value in the cohort, 8 hour-cut off point was decided according to liver donor risk index] [3]). Additional multilevel categorical variables included: recipient race (White, Black/African American, Hispanic [of any race], and other); Karnofsky Performance Status score (10–30, 40–60, and 70–100%); donor cause of death (trauma, anoxia, cerebrovascular accident [CVA], and other); and organ share type (local, regional, or national). All covariates were collected prior to or at the time of LT.

Analysis of the Impact of Donor Age on Post-LT Outcomes

Risk of one-year graft loss after receipt of an organ from the ≥70 donor group was compared to the 40–69 and <40 donor groups. Graft loss was defined as death or re-transplantation. Analyses were adjusted for recipient demographic (age, race, gender) and clinical characteristics (BMI, diabetes, primary liver disease etiologies including HCV infection; alcohol related disease, non-alcoholic steatohepatitis and other diseases, presence of HCC, history of abdominal surgery, portal thrombus, previous liver transplant, status 1 [yes/no], laboratory values [bilirubin, creatinine, INR, sodium], Karnofsky score, and need for mechanical ventilation or dialysis) at the time of transplantation. Analyses were also adjusted for donor (age category, race, gender, BMI, diabetes, history of heavy alcohol use, history of hypertension, and history of myocardial infarction) and organ characteristics (cause of death, donation after cardiac death [DCD; yes/no], cold ischemia time, and organ share type).

Risk Factor Analysis in the ≥70 Donor Group and Risk Stratification

Recipient risk factors for one-year graft loss were determined with multivariable Cox regression. The total risk score for each patient was calculated by multiplying the adjusted hazard ratios (aHRs) of recipient risk factors according to a previously used methodology [17]. If one risk factor, score is equal to the HR of that particular factor. If no risk factor, score is zero. Our risk stratification system classified recipients into low- and high-risk groups; the cut-off risk score value was calculated from Youden index and determined by the receiver operating characteristic (ROC) curve for one-year graft survival. We then compared one-year graft loss in the ≥70 donor group to these risk score categories. We also compared the low- and high-risk ≥70 donor groups to the 40–69 and <40 groups (both with and without DCD). This risk stratification system was then applied to the validation cohort using patient cohort who received LT in 2020 from the STAR files (**Figure 2**).

Statistical Analysis

Patient demographic and clinical characteristics, as well as donor and organ characteristics, were described by donor age groups, using median and interquartile range (IQR) for continuous variables and number and percentages for categorical variables. We used the Mann-Whitney-U test for continuous variables and chi-square test for categorical variables to study differences in patient characteristics among the three donor age groups. Post-transplant graft survival was evaluated using Kaplan-Meier curve analysis and compared by log-rank tests. A multivariable Cox regression model assessed hazards of post-transplant graft loss. For the risk factor analysis in each donor group (older donor, middle-aged donor, and younger donor), multivariable Cox regression models were created using factors which had p value less than 0.157 in univariable analyses [18]. p-values <0.05 were considered statistically significant for all analyses. All statistical analyses were completed using SPSS version 27 (IBM, Chicago IL, United States) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics Among Groups

Of the 31,290 patients eligible for this study, 1,225 received livers from donors in the ≥70 group, 15,445 received livers from donors

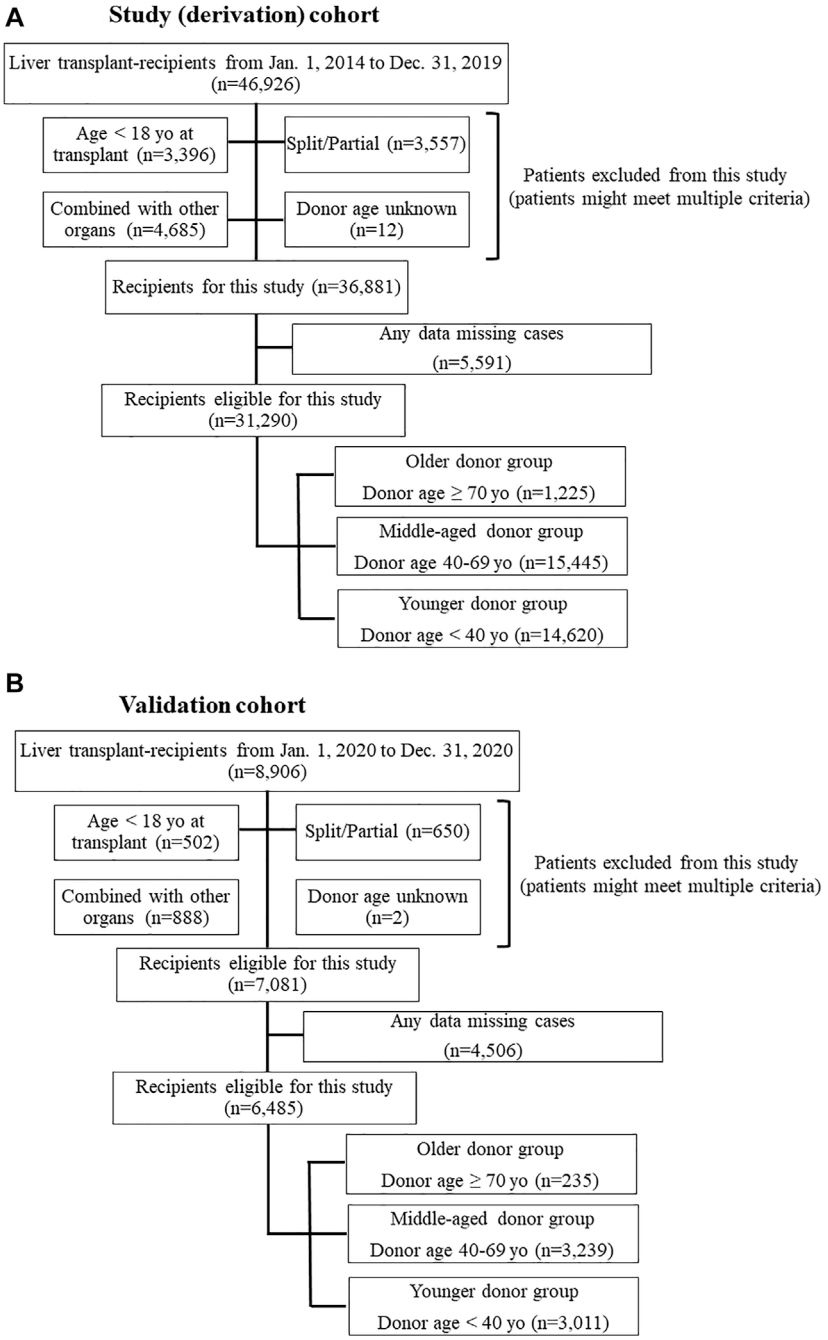
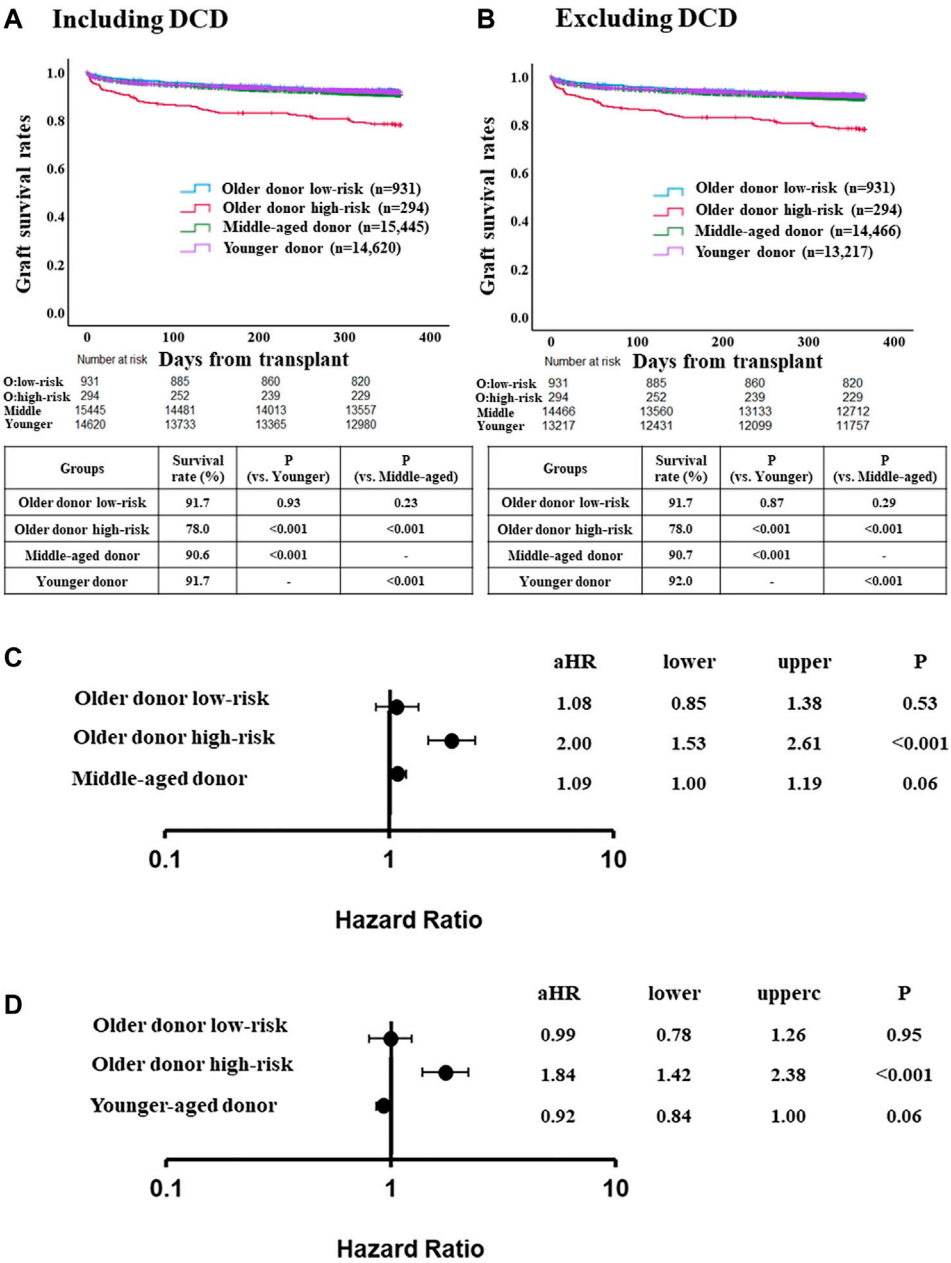


FIGURE 1 | (A) Flow chart of study population (derivation) selection. **(B)** Flow chart of validation population selection.

aged 40–69, and 14,620 received livers from donors <40 years old (**Figure 1**). **Table 1** showed details characteristics of patients from the three donor age groups. Recipients of organs from older donors were themselves significantly older (median age 62 vs. 58 [donors aged 40–69] and 57 [donors <40 years], $p < 0.001$ for both).

Median recipient MELD (MELD-sodium) score was significantly lower in older donor group (18 vs. 22 [donors aged 40–69] and 24 [donors <40 years], $p < 0.001$ for both). More of recipients from older donors had HCC compared to recipients with younger donors (17.6% vs. 14.0% [40–69] and 11.6% [<40], $p = 0.001$ and $p < 0.001$, respectively) but fewer had HCV (18.9% vs. 21.8% and 22.0%, $p = 0.01$ for both). Recipients of organs from donors ≥70 were less likely to have Karnofsky scores of 10–30% (14.7% vs. 27.2% [40–69] and 34.0% [<40], $p < 0.001$ for both), to have previously received a liver transplant (1.1% vs. 3.1% [40–69] and 5.6% [<40], $p < 0.001$ for both), or to be registered as status 1 (1.0% vs. 1.7% [40–69] and 3.0% [<40],



Groups	Survival rate (%)	P (vs. Younger)	P (vs. Middle-aged)
Older donor low-risk	91.7	0.93	0.23
Older donor high-risk	78.0	<0.001	<0.001
Middle-aged donor	90.6	<0.001	-
Younger donor	91.7	-	<0.001

Groups	Survival rate (%)	P (vs. Younger)	P (vs. Middle-aged)
Older donor low-risk	91.7	0.87	0.29
Older donor high-risk	78.0	<0.001	<0.001
Middle-aged donor	90.7	<0.001	-
Younger donor	92.0	-	<0.001

FIGURE 2 | Comparison of post-LT outcome between the older donor derivation group stratified by the risk classification and middle-aged or younger donor group. **(A)** One-year graft survival rate in low-risk recipients of the older donor group was similar to those in middle-aged or younger donor group ($p = 0.23$, $p = 0.93$, respectively). **(B)** One-year graft survival rate in low-risk recipients of the older donor group was similar to those in middle-aged or younger donor group after excluding DCD cases ($p = 0.29$, $p = 0.87$, respectively). **(C)** Adjusted hazards of graft loss in the older donor derivation group stratified by the risk classification and middle-aged donor group (ref. younger donor group). **(D)** ref. middle-aged donor group. Hazards were adjusted by a multivariable Cox regression model for the following variables present at the time of transplantation: recipient age; recipient gender; recipient race; recipient body mass index (BMI); recipient diabetes; recipient primary liver disease etiologies including HCV infection, alcohol related disease, non-alcoholic steatohepatitis and other diseases; hepatocellular carcinoma; international normalized ratio; serum bilirubin; serum creatinine; Karnofsky score; history of abdominal surgery; dialysis requirement; serum sodium; portal thrombus; mechanical ventilation; previous liver transplant; status 1; cold ischemia time; donor gender; donor race; donor BMI; donor diabetes; donor cause of death; organ share type; donor history of heavy alcohol use; donor history of hypertension; and donor history of myocardial infarction.

TABLE 1 | Comparisons of characteristics of liver transplant recipients between donor age groups.

