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Lung transplantation through the fountain of youth

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Transplant International

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Staying connected in the countdown to the ESOT Congress 2023

ESOT Congress
THE INTERNATIONAL TRANSPLANT CONGRESS®
ATHENS | 17-20 SEPTEMBER 2023

After a long period of restricted travel, which led to a shift towards virtual events, the transplant community has truly learned the importance of staying connected. ESOT Congress 2021 was held as a hybrid event, with 1200