Characteristics	Group	Older donor 70 or older	Middle-aged donor 40–69	Younger donor <40	*p* Value	*p* Value
		n = 1,225	*n* = 15,445	*n* = 14,620	O vs. M	O vs. Y
Median recipient age (year), [IQR]		62 [55, 66]	58 [51, 64]	57 [48, 63]	<0.001	<0.001
Recipient gender, n (%)	Male	739 (60.3)	10,404 (67.4)	9,610 (65.7)	<0.001	<0.001
	Female	486 (39.7)	5,041 (32.6)	5,010 (34.3)		
Recipient race, n (%)	White	873 (71.3)	11144 (72.2)	10,267 (70.2)	0.058	0.02
	Black	76 (6.2)	1,191 (7.7)	1,277 (8.7)		
	Hispanic	195 (15.9)	2,269 (14.7)	2,178 (14.9)		
	Others	81 (6.6)	841 (5.4)	898 (6.1)		
Recipient BMI (kg/m^2), n (%)	18.5–24.9	326 (26.6)	3,752 (24.3)	3,926 (26.9)	0.001	0.057
	25.0–29.9	457 (37.3)	5,265 (34.1)	4,931 (33.7)		
	30.0 ≤	424 (34.6)	6,232 (40.3)	5,517 (37.7)		
	<18.5	18 (1.5)	196 (1.3)	246 (1.7)		
Median MELD (MELD-Na) score, [IQR]		18 [12, 24]	22 [14, 30]	24 [15, 34]	<0.001	<0.001
Serum bilirubin (mg/dl), n (%)	<2.0	491 (40.1)	4,773 (30.9)	4,017 (27.5)	<0.001	<0.001
	2.0–4.4	397 (32.4)	3,813 (24.7)	3,214 (22.0)		
	4.5–11.9	232 (18.9)	3,476 (22.5)	3,198 (21.9)		
	12.0 ≤	105 (8.6)	3,383 (21.9)	4,191 (28.7)		
INR, n (%)	<1.5	585 (47.8)	5,977 (38.7)	5,156 (35.3)	<0.001	<0.001
	1.5–1.7	264 (21.6)	2,791 (18.1)	2,424 (16.6)		
	1.8–2.4	264 (21.6)	3,649 (23.6)	3,606 (24.7)		
	2.5 ≤	112 (9.1)	3,028 (19.6)	3,434 (23.5)		
Serum creatinine (mg/dl), n (%)	<1.5	985 (80.4)	11,500 (74.5)	10,499 (71.8)	<0.001	<0.001
	1.5–1.7	93 (7.6)	1,207 (7.8)	1,147 (7.8)		
	1.8–2.5	98 (8.0)	1,412 (9.1)	1,466 (10.0)		
	2.6 ≤	49 (4.0)	1,326 (8.6)	1,508 (10.3)		
Serum sodium (mEq/L), n (%)	135–145	820 (66.9)	9,711 (62.9)	9,247 (63.2)	0.02	0.02
	125–134	355 (29.0)	4,943 (32.0)	4,612 (31.5)		
	<125	30 (2.4)	437 (2.8)	382 (2.6)		
	146 ≤	20 (1.6)	354 (2.3)	379 (2.6)		
History of abdominal surgery, n (%)		611 (49.9)	7,601 (49.2)	7,232 (49.5)	0.67	0.80
Karnofsky score (%), n (%)	70–100	498 (40.7)	4,506 (29.2)	3,831 (26.2)	<0.001	<0.001
	40–60	547 (44.7)	6,737 (43.6)	5,812 (39.8)		
	10–30	180 (14.7)	4,202 (27.2)	4,977 (34.0)		
Recipient diabetes, n (%)		397 (32.4)	4,589 (29.7)	3,899 (26.7)	0.051	<0.001
HCV, n (%)		231 (18.9)	3,372 (21.8)	3,222 (22.0)	0.01	0.01
Alcohol related disease, n (%)		343 (28.0)	4,961 (32.1)	4,586 (31.4)	0.003	0.01
Non-alcoholic steatohepatitis, n (%)		308 (25.1)	3,042 (19.7)	2,478 (16.9)	<0.001	<0.001
HCC, n (%)		215 (17.6)	2,155 (14.0)	1,691 (11.6)	0.001	<0.001
Status 1, n (%)		12 (1.0)	269 (1.7)	442 (3.0)	0.06	<0.001
Previous liver transplant, n (%)		14 (1.1)	482 (3.1)	816 (5.6)	<0.001	<0.001
Dialysis requirement, n (%)		47 (3.8)	1,498 (9.7)	2,059 (14.1)	<0.001	<0.001
Portal thrombosis, n (%)		195 (15.9)	2,345 (15.2)	2,049 (14.0)	0.51	0.07
Mechanical ventilation, n (%)		36 (2.9)	1,170 (7.6)	1,634 (11.2)	<0.001	<0.001
Median Donor age (year), [IQR]		74 [71, 76]	53 [47, 59]	27 [22, 33]	<0.001	<0.001
Donor gender, n (%)	Male	551 (45.0)	8,519 (55.2)	9,639 (65.9)	<0.001	<0.001
	Female	674 (55.0)	6,926 (44.8)	4,981 (34.1)		
Donor race, n (%)	White	837 (68.3)	9,779 (63.3)	9,495 (64.9)	<0.001	<0.001
	Black	171 (14.0)	2,941 (19.0)	2,416 (16.5)		
	Hispanic	141 (11.5)	1,972 (12.8)	2,133 (14.6)		
	Others	76 (6.2)	753 (4.9)	576 (3.9)		
Donor BMI (kg/m^2), n (%)	18.5–24.9	376 (30.7)	3,993 (25.9)	5,717 (39.1)	<0.001	<0.001
	25.0–29.9	427 (34.9)	5,046 (32.7)	4,593 (31.4)		
	30.0 ≤	392 (32.0)	6,141 (39.8)	3,747 (25.6)		
	<18.5	30 (2.4)	265 (1.7)	563 (3.9)		
Cold ischemia time (hours), n (%)	<6.0	739 (60.3)	8,653 (56.0)	7,838 (53.6)	<0.001	<0.001
	6.0–7.9	356 (29.1)	4,507 (29.2)	4,246 (29.0)		
	8.0 ≤	130 (10.6)	2,285 (14.8)	2,536 (17.3)		
DCD donor, n (%)		0 (0)	979 (6.3)	1,403 (9.6)	<0.001	<0.001
Donor cause of death, n (%)	Trauma	176 (14.4)	2,626 (17.0)	5,910 (40.4)	<0.001	<0.001
	Anoxia	222 (18.1)	5,532 (35.8)	6,677 (45.7)		
	CVA	814 (66.4)	6,963 (45.1)	1,611 (11.0)		
	Others	13 (1.1)	324 (2.1)	422 (2.9)		

(Continued on following page)

TABLE 1 | (*Continued*) Comparisons of characteristics of liver transplant recipients between donor age groups.

Characteristics	Group	Older donor 70 or older	Middle-aged donor 40–69	Younger donor <40	*p* Value	*p* Value
		n = 1,225	*n* = 15,445	*n* = 14,620	O vs. M	O vs. Y
Organ share type, n (%)	Local	751 (61.3)	10,237 (66.3)	9,387 (64.2)	<0.001	<0.001
	Regional	329 (26.9)	4,397 (28.5)	4,703 (32.2)		
	National	145 (11.8)	811 (5.3)	530 (3.6)		
Donor diabetes, n (%)		368 (30.0)	3,086 (20.0)	604 (4.1)	<0.001	<0.001
Donor history of heavy alcohol use, n (%)		106 (8.7)	3,190 (20.7)	1,936 (13.2)	<0.001	<0.001
Donor history of hypertension, n (%)		925 (75.5)	8,796 (57.0)	1,816 (12.4)	<0.001	<0.001
Donor history of myocardial infarction, n (%)		145 (11.8)	1,057 (6.8)	191 (1.3)	<0.001	<0.001
One-year graft loss, n (%)		140 (11.4)	1,435 (9.3)	1,196 (8.2)	0.01	<0.001

O vs. M: older group vs. middle-aged group.
O vs. Y: older group vs. younger group.
Abbreviations: BMI, body mass index; CVA, cerebrovascular accident; DCD, donation after circulatory death; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease; MELD-Na, model for end-stage liver disease-sodium.
Data was summarized using the median with interquartile range (IQR) for continuous variables and using percentage for discrete variables. Continuous variables were analyzed using the Mann-Whitney-U test and discrete variables were analyzed using a chi-square test.

TABLE 2 | Comparisons of risk for 1-year graft loss between donor age groups.

	aHR	95% CI	*p* value
Ref. middle-aged donor group	1.30	1.09–1.56	0.004
Ref. younger donor group	1.39	1.15–1.69	<0.001

Abbreviations: aHR, adjusted hazard ratio.
[a]*Hazards were adjusted by a multivariable Cox regression model for the following variables present at the time of transplantation: recipient age, recipient gender, recipient race, recipient body mass index (BMI), recipient diabetes, recipient primary liver disease etiologies including HCV, infection, alcohol related disease, non-alcoholic steatohepatitis and other diseases, hepatocellular carcinoma, international normalized ratio, serum bilirubin, serum creatinine, Karnofsky score, history of abdominal surgery, dialysis requirement, serum sodium, portal thrombus, mechanical ventilation, previous liver transplant, status 1, cold ischemia time, donation after circulatory death, donor gender, donor race, donor BMI, donor diabetes, donor cause of death, organ share type, donor history of heavy alcohol use, donor history of hypertension, and donor history of myocardial infarction.*

$p = 0.06$ and $p < 0.001$ respectively), were also more likely to have recipient diabetes (32.4% vs 29.7% [40–69] and 26.7% [<40], $p = 0.051$ and $p < 0.001$, respectively). Organs from the older donor group were more likely to have <6 h cold ischemia time than from other age groups (60.3% vs. 56.0% [40–69] and 53.6% [<40], $p < 0.001$ for both), to be allocated from a national organ share (11.8% vs. 5.3% [40–69] and 3.6% [<40], $p < 0.001$ for both), to have donor diabetes (30.0% vs 20.0% [40–69] and 4.1% [<40], $p < 0.001$ for both), history of hypertension (75.5% vs 57.0% [40–69] and 12.4% [<40], $p < 0.001$ for both), history of myocardial infarction (11.8% vs 6.8% [40–69] and 1.3% [<40], $p < 0.001$ for both), and to have liver biopsy (70.7% vs 52.0% [40–69] and 26.5% [<40], $p < 0.001$ for both), but those were less likely to have history of heavy alcohol use (8.7% vs 20.7% [40–69] and 13.2% [<40], $p < 0.001$ for both). There were no cases of donation after cardiac death (DCD) among recipients of organs from the ≥70 donor group (**Table 1**).

Donor Age Group as a Risk Factor for One-Year Liver Graft Loss

The adjusted risk of one-year graft loss was significantly higher among recipients of organs from donors aged ≥70 years than from donors aged 40–69 years (aHR 1.30, 95%CI 1.09–1.56, $p = 0.004$) and aged <40 years (aHR 1.39, 95%CI 1.15–1.69, $p < 0.001$; **Table 2**).

Risk Factor Analysis in Older Donor Group and Risk Stratification System

Demographic comparisons between the derivation and validation cohorts are shown in the **Table 3**. In the derivation dataset, the following recipient characteristics were associated with significantly increased risk of graft loss: previous liver transplant (aHR 4.37, 95%CI 1.98–9.65, $p < 0.001$); need for mechanical ventilation (aHR 4.28, 95%CI 1.95–9.43, $p < 0.001$); portal thrombus (aHR 1.87, 95%CI 1.26–2.77, $p = 0.001$); serum sodium <125mEq/L (aHR 2.88, 95%CI 1.34–6.20, $p = 0.007$); Karnofsky score between 10 and 30% (aHR 2.03, 95%CI 1.13–3.65, $p = 0.01$), between 40%–60% (aHR 1.65, 95%CI 1.08–2.51, $p = 0.02$; **Table 4**). HCV status did not increase risk of graft loss in the older donor group. Using these results, a risk stratification system was created using same (derivation) dataset by multiplying the aHRs of the significant risk factors (**Table 5**). Based on ROC curve analysis (**Supplementary Figure S1**), a risk score cut-off

TABLE 3 | Comparisons of characteristics between the derivation and validation cohorts.

Characteristics	Group	Derivation	Validation	*p* Value
		n = 31,290	*n* = 6,485	
Median recipient age (year), [IQR]		58 [50, 64]	57 [48, 64]	0.001
Recipient gender, n (%)	Male	20,753 (66.3)	4,191 (64.6)	0.009
	Female	10,537 (33.7)	2,294 (35.4)	
Recipient race, n (%)	White	22,284 (71.2)	4,575 (70.5)	0.001
	Black	2,544 (8.1)	463 (7.1)	
	Hispanic	4,642 (14.8)	1,063 (16.4)	
	Others	1,820 (5.8)	384 (5.9)	
Recipient BMI (kg/m^2), n (%)	18.5–24.9	8.004 (25.6)	1,650 (25.4)	0.002
	25.0–29.9	10,653 (34.0)	2,067 (31.9)	
	30.0 ≤	12,173 (38.9)	2,673 (41.2)	
	<18.5	460 (1.5)	95 (1.5)	
Median MELD (MELD-Na) score, [IQR]		22 [14, 32]	25 [16, 32]	<0.001
Serum bilirubin (mg/dl), n (%)	<2.0	9,281 (29.7)	1,650 (25.4)	<0.001
	2.0–4.4	7,424 (23.7)	2,067 (31.9)	
	4.5–11.9	6,906 (22.1)	2,673 (41.2)	
	12.0 ≤	7,679 (24.5)	95 (1.5)	
INR, n (%)	<1.5	11,718 (37.4)	2,070 (31.9)	<0.001
	1.5–1.7	5,479 (17.5)	1,187 (18.3)	
	1.8–2.4	7,519 (24.0)	1,736 (26.8)	
	2.5 ≤	6,574 (21.0)	1,492 (23.0)	
Serum creatinine (mg/dl), n (%)	<1.5	22,984 (73.5)	4,570 (70.5)	<0.001
	1.5–1.7	2,447 (7.8)	560 (8.6)	
	1.8–2.5	2,976 (9.5)	664 (10.2)	
	2.6 ≤	2,883 (9.2)	691 (10.7)	
Serum sodium (mEq/L), n (%)	135–145	19.778 (63.2)	3,824 (59.0)	<0.001
	125–134	9,910 (31.7)	2,354 (36.3)	
	<125	849 (2.7)	189 (2.9)	
	146 ≤	753 (2.4)	118 (1.8)	
History of abdominal surgery, n (%)		15,444 (49.4)	3,021 (46.6)	<0.001
Karnofsky score (%), n (%)	70–100	8,835 (28.2)	1,922 (29.6)	<0.001
	40–60	13,096 (41.9)	2,537 (39.1)	
	10–30	9,359 (29.9)	2,026 (31.2)	
Recipient diabetes, n (%)		8,885 (28.4)	1,827 (28.2)	0.72
HCV, n (%)		6,825 (21.8)	1,023 (16.1)	<0.001
Alcohol related disease, n (%)		9,890 (31.6)	2,682 (41.4)	<0.001
Non-alcoholic steatohepatitis, n (%)		5,828 (18.6)	1,520 (23.4)	<0.001
HCC, n (%)		4,061 (13.0)	1,514 (23.3)	<0.001
Status 1, n (%)		723 (2.3)	0 (0)	<0.001
Previous liver transplant, n (%)		1,313 (4.2)	268 (4.1)	0.84
Dialysis requirement, n (%)		3,604 (11.5)	887 (13.7)	<0.001
Portal thrombosis, n (%)		4,589 (14.7)	859 (13.2)	0.003
Mechanical ventilation, n (%)		2,840 (9.1)	535 (8.2)	0.03
Median Donor age (year)		41 [28, 55]	41 [29, 55]	0.10
Donor age (year), n (%)	<40	14,620 (46.7)	3,011 (46.4)	0.43
	40–69	15,445 (49.4)	3,239 (49.9)	
	70 ≤	1,225 (3.9)	235 (3.6)	
Donor gender, n (%)	Male	18,709 (59.8)	3,962 (61.1)	0.053
	Female	12,581 (40.2)	2,523 (38.9)	
Donor race, n (%)	White	20.111 (64.3)	4,146 (63.9)	0.08
	Black	5,528 (17.7)	1,155 (17.8)	
	Hispanic	4,246 (13.6)	930 (14.3)	
	Others	1,405 (4.5)	254 (3.9)	
Donor BMI (kg/m^2), n (%)	18.5–24.9	10,086 (32.2)	1,996 (30.8)	0.055
	25.0–29.9	10.066 (32.2)	2,086 (32.2)	
	30.0 ≤	10,280 (32.9)	2,230 (34.4)	
	<18.5	858 (2.7)	171 (2.6)	
Cold ischemia time (hours), n (%)	<6.0	17,230 (55.1)	3,613 (55.7)	<0.001
	6.0–7.9	9,109 (29.1)	2,048 (31.6)	
	8.0 ≤	4,951 (15.8)	824 (12.7)	
DCD donor, n (%)		2,382 (7.6)	697 (10.7)	<0.001

(Continued on following page)

TABLE 3 | (*Continued*) Comparisons of characteristics between the derivation and validation cohorts.

Characteristics	Group	Derivation	Validation	*p* Value
		***n* = 31,290**	***n* = 6,485**	
Donor cause of death, n (%)	Trauma	8,712 (27.8)	1,640 (25.3)	<0.001
	Anoxia	12,431 (39.7)	2,948 (45.5)	
	CVA	9,388 (30.0)	1,752 (27.0)	
	Others	759 (2.4)	145 (2.2)	
Organ share type, n (%)	Local	20,375 (65.1)	2,553 (39.4)	<0.001
	Regional	9,429 (30.1)	2,022 (31.2)	
	National	1,486 (4.7)	1,910 (29.5)	
Donor diabetes, n (%)		4,058 (13.0)	867 (13.4)	0.39
Donor history of heavy alcohol use, n (%)		5,232 (16.7)	1,176 (18.1)	0.006
Donor history of hypertension, n (%)		11,537 (36.9)	2,418 (37.3)	0.53
Donor history of myocardial infarction, n (%)		1,393 (4.5)	336 (5.2)	0.01
One-year graft loss, n (%)		2,771 (8.9)	573 (8.8)	0.97

Abbreviations: BMI, body mass index; CVA, cerebrovascular accident; DCD, donation after circulatory death; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease; MELD-Na, model for end-stage liver disease-sodium.
Data was summarized using the median with interquartile range (IQR) for continuous variables and using percentage for discrete variables. Continuous variables were analyzed using the Mann-Whitney-U test and discrete variables were analyzed using a chi-square test.

TABLE 4 | Risk for 1-year graft loss after liver transplantation in older donor derivation group.

Factors	aHR	95% CI	*p* value
Previous liver transplant	4.37	1.98–9.65	<0.001
Mechanical ventilation	4.28	1.95–9.43	<0.001
Portal thrombus	1.87	1.26–2.77	0.001
Serum sodium <125 mEq/L [ref. 135–145 mEq/L]	2.88	1.34–6.20	0.007
Serum sodium 125–135 mEq/L [ref. 135–145 mEq/L]	1.35	0.92–1.99	0.13
Serum sodium 146 mEq/L or higher [ref. 135–145 mEq/L]	1.36	0.51–3.65	0.54
Karnofsky score 10–30% [ref. 70–100%]	2.03	1.13–3.65	0.01
Karnofsky score 40–60% [ref. 70–100%]	1.65	1.08–2.51	0.02
Cold ischemia time 8 h or longer [ref. < 6.0 h]	1.67	1.05–2.65	0.03
Cold ischemia time 6.0–7.9 h [ref. < 6.0 h]	0.86	0.57–1.30	0.47
Serum bilirubin 12 mg/dl or higher [ref. < 2.0 mg/dl]	0.82	0.39–1.72	0.60
Serum bilirubin 4.5–11.9 mg/dl [ref. < 2.0 mg/dl]	0.85	0.47–1.55	0.60
Serum bilirubin 2.0–4.4 mg/dl [ref. < 2.0 mg/dl]	1.29	0.84–1.98	0.25
INR 2.5 or higher [ref. < 1.5]	1.03	0.56–1.88	0.93
INR 1.8–2.4 [ref. < 1.5]	0.59	0.34–1.01	0.056
INR 1.5–1.7 [ref. < 1.5]	0.72	0.45–1.17	0.18
Serum creatinine 2.6 mg/dl or higher [ref. < 1.5 mg/dl]	1.91	0.95–3.82	0.07
Serum creatinine 1.8–2.5 mg/dl [ref. < 1.5 mg/dl]	0.72	0.38–1.38	0.32
Serum creatinine 1.5–1.7 mg/dl [ref. < 1.5 mg/dl]	0.96	0.51–1.79	0.89
HCV positive	0.68	0.41–1.12	0.13
Status 1	0.62	0.16–2.45	0.50
Dialysis requirement	0.64	0.27–1.50	0.30
Donor BMI 30 kg/m^2 or higher [ref. 18.5–24.9 kg/m^2]	0.93	0.61–1.44	0.76
Donor BMI 25.0–29.9 kg/m^2 [ref. 18.5–24.9 kg/m^2]	1.07	0.70–1.63	0.77
Donor BMI <18.5 kg/m^2 [ref. 18.5–24.9 kg/m^2]	1.49	0.60–3.69	0.39

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; HCV, hepatitis C virus; INR, international normalized ratio.
[a]*Hazards were adjusted by a multivariable Cox regression model for the following variables present at the time of transplantation: hepatitis C virus, international normalized ratio, serum bilirubin, serum creatinine, Karnofsky score, dialysis requirement, serum sodium, portal thrombus, mechanical ventilation, previous liver transplant, status 1, cold ischemia time, and donor BMI.*

value of 2.03 was used to divide patients into low-risk (<2.03; n = 931) and high-risk groups (≥2.03; n = 294).

Although patient age was not a significant risk factor for graft loss among recipients in the older donor group, age ≥65 years was a significant risk factor for graft loss among recipients who received organs from the middle-aged or younger donors (aHR 1.19, 95%CI 1.01–1.40 and aHR 1.71, 95%CI 1.44–2.04; p = 0.04 and p < 0.001, respectively). Recipient age of 50–64%years was also a significant risk factor for graft loss in the younger donor group (aHR 1.27, 95%CI 1.09–1.47, p = 0.001; **Supplementary Tables S1, S2**).

TABLE 5 | Assigned risk score points and categorization of risk groups in older donor group.

Risk factors	aHR
Previous liver transplant	4.37
Mechanical ventilation	4.28
Portal thrombus	1.87
Serum sodium <125 mEq/L [ref. 135–145 mEq/L]	2.88
Karnofsky score 10–30% [ref. 70–100%]	2.03
Karnofsky score 40–60% [ref. 70–100%]	1.65

aHR, adjusted hazard ratio.

Comparison of 1-Year Risk of Graft Loss in the Older Donor Group Using the Risk Score System

One-year graft survival rate was significantly higher in low-risk recipients than in high-risk recipients (91.7% [low-risk] vs. 78.0% [high-risk], $p < 0.001$) (**Supplementary Figure S2A**). Three- and 5-year graft survival rate were also significantly higher in low-risk recipients than in high-risk recipients (3-year; 82.5% [low-risk] vs. 70.5% [high-risk], $p < 0.001$, 5-year; 76.0% [low-risk] vs. 64.1% [high-risk], $p < 0.001$) (**Supplementary Figures S2B,C**). One-year graft survival rate in low-risk recipients of the older donor group was similar to the younger or middle-aged donor group (**Figure 2A**). After excluding DCD cases from the middle-aged and younger donor groups (for consistency with the older donor group, in which there was no DCD donors), similar trends were observed (**Figure 2B**).

The adjusted risk of one-year graft loss in the low-risk older donor group was similar to that of the younger donor group (aHR 1.08, 95% CI 0.85–1.38, $p = 0.53$; **Figure 2C**). In contrast, the adjusted risk of one-year graft loss in the high-risk recipients was significantly higher than in the younger donor group (aHR 2.00, 95% CI 1.53–2.61, $p < 0.001$). While the adjusted risk of one-year graft loss in the high-risk recipients was also significantly higher compared to the middle-aged donor group (aHR 1.84, 95% CI 1.42–2.38, $p < 0.001$), those in the low-risk older donor group was similar to that of the middle-aged donor group (aHR 0.99, 95% CI 0.78–1.26, $p = 0.95$; **Figure 2D**).

Comparison of Risk for Graft Loss in the Older Donor Using the Validation Dataset

Among the validation cohort, one-year graft survival rate in low-risk recipients of the older donor group was similar to those in the younger or middle-aged donor group (**Figure 3A**). After excluding DCD cases from the younger and middle-aged donor groups, the one-year graft survival rate in low-risk recipients of the older donor group was similar to those in the younger or middle-aged donor group (**Figure 3B**).

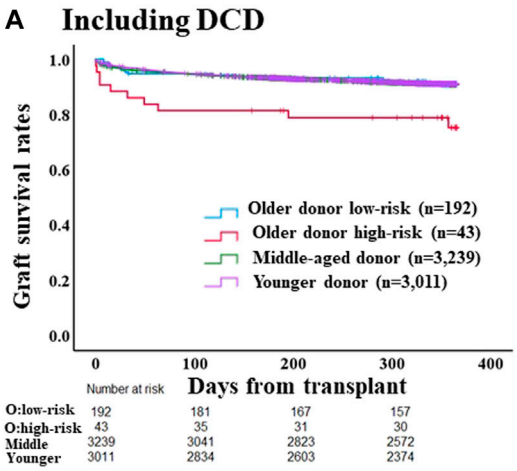
The adjusted risk of one-year graft loss was similar between low-risk older donor recipients and younger donor recipients (aHR 0.95, 95% CI 0.56–1.62, $p = 0.86$; **Figure 3C**), but was significantly higher for high-risk recipients (aHR 2.00, 95% CI 1.02–3.92, $p = 0.04$). While the adjusted risk of one-year graft loss in the high-risk recipients was also significantly higher compared to the middle-aged donor group (aHR 2.14, 95% CI 1.11–4.12, $p = 0.02$), those in the low-risk older donor group was similar to that of the middle-aged donor group (aHR 1.00, 95% CI 0.60–1.66, $p = 0.97$; **Figure 3D**).

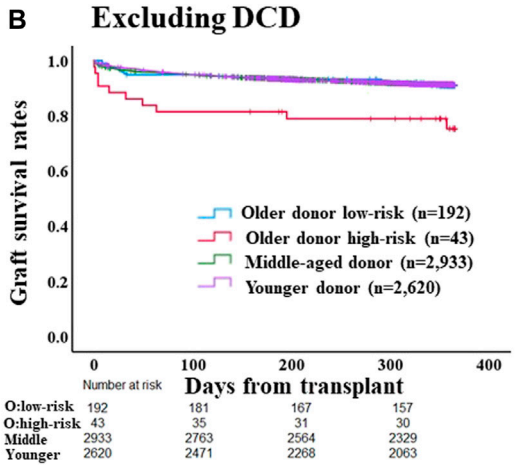
DISCUSSION

Using a systematic approach to identify risk factors for graft loss among recipients of liver transplant from donors ≥70 years old, we were able to categorize patients into low- and high-risk groups. In general, the recipients of organs from older donors at highest risk of one-year graft loss had multiple risk factors—including previous liver transplant, mechanical ventilation, portal thrombus, low serum sodium value, and low Karnofsky score—that indicated they were often considerably more ill at the time of transplantation, compared to others. With regard to laboratory values associated with MELD-sodium score, serum sodium was considered as a significant risk factor, but not total bilirubin, INR, or serum creatinine. As expected, donor age of 70 years or older was found to be a risk factor for one-year graft loss. However, according to our risk stratification system, low-risk recipients of organs from older donors had similar outcomes to those of recipients from younger and middle-aged donor groups. We further evaluated our risk stratification system in a separate validation dataset with consistent results, confirming its applicability. These findings indicate that, while advanced donor age may be a risk factor for negative post-LT outcomes, organs from older donors can be safely used with careful recipient selection, which might help expand donor pool without compromising LT outcomes.

A strength of our approach was adjustment for both recipient and donor characteristics. Although donor and organ characteristics such as race, BMI, cold ischemia time, and donor location have been shown to be associated with post-LT outcomes [3, 19], there were no significant donor characteristics other than prolonged CIT among the risk factors for one-year graft loss in our sample of recipients of organs from donors ≥70 years. While DCD donor is usually considered as a donor risk factor associated with poor post-LT outcomes, there was no DCD donor in this older donor group (≥70 years). Therefore, the prognostic impact of these donor characteristics in the older donor group could not be assessed in this study. It should be noted that possible risks associated with these factors should not be ignored when using older donors. However, we acknowledge that no stratification system should be considered "one-size-fits-all," and that it remains important to carefully assess donor characteristics when using liver grafts from older donors. Of note, in our between-group comparisons of graft loss among recipients of organs from younger, middle-aged, and low-risk/older donors, analyses were adjusted for a number of donor characteristics that are known risk factors for graft loss.

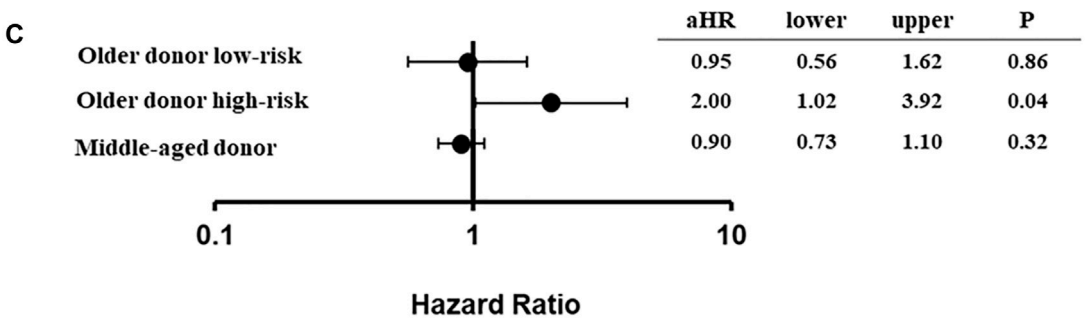
According to a previous report by Haugen et al. [20], outcomes among recipients of liver grafts from donors ≥70 years have improved over time, with a 40% reduction in risk of graft loss in 2010–2016 versus 2003–2009; however, rates of graft loss are





Groups	Survival rate (%)	P (vs. Younger)	P (vs. Middle-aged)
Older donor low-risk	90.8	0.95	0.98
Older donor high-risk	75.3	<0.001	<0.001
Middle-aged donor	90.8	0.84	-
Younger donor	91.0	-	0.84

Groups	Survival rate (%)	P (vs. Younger)	P (vs. Middle-aged)
Older donor low-risk	90.8	0.89	0.91
Older donor high-risk	75.3	<0.001	<0.001
Middle-aged donor	91.1	0.97	-
Younger donor	91.1	-	0.97



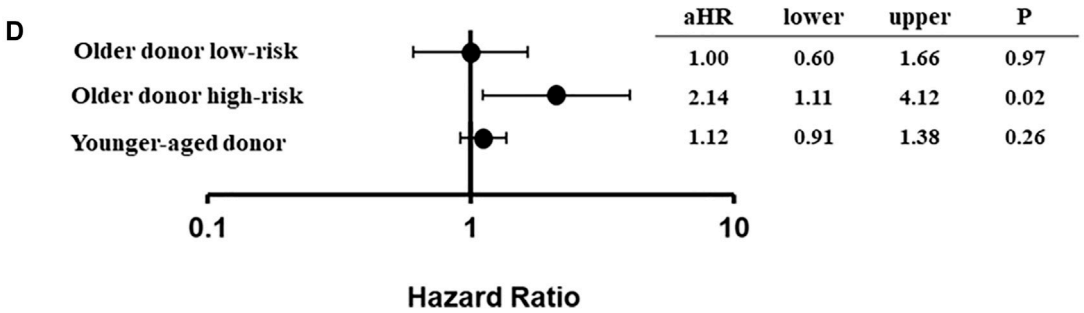


FIGURE 3 | Comparison of post-LT outcome between the older donor validation group stratified by the risk classification and middle-aged or younger donor group. **(A)** One-year graft survival rate in low-risk recipients of the older donor group was similar to those in middle-aged or younger donor group ($p = 0.98$, $p = 0.95$, respectively). **(B)** One-year graft survival rate in low-risk recipients of the older donor group was similar to those in middle-aged or younger donor group after excluding DCD cases ($p = 0.91$, $p = 0.89$, respectively). **(C)** Adjusted hazards of graft loss in the older donor validation group stratified by the risk classification and middle-aged donor group (ref. younger donor group). **(D)** ref. middle-aged donor group. Hazards were adjusted by a multivariable Cox regression model for the following variables present at the time of transplantation: recipient age; recipient gender; recipient race; recipient body mass index (BMI); recipient diabetes; recipient primary liver disease etiologies including HCV infection, alcohol related disease, non-alcoholic steatohepatitis and other diseases; hepatocellular carcinoma; international normalized

(*Continued*)

FIGURE 3 | ratio; serum bilirubin; serum creatinine; Karnofsky score; history of abdominal surgery; dialysis requirement; serum sodium; portal thrombus; mechanical ventilation; previous liver transplant; cold ischemia time; donor gender; donor race; donor BMI; donor diabetes; donor cause of death; organ share type; donor history of heavy alcohol use; donor history of hypertension; and donor history of myocardial infarction.

still higher than with grafts from donors <70 years. In our analysis of more recent data (2014–2019) we found that donor age ≥70 years remains a significant risk factor for graft loss. Notably, the proportion of donors aged ≥70 in Haugen's report—3.2% of all recipients—is consistent with our own [20]. Although this is a relatively small number, confidence in the safety of liver grafts from older donors could lead to expansion of the donor pool.

In our risk-stratification system, low-risk recipients of livers from older donors accounted for 76.0% of patients who received from donors of 70 years or older. Also, post-LT outcomes in these patients were similar to those of recipients with organs from younger (<40 years) and middle-aged donors (40–69 years). These results suggest that careful recipient selection may reduce risks associated with using old donors, which might decrease organ discard rate and expand the donor pool safely. A number of previous reports have focused on preferred recipient characteristics for grafts from elderly donors [8–10]. [9] suggested that preferred patient profile for using grafts from donors ≥70 years were being a first-time recipient over the age of 45, with BMI <35, non-status 1 registration, cold ischemic time <8 h, and either a non-HCV indication for transplant or hepatocellular carcinoma [9]. According to a French study, elderly grafts (age >75) may be safely used if donation occurred after brain death and recipients were HCV negative and had not previous undergone transplantation [21]. Previous liver transplant has been commonly reported as a strong risk factor for poor post-LT outcomes, which is consistent with our results. In contrast, although previous studies have indicated that grafts from older donors may lead to worse post-LT outcomes in patients with HCV [8–10], we did not observe the same impact of HCV-positive status on negative outcomes. At least one study has found that direct-acting antiviral treatments allowed a safe use of liver grafts from donors >70 years in HCV-positive recipients [22]. Given that our study included only patients transplanted after 2014, when direct-acting antiviral therapy became widely available, this may explain why HCV was no longer a significant risk factor in our results.

Advanced recipient age is also a known risk factor for liver graft loss [3, 4]. However, we did not find recipient age to be significantly associated with loss of grafts in the older donor group, but it was a risk factor in recipients of organs from the middle-aged and younger donor groups. Other studies have reported conflicting results regarding recipient-donor age matching. Bittermann et al. reported that in younger recipients (<40 years), the risk of graft failure increased with donor age, but that risk of loss in grafts from older donors (≥60 years) were similar regardless of recipient age [23]. Likewise, Chapman et al, reported comparable outcomes in graft and patient survival with older donors (≥60 years old), without an increased rate of complications, regardless of recipient age [24]. Our results concurred with the above results. While the use of older donor liver grafts might achieve satisfactory post-LT outcomes regardless of recipient age, the possibility of increased risk with increased recipient age should be acknowledged.

In the past, many transplant centers would not accept DCD donors older than 60 years old, as there were reports of higher risk of graft loss with older DCD donors [25-27]. More recent studies have suggested that selected grafts from elderly DCD donors could achieve an acceptable graft survival rate [28, 29]. In our study, there were no DCD grafts in patients who received grafts from donors 70 years or older, and thus we could not evaluate the impact of DCD grafts on recipients from elderly donors. Recently, the utility of normothermic perfusion for DCD grafts has been reported [30, 31]. Normothermic perfusion has proven its beneficial effect on ischemia-reperfusion injury, which could potentially lead to improved post-LT outcomes, when using older DCD donors. Although there was no report about normothermic perfusion for older DCD grafts, it may be a promising strategy. Czigany et al. reported that among patients who received extended criteria liver (median donor age 72 years old) from donation after brain death grafts, hypothermic oxygenated machine perfusion reduced early allograft injury and improved post-transplant outcomes by multicenter randomized controlled trial [32].

There are a number of limitations to our analysis. This is a retrospective study using the OPTN/UNOS registry, which lacks detailed post-transplant clinical data, such as surgical complications after transplantation. We were also limited by the small proportion of donors ≥70 years in the dataset. Although we were able to detect a number of significant risk factors despite the relative small sample size, it is possible that a larger sample size would have provided more precision in our estimates. The primary outcome examined in this study (one-year graft loss) was a short-term outcome and may not be applicable to mid-to long-term outcomes. Three-year and 5-year graft survival were evaluated, which demonstrated that the negative impact of recipient risk factors was more prominent in the first year post-transplant, then the survival curves became parallel after 1 year between the low and high risk groups. Also, we could not evaluate the impact of grafts after DCD in elderly donors due to the absence of such donors in the dataset. Despite these limitations, the scoring system could be useful to determine suitable recipient selection when using the liver graft from older donors. Our scoring system would not be used to regulate organ acceptance practice. Transplant physicians and centers could use it to estimate its risk and should decide indications at their discretion if those risks are acceptable for each case.

In conclusion, our risk stratification system using the following recipient factors, history of the previous liver transplant, low Karnofsky Performance Status score, need for mechanical ventilation, presence of portal vein thrombosis, and hyponatremia,

might be useful for recipient selection who are eligible for liver grafts from older donors. This could lead to further expansion of the donor pool without compromising outcomes.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Organ Procurement and Transplantation Network (OPTN). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from OPTN at https://optn.transplant.hrsa.gov/data/request-data/with the permission of OPTN and United Network of Organ Sharing (UNOS).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Henry Ford Health System Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SS and SN contributed to study concept/design, and drafting of this article. SS and TK contributed to data collection/acquisition. SS and SN contributed to data analysis/interpretation. ML contributed to statistical analysis. TK, TS, TI, KC, MR, AY, MA, and DM contributed to drafting and critical revision of this article. All authors have approved the final article.

AUTHOR DISCLAIMER

The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the US Government.

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.

ACKNOWLEDGMENTS

The data reported here have been supplied by the UNOS as the contractor for the OPTN.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2022.10489/full#supplementary-material

Supplementary Figure S1 | ROC curve between a risk score and one-year graft survival.

Supplementary Figure S2 | Comparison of post-LT outcome between the older donor low and high-risk groups stratified by the risk classification. One-year graft survival rate in low-risk recipients of the older donor group was significantly higher than those in high-risk recipients (91.7% vs. 78.0%, $p < 0.001$). **(B)** Three-year graft survival rate in low-risk recipients of the older donor group was significantly higher than those in high-risk recipients (82.5% vs. 70.5%, $p < 0.001$). **(C)** Five-year graft survival rate in low-risk recipients of the older donor group was significantly higher than those in high-risk recipients (76.0% vs. 64.1%, $p < 0.001$).

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BRIEF RESEARCH REPORT
published: 04 August 2022
doi: 10.3389/ti.2022.10677

SARS-CoV2 mRNA Vaccine-Specific B-, T- and Humoral Responses in Adolescents After Kidney Transplantation

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Protection of adult kidney transplant recipients against SARS-CoV2 was shown to be strongly impaired owing to low reactogenicity of available vaccines. So far, data on vaccination outcomes in adolescents are scarce due to later vaccination approval for this age group. We therefore comprehensively analyzed vaccination-specific humoral-, T- and B-cell responses in kidney transplanted adolescents aged 12–18 years in comparison to healthy controls 6 weeks after standard two-dose BNT162b2 ("Comirnaty"; Pfizer/BioNTech) vaccination. Importantly, 90% (18/20) of transplanted adolescents showed IgG seroconversion with 75% (15/20) developing neutralizing titers. Still, both features were significantly diminished in magnitude compared to controls. Correspondingly, spike-specific B cells were quantitatively reduced and enriched for non-isotype-class-switched IgD^+27^+ memory cells in patients. Whereas spike specific $CD4^+$ T cell frequencies were similar in both groups, cytokine production and memory differentiation were significantly impaired in transplant recipients. Although our data identify limitations in all arms of vaccine-specific immunity, the majority of our adolescent patients showed robust humoral responses despite antimetabolite-based treatment being associated with poor vaccination outcomes in adults.

Keywords: kidney transplantation, vaccination, immunity, SARS-CoV2, adolescents

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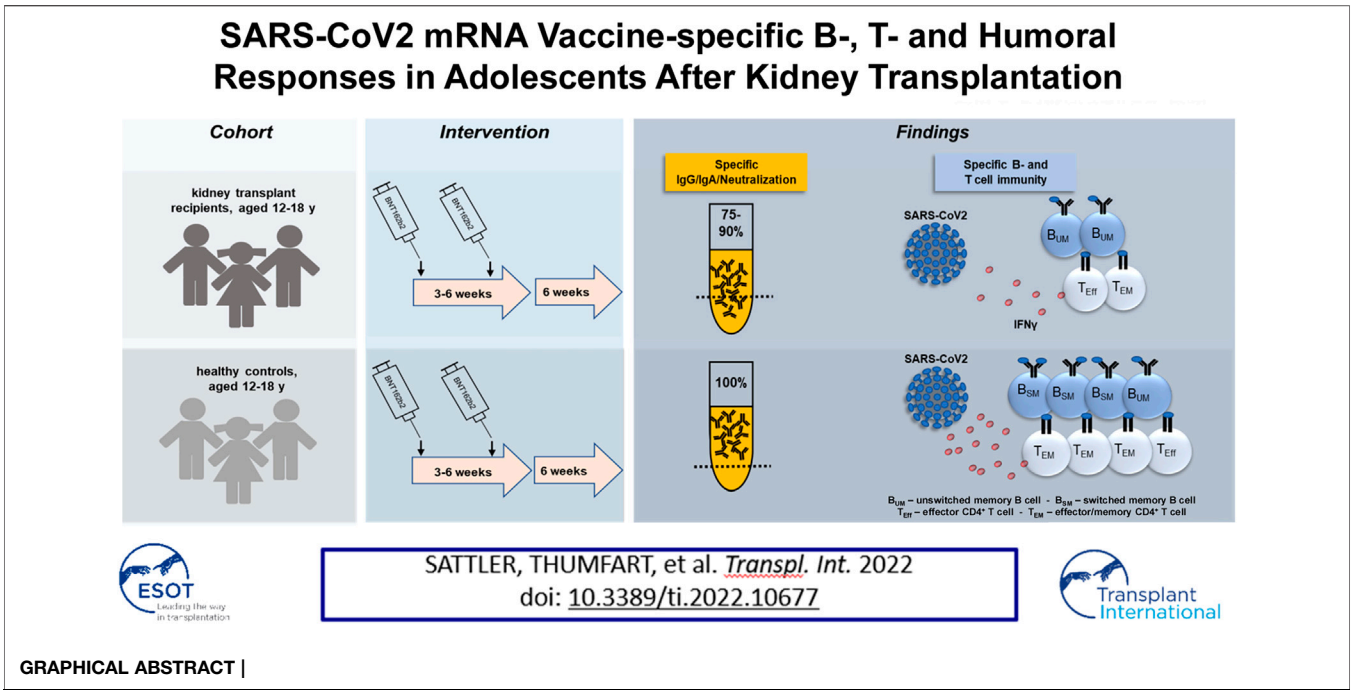
Received: *27 May 2022*
Accepted: *11 July 2022*
Published: *04 August 2022*

Citation:
Sattler A, Thumfart J, Tóth L, Schrezenmeier E, Proß V, Stahl C, Siegle J, He A, Thole LML, Ludwig C, Straub-Hohenbleicher H, Friedersdorff F, Jahrsdörfer B, Schrezenmeier H, Bufler P and Kotsch K (2022) SARS-CoV2 mRNA Vaccine-Specific B-, T- and Humoral Responses in Adolescents After Kidney Transplantation. Transpl Int 35:10677. doi: 10.3389/ti.2022.10677

Abbreviations: ARPKD, autosomal recessive polycystic kidney disease; CAKUT, congenital anomalies of kidney and urinary tract; CS, corticosteroids; Eve, everolimus; HC, healthy control(s); IS, immunosuppression; KTx, kidney transplantation; KTR, kidney transplant recipients; MPA, mycophenolic Acid; NS, nephrotic syndrome; PBMC, peripheral blood mononuclear cells; RBD, receptor binding domain; Rapa, rapamycin; Tac, tacrolimus.



GRAPHICAL ABSTRACT |

INTRODUCTION

Children and adolescents frequently experience asymptomatic SARS-CoV-2 infections or exhibit mild respiratory symptoms with fever, headache, and cough. Nevertheless, both groups can suffer from severe COVID-19 with respiratory failure or pediatric inflammatory multisystem syndrome (1). Children on renal replacement therapy or after kidney transplantation (KTx) have an increased risk for hospitalization after infection (2). Even if mortality is low, pediatric COVID-19 can seriously burden health care systems in times of pandemic, as treatment resources may become scarce. It should also be noted that parents are particularly concerned about the health of their chronically ill children, resulting in higher rates of homeschooling, with adverse consequences for social interaction with peers (3). Vaccination against SARS-CoV-2, being recommended by the World health organization for children and adolescents with underlying chronic diseases (4), is therefore key for protection of pediatric at-risk groups. However, many studies (5–7) revealed that adult solid organ recipients show a broad impairment in CoV2-vaccination-induced immunity, affecting both humoral and cellular responses, likely due to mycophenolate (MPA)-based immunosuppression (IS) (8). To provide comprehensive data on mRNA vaccine induced responses in kidney transplant recipients (KTR) aged 12–18 years, we conducted an observational study after approval for this age group where vaccine-specific IgG, IgA and virus neutralizing capacity was assessed in concert with comprehensive quantification and functional characterization of spike protein-specific B- and T cells. Our results suggest that the majority of pediatric patients, despite being on antimetabolite treatment, mount robust vaccine-specific humoral responses, with selective impairments in various adaptive immune compartments.

MATERIALS AND METHODS

Study Design and Medication

For this observational study, adolescent KTx patients were recruited at the Charité Department of Pediatric Gastroenterology, Nephrology and Metabolic Diseases. As per medical center guideline, patients had initially received triple IS therapy consisting of corticosteroids (CS), Tac and MPA immediately after KTx. Except for patient 1 (**Table 2**), none of the patients had received induction therapy. After the first year, CS had been discontinued according to the standard protocol of the center. Healthy controls included age- and sex-matched individuals without any documented acute or chronic disease conditions (**Table 1**). They were routinely vaccinated according to the national vaccination program. The inclusion criteria for the study groups were age between 12 and 18 years, absence of previous SARS-CoV2 or other severe infections prior to vaccination and completion of the 2-dose vaccination protocol with BNT162b2 vaccine (Comirnaty; BioNTech/Pfizer) according to the manufacturer's recommended dose (30 μg) and time schedule (two doses at a 3–6 weeks interval). All patients received the 2nd dose between June and October 2021. Blood and serum samples were collected approximately 6 weeks after the second dose with no significant differences between groups. IS trough levels (**Table 2**) were analyzed at the same time point. The study was approved by the local ethical committee of the Charité Universitätsmedizin (EA2/227/21). All

TABLE 1 | Basic characteristics of KTx patients and healthy controls.

Variable	KTx (*n* =20)	HC (*n* = 13)	*p value*
Age (mean yrs ±SD)	14.17 (1.31)	13.99 (1.99)	0.7595
Females (n, %)	7 (35.00)	5 (38.46)	>0.9999
Caucasians (n, %)	16 (80.00)	12 (92.00)	0.6253
Time since 2nd vaccination dose (mean days±SD)	39.30 (11.06)	44.54 (16.87)	0.2306

(K)Tx, (Kidney) Transplantation; HC, healthy control.

TABLE 2 | Detailed characteristics of KTx patients.

Patient	Gender	Underlying disease	Age (years)	Time since KTx (years)	Current IS[b]	Tac trough level (μg/l)[b]	MPA trough level (mg/l)[§]	Former rejection episodes (date)
1[a]	F	unknown	17.5	0.9	Tac, MMF, CS	5.1	3.3	Yes (2021/2, 2021/3)
2	F	CAKUT	13.1	9.2	Tac, MMF	2.7	8.3	No
3	M	CAKUT	12.6	9.6	Tac, MMF	3.3	0.9	No
4	M	CAKUT	12.5	10.0	Tac, MMF	3.3	1.3	No
5	M	CAKUT	13.2	7.1	Tac, MMF	3.3	2.1	No
6	M	ARPKD	12.8	1.8	Tac, MMF	4.8	1.8	No
7	M	CAKUT	14.9	13.2	Tac, MMF	4.2	3.5	No
8	M	CAKUT	15.0	8.3	Tac, MMF	3.6	0.8	No
9	F	NS	14.6	10.2	Tac, MMF	5	2.5	No
10	F	NS	15.1	10.2	Tac, CS	3.3	n.a	No
11	F	NS	14.1	2.6	Tac, Eve	5.7	n.a	Yes (2019/4)
12	M	HNF1 Beta	14.9	2.1	Tac, MMF	4.7	1.2	No
13	M	NS	16.1	10.6	Tac, CS	4.9	n.a	No
14	F	Papillorenal syndrome	13.1	1.0	Tac, MMF	3.6	4.3	No
15	M	NS	15.3	7.4	Rapa, MMF, CS		4.5	No
16	M	Sartan nephropathy	14.2	10.5	Tac, CS	2.8	n.a	No
17	M	CAKUT	14.0	11.7	Tac, MMF	4.1	0.4	Yes (2012/10)
18	F	NS	14.3	9.2	Tac, MMF, CS	5.7	1.7	Yes (2014/9, 2014/12)
19	M	Cystinosis	12.6	2.1	Tac, Eve	1.8	n.a	No
20	M	CAKUT	13.4	3.3	Tac, MMF	3.7	1.8	No
Mean ± SD			14.2 ± 1.3	7.0 ± 4.1		4.0 ± 1.1	1.8 ± 2.0	

(K)Tx, (Kidney) Transplantation; IS, immunosuppression; Tac-Tacrolimus; MPA-Mycophenolic Acid; CS-Corticosteroids; Eve-Everolimus; Rapa-Rapamycin; CAKUT, congenital anomalies of kidney and urinary tract; NS, nephrotic syndrome; ARPKD-Autosomal recessive polycystic kidney disease; SD, standard deviation; n.a., not applicable.

[a]*Patient 1 had received her 2nd transplant with induction therapy (basiliximab).*

[b]*At time of humoral and cellular analysis.*

individuals (over 14 years) and their legal guardians signed informed consent.

Assessment of Humoral Immunity

Previous or current SARS-CoV2 infection was excluded based on medical history data available from our clinic, continuous negative point of care antigen tests conducted thrice-weekly during school visits and a negative SARS-CoV2 nucleoprotein specific ELISA (Euroimmun) (**Supplementary Figure S1A**). SARS-CoV-2 S1 domain specific IgG (QuantiVac, Euroimmun) and IgA (Euroimmun) was determined by ELISA. For IgA quantification, serum samples exceeding O.D. ratios of 6 were pre-diluted tenfold and re-measured. Serum samples with OD ratios of ≥1.1 (Nucleoprotein and IgA) or ≥35.2 BAU/ml (IgG) were considered positive according to the manufacturer´s guidelines. OD ratios were calculated based on the ratio of the OD of the respective sample over the OD of the calibrator provided with the ELISA kit. For quantification of virus neutralizing capacity in our study, a blocking ELISA (sVNT kit, GenScript) was used that mimics the virus neutralization process. In detail, serum antibodies are tested for blocking the binding of recombinant SARS-CoV2 RBD (alpha = vaccine variant) to human ACE2 receptor protein. A neutralization capacity of more than 30% was defined as positive as per the manufacturer's recommendation.

Assessment of SARS-CoV2 Vaccine-Specific B and T Cells

Peripheral blood mononuclear cells (PBMCs) were isolated from EDTA blood by density gradient centrifugation using Ficoll-Paque PLUS (GE Healthcare Bio-Sciences, Chicago, IL, United States). Within 5–10 × 10^6 PBMC, B cells were detected by flow cytometry and gated as $CD19^+CD3^-CD14^-CD56^-$

among single live lymphocytes (gating strategy depicted in **Supplementary Figure S1B**). SARS-CoV2-specific B cells were identified as shown before (8, 9) by double staining with AlexaFluor488 coupled recombinant receptor binding domain (RBD) protein and biotinylated recombinant full spike protein (both alpha-variant, RnD Systems, Minneapolis, MN, United States) with the latter being detected by streptavidin-APC (Biolegend, San Diego, CA, United States). For flow cytometric analysis, the following fluorochrome-labeled antibodies were used: CD19 (SJ25C1, BL), CD3 (SK7, BL), CD56 (NCAM, BL), CD14 (M5E2, BL), IgD (IA6-2, BL), IgG (G18-145, BD) and CD27 (M-T271, BL). For identification of vaccine-specific T cells, 3×10^6 PBMC were stimulated or not for 16 h with overlapping 15-mers covering the complete SARS-CoV2 spike (alpha-variant) protein. A combination of overlapping 15-mer peptide mixes including cytomegalovirus (CMV, "Peptivator pp65," Miltenyi Biotech, Bergisch Gladbach), Epstein Barr virus (EBV, "Peptivator consensus", Miltenyi Biotech) and influenza H1N1 ("Peptivator matrix protein 1," and "Peptivator nucleoprotein," Miltenyi Biotech) served as control and is termed CEF throughout. Antigens were used at a final concentration of 0.5 µg/ml per peptide. Specific $CD4^+$ T helper cells were identified based on CD137 and CD154 coexpression as shown in **Supplementary Figure S2**. A response was defined as positive when stimulated cultures contained at least twofold higher frequencies of $CD137^+CD154^+$ cells as compared to the respective unstimulated control with at least twenty events, as resported earlier (5). For surface labelling, antibodies against CD3 (SK7, Biolegend), CD4 (SK3, BD), CD8 (SK1, Ebioscience, San Diego, CA, United States), CD45RO (UCHL1, BL), CD62L (DREG-56, BL) and PD1 (EH12.1, BD) were used. A dump channel excluded unwanted cells and contained $CD14^+$ (M5E2, BL), $CD19^+$ (HIB19, BL), and dead (fixable live/dead, BL) events. Cells were fixed with FACS Lysing Solution (BD) after surface staining, followed by permeabilization in FACS Perm II Solution (BD) and stained intracellularly with anti-CD154 (24–31, BL), anti-CD137 (4B4-1, BL), anti-TNF-α (MAb11, BL), anti-IFN-γ (4SB3, Ebioscience), anti-IL-2 (MQ1-17H12, BL), and anti-IL-4 (MP4-25D2, BL). Data was acquired using a BD FACS Fortessa X20.

Data Analysis and Statistics

FACS data analysis was conducted with FlowJo 10 (BD). Gating strategies for analysis of antigen-reactive B- and T cells are illustrated in **Supplementary Figures S1, S2**. Depicted frequencies of spike-specific $CD4^+$ T cells were background (=unstimulated control) -substracted. Co-expression of cytokines was quantified by Boolean gating in Flowjo. Statistical analysis and graph preparation was performed in GraphPad Prism 8 (GraphPad, La Jolla, CA, United States). Data distribution was assessed using the Kolmogorov-Smirnov test. Given that all data sets did not show normal distribution, a Mann-Whitney test was used throughout for two-group comparisons. For analysis of contingency tables, Fisher's exact test was applied.

RESULTS

Patient Characteristics

Twelve patients received dual IS therapy with Tac and MPA according to the standard protocol of the center after the first year after KTx. Two patients received triple IS therapy (Tac, MPA and CS) due to former rejection episodes. Three patients received Tac and CS due to side effects of MPA. Two patients were treated with Everolimus and Tac because of ongoing Epstein-Barr- and polyoma virus BK viremia. One patient received triple IS (Rapamycin, MPA and corticosteroids) due to calcineurin inhibitor toxicity. Mean trough levels were 4.0 ± 1.1 for Tac and 1.8 ± 2.0 for MPA at the time point of immunity analysis (**Table 2**); no changes in medication were undertaken from 2 months before vaccination until time point of humoral and cellular analyses. Last rejection episodes with methylprednisolone treatment were at least 4 months before first vaccination. After vaccination, no rejection episodes were observed in the KTx cohort. No other adjunctive immunosuppressive drugs were taken within the last 6 months prior to analysis. As per inclusion criteria, all patients and controls were virus-naïve at the timepoint of analyses and none of the individuals became SARS-CoV2-positive until the end of the study (12/2021).

Characterization of SARS-CoV2-Vaccination-Specific Humoral and B Cell Immunity

Humoral BNT162b2-vaccination-specific immunity above threshold was detected in all healthy individuals and in 90% (18/20) of KTR for IgG, 85% (17/20) for IgA and in 75% (15/20) with respect to neutralizing capacity. Two of three patients receiving triple IS therapy showed no or low IgG and neutralizing antibody levels. One of the two patients under Everolimus treatment showed low IgG and no neutralizing antibody titers whereas both did not develop IgA responses. Overall, KTx patients showed significantly reduced spike-specific IgG, IgA- and neutralization capacity levels as compared to controls (**Figure 1A**). Employing a robust FACS-based assay (9), transplant recipients were further characterized by significantly reduced frequencies of spike protein receptor binding domain (RBD)-specific B cells (**Figure 1B**, left) that were approximately ten-fold higher in humoral responders as compared to non-responders (**Figure 1B**, right). Antigen-specific B cells in patients contained reduced portions of isotype class switched IgD^-CD27^+ memory-type cells (**Figure 1C**, left), being in line with diminished frequencies of specific IgG^+ cells (**Figure 1C**, right). An exemplary gating strategy for B cell characterization is depicted in **Supplementary Figure S1**.

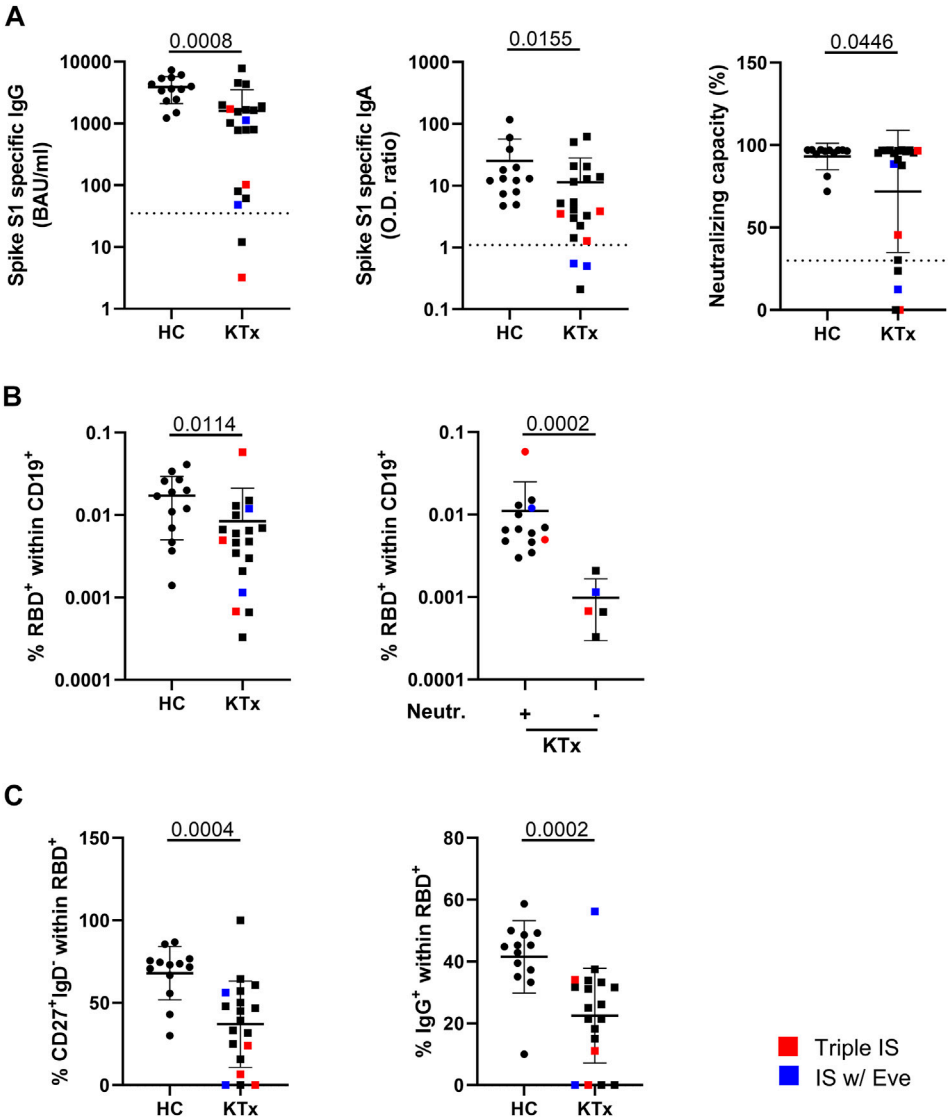


FIGURE 1 | Humoral immune responses and vaccination-specific B cell immunity. **(A)** Humoral vaccine-specific immune responses were assessed for anti-spike protein S1 domain specific IgG, IgA and virus neutralization capacity in healthy controls (HC) and KTx patients around 6 weeks after administration of the second standard BNT162b2 dose. Thresholds defining a positive response are indicated by dotted lines. **(B)** Relative frequencies of RBD-specific $CD19^+$ B cells identified by FACS in HC vs KTx (left) and in KTx that were stratified according to responders (+) and non-responders (–) regarding neutralizing capacity above threshold (right). **(C)** Memory-type of spike-RBD-specific B-cells according to IgD and CD27 expression (left) and portions of class-switched IgG^+ cells (right). In all analyses, $n = 20$ KTx and $n = 13$ HC were enrolled. Mann-Whitney test was applied throughout based on non-normal distribution of values. Graphs show means ± SD. Patients receiving triple immunosuppressive (IS) therapy are depicted in red, those under Everolimus-containing IS in blue.

Quantitative and Qualitative Features of Vaccination-Specific $CD4^+$ T Cells

Vaccination-specific SARS-CoV2 spike protein- and CEF control antigen-reactive $CD4^+$ T cells were identified based on CD154 and CD137 coexpression after peptide mix stimulation with the gating strategy illustrated in **Supplementary Figure S2**. We detected spike-specific $CD4^+$ T cells in all individuals included in the study (**Figure 2A**, left) with frequencies being similar in patients and controls (**Figure 2A**, right). However, KTx patients were characterized by significantly reduced portions of $IFN\gamma^+$-, but not $TNF\alpha^+$, IL-2^+ or IL-4^+ T cells (**Figure 2B**). Furthermore, antigen-reactive polyfunctional T cells co-expressing IFNγ, TNFα and IL-2 were less frequently detected in transplanted individuals, along with higher frequencies of cytokine non-producing cells (**Figure 2C**). IL-4 was excluded from polyfunctionality analyses due to comparably low frequencies of positive cells.

With respect to subset classification of antigen-specific cells, we found a significant increase of $CD45RO^-CD62L^-$ effector T cells in patients in concert with lower portions of $CD45RO^+CD62L^-$ effector/memory-type T cells (**Figure 2D**).

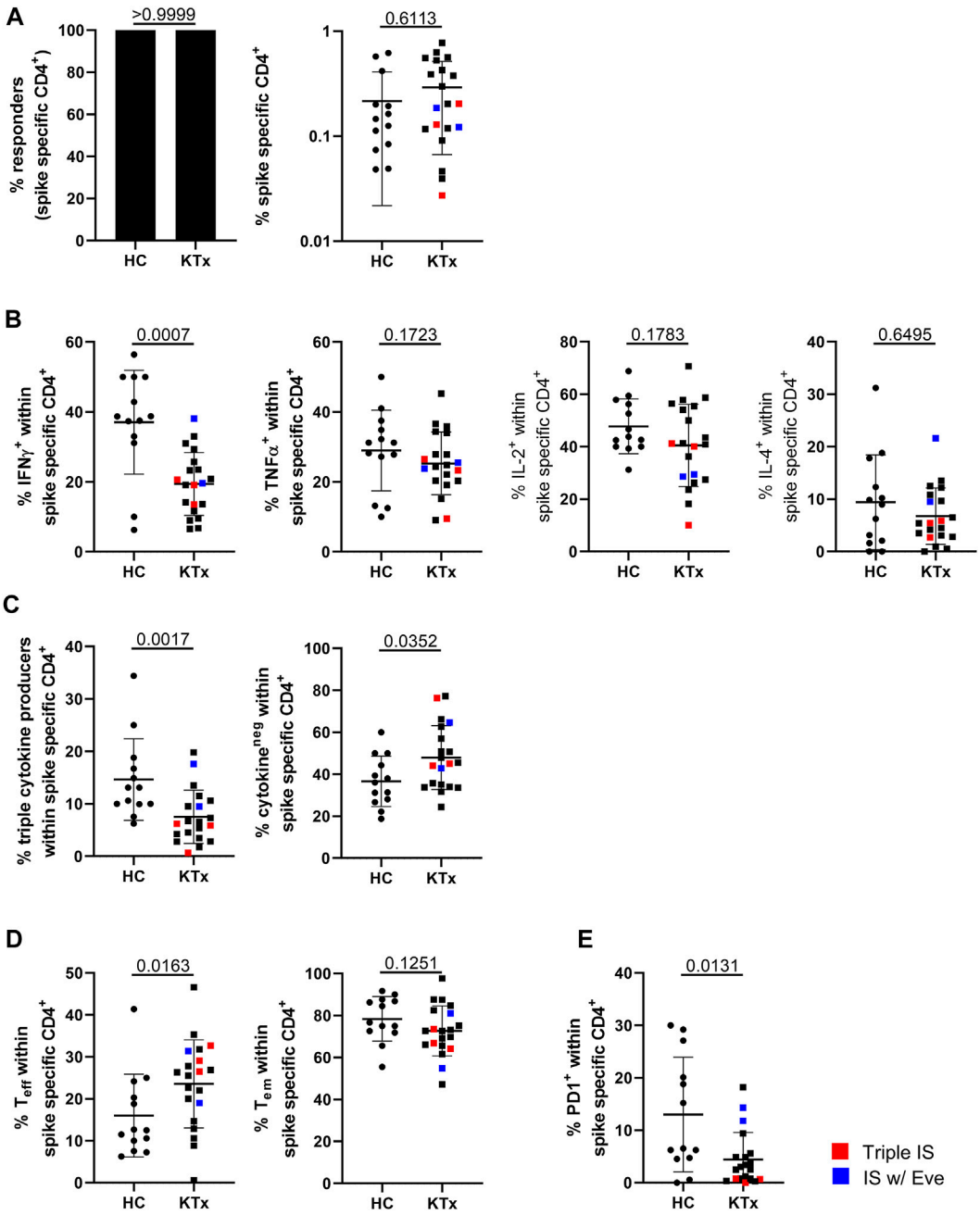


FIGURE 2 | Assessment of spike-specific T cell responses. PBMC were stimulated with spike peptide mix or left unstimulated. Specific $CD4^+$ T cells were detected by flow cytometry according to co-expression of CD154 and CD137. **(A)** Depicts responder rates (left) and portions of spike-specific $CD4^+$ T cells in HC vs. KTx after unstimulated control background substraction (right), **(B)** frequencies of cytokine producers as indicated within the antigen-specific population. **(C)** Quantifies $IFN\gamma^+TNF\alpha^+IL\text{-}2^+$ "triple$^+$" polyfunctional (left) and cytokine-non-producing (right) cells. **(D)** Analysis of effector and effector/memory-type differentiation of antigen-specific $CD4^+$ T cells. **(E)** Portions of specific, recently *in vivo* activated $PD\text{-}1^+$ T cells. N in all experiments as in **Figure 1**. Mann-Whitney test was applied throughout based on non-normal distribution of values. Graphs show means ± SD. Patients receiving triple immunosuppressive therapy are depicted in red, those under Everolimus-containing IS in blue.

Furthermore, healthy donors showed significantly elevated portions of antigen-specific $PD1^+$ cells than KTx, reflecting recent *in vivo* activation (**Figure 2E**). Overall frequencies of antigen-specific T cells were within the lower range in one patient, and *in vivo* activated $PD\text{-}1^+$ cells were rarely found in all three patients under triple IS treatment. Of note, CEF control antigen mix specific $CD4^+$ T cell responses did not significantly differ between healthy controls and patients except for slightly reduced frequencies of $IL\text{-}2^+$ T cells in the latter (**Supplementary Figures S3A–E**).

DISCUSSION

A plethora of studies suggests that vaccination of adult KTx patients against SARS-CoV2 results in blunted antiviral immunity (6, 7), mirrored by the broad inability to develop neutralizing antibody titers in individuals receiving standard triple IS including antimetabolites (5, 9). So far, reactogenicity of mRNA vaccines in pediatric patients has only been examined for individuals with a mean age of 18 years and only with respect to IgG responses in the absence of matched healthy controls (10, 11). Importantly, our data presented herein demonstrate that 85–90% of our KTx patient cohort between 12 and 18 years of age developed IgA and IgG responses, respectively, while 75% reached neutralizing antibody titers. According to recent literature, the latter data based on sVNT assay measurement might potentially even underestimate neutralizing capacity as compared to the Plaque Reduction Neutralization Test (12).

Whereas these results are encouraging and suggest that high humoral responder rates can be achieved despite MPA treatment, our data at the same time reveal that all arms of adaptive immunity are compromised in young patients as compared to controls. This includes frequencies of spike-reactive B cells and their capacity to undergo class switching to IgG, a phenomenon already reported for adult cohorts (9) and likely resulting from Everolimus- (13) or MPA-based suppression of B cell differentiation and plasma blast formation (14, 15). In fact, we could recently show that short-term pausing of MPA during SARS-CoV2 re-vaccination enables previous non-responders to mount robust anti-viral immunity including expansion of antigen-specific B cells (8). The absence of antimetabolites also supported specific T cell proliferation and *ex vivo* activation, whereas cytokine production capacity was only marginally affected (8). Interestingly, pediatric KTx patients showed selective limitations within spike-specific T cells as compared to controls that mainly included memory differentiation, IFNγ production and polyfunctionality. Whereas the exact role of multifunctional T cells is not completely understood, they might contribute to a better protection given that quantities are elevated in individuals experiencing mild as compared to severe SARS-COV2 infections (16), a feature also observed in other infections such as tuberculosis (17).

With respect to cytokine production, adolescent KTx patients obviously show less impairment than their adult counterparts where production of all spike- induced, but not CEF-induced cytokines, was strongly blunted (5). As one limitation of our study, it remains to be determined whether these differences predominantly depend on patient age, as has been already discussed for HBV vaccination in transplant recipients (18) or arise from different treatment regimens, given that the default medication recommendation of adult transplant recipients comprises triple IS including corticosteroids, whereas 60% of our pediatric patients received dual IS with Tac and MPA. In support of the latter hypothesis, two of three adolescents under triple IS in our study showed no or low specific IgG levels; the same applied to frequencies of class-switched memory B-cells. Given the potential risk of rejection episodes, however, therapeutic modifications including MPA hold are probably not reasonable in pediatric KTx patients.

The main limitation of our study is the relatively small study cohort. However, due to ethical guidelines limiting blood donation volumes from young individuals for cellular assays and a high dissemination of CoV2-infection in this group (thereby preventing inclusion of more virus-naive individuals), studies on adolescents will likely remain comparably small. Additionally, the overall number of adolescent KTx patients is substantially lower and vaccine approval was delayed as compared to adults. These facts may explain the comparably small size of other pediatric studies (10, 11). Due to the completion of our study by the end of 2021, we were not able to include data after a third vaccination of our cohort that is meanwhile standard of care. Given that recent literature demonstrates a considerable impact of a booster immunization on IgG levels in adolescent transplant recipients (19), it will not only be important to examine all arms of immunity after a third dose to better understand differential vaccine-specific immunity of young vs adult KTx patients, but also include neutralization data on virus variants of concern that have emerged meanwhile and have not been considered in this study.

In summary, based on comprehensive SARS-CoV2 vaccine-specific serological and cellular analysis, our data demonstrate that the majority of pediatric KTx patients under dual IS therapy in our cohort develops robust humoral immunity, but shows distinct differentiation- and function-related impairments within B- and T helper cell compartments.

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 human participants were reviewed and approved by the local ethical committee of the Charité Universitätsmedizin (EA2/227/21). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AS, JT, PB, and KK designed the study, supervised experiments, analyzed data and wrote the manuscript. LT, ES, VP, CS, JS, AH, LLT, and CL performed experiments and

analyzed data. HS-H, FF, BJ, and HS designed the study and supervised experiments.

FUNDING

AS and KK received funding by the Sonnenfeldstiftung Berlin, Germany. KK was supported by grants from the Deutsche Forschungsgemeinschaft (KO-2270/71 and KO-2270/4-1) and unconditional project funding from Chiesi GmbH. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication. ES is funded by the Federal Ministry of Education and Research (BMBF) grant (BCOVIT and 01KI20161) and is enrolled in the Charité Clinician Scientist Program funded by the Charité–Universitätsmedizin Berlin and the Berlin Institute of Health. HS receives funding by the Ministry for Science, Research and Arts of Baden-Württemberg, Germany and the European Commission (HORIZON2020 Project SUPPORT-E, 101015756).

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.

ACKNOWLEDGMENTS

The authors thank all participants for their willingness to donate blood, thereby greatly supporting this study. We further thank Sofia Friedersdorff for special support.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2022.10677/full#supplementary-material

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LETTER TO THE EDITOR
published: 12 August 2022
doi: 10.3389/ti.2022.10681

Abatacept Rescue Therapy in Kidney Transplant Recipients: A Case Series of Five Patients

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Keywords: belatacept conversion, abatacept, kidney transplant, CMV infection, immunosuppression, rescue therapy

Dear Editors,

Abatacept, a cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin (CTLA4-Ig), is a subcutaneously administered immunosuppressive drug that selectively inhibits T-cell activation by blocking the CD28-CD80/86 costimulatory pathway. Abatacept is widely used in rheumatology, especially in the treatment of rheumatoid arthritis (1). More recently, intravenously administered belatacept, another CTLA4-Ig, has shown better renal transplant (RT) survival results, improvement in long-term renal function, and less *de novo* donor-specific antibody (DSA) formation than a calcineurin inhibitor (CNI) regimen, either in induction therapy or after conversion from CNIs (2–4). However, to date, abatacept has been reported only exceptionally as maintenance treatment in patients who have undergone renal transplantation (5).

This letter reports on our experience with CNI conversion to self-administered subcutaneous abatacept in five patients who benefited from RT for 1.5–84 months (**Table 1**). The initiation of CTLA4-Ig therapy was motivated by graft biopsy-confirmed CNI toxicity in four patients (P1, P2, P3, and P4) and varying concentrations of tacrolimus owing to severe gastroparesis (P5). Abatacept maintenance therapy was chosen due to difficult peripheral venous access or to avoid hospitalization in the context of the COVID-19 pandemic. All patients received a 125 mg subcutaneous injection of abatacept every week (6). The first injection was performed in Day Hospital for monitoring and injection education. Treatment with CNIs was progressively withdrawn over 1–3 months (7). All patients received prednisone 5 mg/day and mycophenolate mofetil (P1, P2, P4, and P5) or everolimus (P3).

The mean follow-up after switching to abatacept was 13.6 months. In all patients, renal function was similar between baseline and the last follow-up (**Table 1**). We did not observe any transplant rejection or any appearance of or increase in DSAs, which were routinely screened every 3 months (screening and single antigen identification, One Lambda Thermo Fisher). Two patients developed CMV disease (P1 and P5). It is of note that P5 was not receiving any CMV prophylaxis. In P1, CMV infection was refractory to available antivirals (valganciclovir, foscarnet) and the discontinuation of abatacept. Treatment with maribavir for 8 weeks reduced the viral load to less than 2,000 IU/ml, and viral load remained stable with only azathioprine and prednisone. In addition, we observed better control of blood pressure in P2 and P3, allowing the cessation of some of the antihypertensive drugs.

In RT recipients with CNI intolerance, conversion to belatacept is an effective and validated option. However, this treatment has logistical drawbacks due to its intravenous formulation and its nurse-supervised infusion for 30–60 min (8). In patients with rheumatoid arthritis, a fixed-dose SC administration of 125 mg weekly compared with the body-weight-based monthly IV administration of 10 mg/kg allowed to obtain therapeutic concentrations and similar clinical remission rates irrespective of baseline patient body mass index (6).

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Received: 31 May 2022
Accepted: 30 June 2022
Published: 12 August 2022

Citation:
Uro-Coste C, Atenza A, Heng A-E, Rouzaire P-O and Garrouste C (2022) Abatacept Rescue Therapy in Kidney Transplant Recipients: A Case Series of Five Patients. Transpl Int 35:10681. doi: 10.3389/ti.2022.10681

TABLE 1 | Patient characteristics, conversion and follow-up data.

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Patients' characteristics	Age at Tx (y)	76	47	67	61	26
	Sex	M	M	M	M	F
	Weight (kg)	60	98	89	80	57
	ESRD diagnosis	Diabetes	APLS	Glomerulonephritis	IgA nephropathy	Lupus
Transplant characteristics	Re Tx	No	No	No	No	Yes
	Induction therapy	Antithymocyte globulin	Basiliximab	Basiliximab	Basiliximab	Antithymocyte globulin
	CMV status	D+/R+	D+/R−	D+/R−	D−/R+	D−/R+
Switch data	Conversion indication	CNI toxicity	CNI toxicity	CNI toxicity	CNI toxicity	gastroparesis
	Reason for choosing abatacept	COVID-19 pandemic	Difficult venous access	Difficult venous access	Difficult venous access	Difficult venous access
	Time of conversion post-Tx (m)	1,5	84	32	84	13
	Associated treatment	MPA	MPA	Everolimus	MPA	MPA
Complication	Rejection	No	No	No	No	No
	Viral complication	CMV disease at M5	No	No	No	CMV disease at M3
Creatinine (µmol/L)/eGFR MDRD (ml/min/1.73 m^2)	Month -1	193/31	266/23	263/22	309/19	181/31
	Month 0	190/32	258/24	230/26	320/18	172/33
	Month 1	175/35	270/23	271/22	272/22	170/33
	Month 2	168/37	303/20	270/22	322/18	187/30
	Month 3	181/34	236/27	279/21	289/20	191/29
	Month 6	213/28	238/26	269/22	295/20	188/30
	Last follow-up	194/31	238/26	256/23	303/19	169/33
DSA follow-up	DSA at switch	Yes (score 4)	No	No	No	No
	Last DSA	Neg	Neg	Neg	Neg	Neg
Time on abatacept (m)		5	6	16	9	17

APLS, antiphospholipid syndrome; CNI, calcineurin inhibitor; D, donor; DSA, donor-specific antibody; eGFR, estimated glomerular function rate; ESRD, end-stage renal disease; kg, kilogram; m, month; MPA, mycophenolic acid; R, recipient; Tx, transplant; y, year.

In the literature, only one case series reported nine adult RT recipients who received abatacept due to CNI intolerance and belatacept unavailability (5). In this cohort, patients received abatacept at approximately 10 mg/kg, mainly intravenously (N = 8), for a median duration of 82 months, and the authors reported stable long-term RT function, even though one patient developed a grade 1A acute cellular rejection episode with a favorable outcome.

In our cohort of patients treated subcutaneously with a fixed weekly dose of 125 mg, irrespective of the patient weight (from 1.27 to 2.19 mg/kg), no transplant rejection or DSA appearance was observed. Even though abatacept is known to display lower binding avidity to CD80 and CD86 than belatacept (9), these encouraging data are consistent with the fact that CD86 occupancy in belatacept-treated kidney transplant patients seems not to be associated with clinical and infectious outcomes.

Special attention should, however, be paid to the occurrence of opportunistic infections and their prophylactic treatments (10). Indeed, CMV infection is a frequently reported complication after conversion to belatacept, especially in the first 6 months after transplantation in elderly patients and patients with an estimated glomerular filtration rate <25/ml/min/1.73 m^2 (10).

In conclusion, our local experience suggests that weekly subcutaneous administration of 125 mg abatacept may be an effective alternative to belatacept, with a similar safety profile, as rescue therapy in RT recipients with peripheral difficult venous access and/or wishing to be more autonomous. These exciting findings need to be confirmed by further larger, prospective, and randomized studies.

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 review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CG designed the study. CG and CU-C collected data. CU-C, CG, and P-OR analyzed data and wrote the first draft of the manuscript. All authors reviewed the manuscript and approved the submitted version of the manuscript.

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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LETTER TO THE EDITOR
published: 25 August 2022
doi: 10.3389/ti.2022.10716

Kidney Transplantation in Patients With Active SARS-CoV-2 Replication: An Initial Case Series

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Keywords: SARS-CoV-2, kidney transplantation, vaccination, immunosuppression, monoclonal antibodies, induction therapy

Dear Editors,

Since 2020, the severe acute respiratory syndrome coronavirus (SARS-CoV-2) pandemic has had a negative impact on transplant recipients and on many transplantation programs. With the persisting high prevalence of infections in the general population, transplant nephrologists will be facing patients with positive swabs at the time of organ allocation and transplantation. Patients with end-stage renal disease (ESRD) and kidney transplant (KTx) recipients have low serologic responses to vaccination and are at high risk of severe COVID-19 (1). In the immediate post-transplant period, patients are under a high burden of immunosuppressive therapies, including induction regimens based on anti-lymphocytes antibodies, to prevent acute rejection and early immunization. Current international guidelines generally recommend to wait for at least 2 weeks after acute infection and to have a negative detection of SARS-CoV-2 RNA in a nasopharyngeal swab before moving forward to transplantation (2). It is also highly suggested to postpone transplantation in case of suspected or confirmed SARS-CoV-2 infection (2). However, with the advent of the omicron variant, associated with lower severity, it is not known whether transplantation is safe in patients within shorter time from infection and with detectable RNA in the nasopharyngeal swab (3). We present our recent cases of KTx performed in SARS-CoV-2 positive patients.

Our institution is a tertiary hospital in Switzerland, performing approximately 60 KTx per year with around 50% living donors. Since the beginning of the pandemic, all patients called in hospital following an organ offer undergo a nasopharyngeal swab, as part of the routine tests performed before transplantation. Between January, 1st and March, 31st 2022, four patients with significantly detectable SARS-CoV-2 RNA in a nasopharyngeal swab at the time of surgery underwent KTx. Three out of four organs came from deceased donors. For the patient with a living donor, the planned transplantation was previously postponed due to the shutdown of elective surgical activities in our institution at the peak of the pandemic. Baseline characteristics of the patients and their outcome are detailed in **Table 1**. Three patients had an mRNA-based SARS-CoV-2 vaccination history. The decision to transplant was taken regardless of post-vaccination serology values, as these results were not rapidly available. Viral genotyping was not done systematically in our center, but all transplantations occurred during the peak of the omicron wave in Switzerland, and in particular of the initial BA.1 sublineage (>90% of SARS-CoV-2 infections, as monitored by the Swiss Federal Office of Public Health) (4). The mean time between the diagnosis of infection and transplantation was 13 (range 5–16) days. All patients were paucisymptomatic (slight rhinitis or dysphagia) at the time of surgery. After transplantation, the recipients were carefully monitored clinically, together with daily blood tests and SARS-CoV-2 nasal swabs every 48 h (until a negative PCR). In 2 out of 4 patients, repeated nasal swabs showed still increasing viral titers in the first 48 h, but for all patients the tests became negative by day 10 after transplantation with full resolution of the initial mild symptoms. Induction regimen was basiliximab for all recipients, together with high dose

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***Received:** 20 June 2022*
***Accepted:** 27 July 2022*
***Published:** 25 August 2022*

Citation:
Halfon M, Stavart L, Venetz J-P, Manuel O and Golshayan D (2022) Kidney Transplantation in Patients With Active SARS-CoV-2 Replication: An Initial Case Series. Transpl Int 35:10716. doi: 10.3389/ti.2022.10716

TABLE 1 | Patients' characteristics at transplantation and outcome.

Patient	1	2	3	4
Age at Tx (y), gender	53, male	30, female	38, male	54, male
Nephropathy	Hypertensive nephropathy	Lupus nephritis	IgA nephropathy	Diabetic nephropathy
First Tx	Yes	Yes	Yes	Yes
HLA immunization status	Preformed class II DSA	No DSA	No DSA	No DSA
Preemptive Tx	No, HD for 2.3 years; since 4 months on the waiting list	Yes	Yes	No, HD for 3.5 years; since 3 years on the waiting list
Diabetes	No	No	No	Yes
Cardiovascular comorbidities	No	No	No	Yes
Days between SARS-CoV-2 infection[a] and Tx surgery	15	16	16	5
Vaccination status at the time of Tx	3 injections of mRNA vaccine, last injection 18 days before Tx	3 injections of mRNA vaccine, last injection 100 days before Tx	Not vaccinated before Tx	2 injections of mRNA vaccine, last injection 24 days before Tx
Viral load by PCR (nasal swabs) at the time of Tx	7200 copies/ml (pic value at 46,000 copies/ml, at day 6)	36,000 copies/ml (pic value at 89,000 copies/ml, at day 2)	3500 copies/ml (highest value)	150,000 copies/ml (highest value)
Induction immunosuppressive regimen	Bas/CS/TAC/MMF and IVIG	Bas/CS/TAC/MMF	Bas/CS/TAC/MMF	Bas/CS/TAC/MMF
Sotrovimab injection	Yes, 15 days before Tx	Yes, 1 day after Tx	Yes, 1 day after Tx	Yes, 3 days before Tx
Outcome at 1 month	No COVID-19-related symptoms or complications Negative nasal swab PCR 8 days after Tx	No COVID-19-related symptoms or complications Negative nasal swab PCR 10 days after Tx	No COVID-19-related symptoms or complications Negative nasal swab PCR 4 days after Tx	No COVID-19-related symptoms or complications Negative nasal swab PCR 9 days after Tx
Kidney function after Tx (serum creatinine)	133 and 128 µmol/L, at 1 and 3 months, respectively	69 and 73 µmol/L, at 1 and 3 months, respectively	135 and 127 µmol/L, at 1 and 3 months, respectively	81 and 78 µmol/L, at 1 and 3 months, respectively

[a]*As per patients' history and available PCR tests performed in the dialysis centers before Tx.*

Bas, basiliximab; CS, corticosteroids; DSA, donor-specific anti-HLA antibodies; HD, hemodialysis; IVIG, intravenous immunoglobulins; MMF, mycophenolate mofetil; TAC, tacrolimus; Tx, transplantation; y, years.

corticosteroids (methylprednisolone pulses during the first days at tapering doses followed by prednisolone 20 mg/day from day 5 onwards), tacrolimus and mycophenolate mofetil. One patient with preformed donor-specific anti-HLA antibodies (DSA) received in addition intravenous immunoglobulins (IVIG, 2 g/kg). At 1 month, no patient had presented symptomatic COVID-19 or other related infections. None of the patients developed an episode of acute rejection or detectable anti-HLA antibodies in the first 3 months of follow-up, with excellent and stable kidney function at 1 and 3 months. Thus, in our small case series, a positive nasopharyngeal swab at the time of transplantation was not associated with COVID-19 disease progression or other unfavorable post-transplant outcomes.

The cumulative dose of immunosuppression received during the induction period and early months after transplantation is well described to put the patients at high risk of infections. However, the risk of undergoing KTx with acute SARS-CoV-2 infection is still unknown and could expose those recipients to severe complications. So far, immunocompromised patients, such as patients with autoimmunity or after transplantation, were shown to have higher rates of severe disease progression after SARS-CoV-2 infection compared to the general population (5). Thus, facing the decision to perform an elective KTx, clinicians have to balance the risk of worsening of COVID-19 in a paucisymptomatic recipient, versus declining the organ and possibly an excellent transplantation opportunity in particular in immunized recipients. However, compared to the delta variant, current data suggest that omicron has a reduced severity, particularly in vaccinated patients.

The availability of antiviral as well as monoclonal antibodies (mAbs) against SARS-COV-2 may offer new possibilities to allow the transplantation of patients in a context where the virus is still endemic. At least for low-immunological risk recipients, the procedure should be safe providing the use of induction protocols without lymphocytes-depleting therapies. Indeed, T cells play a major role in the immune response against viruses, including SARS-CoV-2 (6). Administration of anti-thymocyte globulins was associated with more complications and more severe COVID-19, compared to basiliximab-based induction in transplant recipients (7). B cells and the antibody response against SARS-CoV-2 are also important to prevent severe disease. The B-cell depleting mAb rituximab is widely used in patients with DSA and is associated with three times more risk to develop severe COVID-19 and longer hospital stays (8). Thus, high-immunological risk patients appear to have few safe options for induction therapies. In our small series, three out of four patients were at low-immunological risk, and one patient with preformed DSA could be successfully transplanted with basiliximab induction combined with IVIG, without early acute rejection. Because dialysis patients are known to have lower titers of protective antibodies after SARS-CoV-2 vaccination (9), sotrovimab was administered in all our recipients following the positive PCR test.

In conclusion, an induction protocol based on a combination of basiliximab with mAbs against SARS-CoV-2 Spike protein (sotrovimab at the time of our study) seems to be safe and effective to prevent symptomatic disease and complications in newly transplanted ESRD patients infected with the virus, at least in the context of paucisymptomatic infections and/or low viral loads. With the persisting high prevalence of SARS-CoV-2 in the general

population, our preliminary findings are important for KTx programs. If the safety is confirmed in bigger series, the transplantation activity could be maintained despite the pandemic, in particular for patients that have been on the waiting list for a long time, such as the immunized recipients for whom suitable organs are scarce.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study involving human participants was reviewed and approved by the institution's Ethics Committee (CER-VD) for the retrospective use of clinical data. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the follow-up of the patients, the collection of data and reviewed the manuscript. MH and LS collected and analysed the data in more detail and prepared **Table 1**. MH, OM, and DG reviewed and interpreted the data, wrote and submitted the manuscript.

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.

ACKNOWLEDGMENTS

We would like to thank the staff of the Transplantation Center for their assistance in the follow-up of renal transplant recipients.

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LETTER TO THE EDITOR
published: 17 August 2022
doi: 10.3389/ti.2022.10666

Would Major Incompatible Blood Type Lung Transplants be Standard Care?

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Keywords: ethics, donor, lung, ABO-incompatible, coercion

Dear Editors

On 12 April 2022, Kyoto University Hospital (Japan) announced a successful incompatible blood type lung transplant from living donors (1). Specifically, a right lower lobe from a father with blood type B and a left lower lobe from a mother with blood type O were transplanted into their pre-teen/teenage daughter, with blood type O, who had severe obstructive bronchiolitis. This **living-donor** lung transplant is noteworthy because it was performed in a **major incompatible state** (wherein a recipient with type O blood receives a transplant from a donor with type A/B/AB). To date, only one major incompatible blood type lung transplant (MIBTLT), from a brain-dead donor, has been reported in Germany (2). The patient from the German operation is alive as of 5 July 2022, without any signs of long-term chronic rejection (as per personal communication from Dr. Axel Haverich).

In this case, Rituximab was administered 3 weeks prior to surgery, immunosuppressive drugs were administered, and plasmapheresis was performed to remove anti-B antibodies. This is the same strategy used for kidney and liver incompatible blood type transplants. Unlike kidneys and livers, lungs are subject to strong rejection and are vulnerable to infection, due to their exposure to air. Therefore, lung transplantation from organs with incompatible blood types is considered difficult.

We will make seven points.

First, the immunological mechanism in the lungs: This method has not been successful in lungs, despite favorable outcomes having been achieved in livers and kidneys. However, it was successful when **living-donor** lungs were used. The originality of this case pertains to **living-donor** lungs being used for a **MIBTLT**.

Most candidate lungs are considered unsuitable because of lung injuries that occur with brain-death and ICU-related complications (i.e., barotrauma or lung edema associated with fluid resuscitation) (3). However, the success of this case infers that **MIBTLT** may be feasible in clinical settings if the underlying immunological mechanisms are clarified. We assume that different immunological conditions exist between the lungs of brain-dead versus living-donor.

The clinical preservation time limit for lungs seems to be roughly 8 h. It is important to note that the clinical preservation time was absent in this case. The success of the **MIBTLT** procedure may be due to the freshness of the living-donor lungs. We need to know how long after brain-death the lung was transplanted in the German operation. Studying what immunological and histological events occur in those 8 hours of clinical preservation is necessary.

We are fully aware of the Toronto group's attempts at *ex-vivo* lung perfusion (**EVLP**). However, it appears that the main purpose of **EVLP** is to prolong clinical preservation time. **EVLP** trials have so far provided little insight into the immunological mechanisms that make **MIBTLT** possible.

Second, information of successful cases: The recipient who underwent **MIBTLT** from a brain-dead lung donor, in Germany in 2007 (2), has maintained a high QOL with no chronic rejection in the 15 years following the operation. The common belief surrounding transplants from a major incompatible blood type has been that "liver and kidney transplants can work (even with ABO major incompatibility), but lungs don't work." The prognosis and condition of the recipient urged us to share this information with the global transplant community immediately.

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Received: *23 May 2022*
Accepted: *18 July 2022*
Published: *17 August 2022*

Citation:
Akabayashi A and Nakazawa E (2022) Would Major Incompatible Blood Type Lung Transplants be Standard Care? Transpl Int 35:10666. doi: 10.3389/ti.2022.10666

Third, potential to address emergencies: ABO **MIBTLT**, using living-donor lungs, may be a treatment option when no ABO-compatible donor is present—typically during emergency surgery. EVLP allows for transplantation with extended ischemic time, since the issue of ischemic time is not relevant to living-donor lungs.

Fourth, evidence for effectiveness of EVLP: Is EVLP effective for ABO **MIBTLT**? A retrospective study that examined data from the Toronto Lung Transplant Program database (N = 906) (4) reported that outcomes were not different amongst procedures where total preservation time exceeded 12 h versus those where total preservation time was less than 12 h. However, the study in question did not list ABO incompatibility as being compatible, minor incompatible, or major incompatible. It is unclear whether all surgeries from the Toronto Lung Transplant Program were compatible. Comparing the outcomes of **MIBTLT** with those of compatible and minor incompatible lung transplantations is essential. If the outcome of the former is significantly worse than the others, **MIBTLT** should be considered a compassionate treatment rather than a standard care.

Fifth, cost: The **EVLP** technique requires a circuit with multiple, complex components, depending on the device used. It commonly includes some form of drainage from the left atrium, chamber reservoir, centrifugal pump, membrane gas/heat exchanger, filtered gas. It commonly includes some form of drainage from the left atrium, chamber reservoir, centrifugal pump, membrane gas/heat exchanger, filtered gas line for deoxygenation, leucocyte filter, inflow cannula into the pulmonary artery and a ventilator connected to the trachea (5) Additionally, **EVLP** takes 12 h to complete. Methods to reduce the cost of EVLP such as hubbing (6) are proposed; however, the expense of the equipment and time of medical personnel remain substantial.

It is unclear whether the use of Rituximab, immunosuppressants, and plasmapheresis is less expensive. A rigorous cost-benefit analysis must be done to determine which of these options is more inexpensive. While beneficiary's financial burden may increase, we do not support treatments that could be characterized as those that "only the rich can afford."

Sixth, ethical issues: Serious ethical issues emerge when considering **MIBTLT**—particularly regarding the donor selection process. In Japan, the number of brain-dead donors is remarkably small, while living-donor transplants are the norm (7). If **MIBTLT** becomes standard care, refusal to be a donor (based on having a different blood type) becomes difficult. The psychological pressure that is placed on potential donors (who are often family members) will undoubtedly increase. In the case of living-donor transplantation, voluntariness is essential, since donors are healthy individuals. Strict regulations need to be established in each country to prevent coercion of potential donors.

Lastly, this is the first case of ABO **MIBTLT** being performed in living-donor lungs, where a favorable outcome was achieved. This report is significant because the success of ABO **MIBTLT** (along with other attempts, such as **EVLP**) may increase treatment selection, thereby reducing potential organ shortages.

AUTHOR CONTRIBUTIONS

AA designed and wrote the first draft. EN collected literatures and provided advice on the composition of the manuscript. All authors read and approved the final manuscript.

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.

ACKNOWLEDGMENTS

The authors thank Prof. Dr. Axel Haverich, Hannover, Germany for providing invaluable information.

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Transplant International

Official journal of the European Society for Organ Transplantation

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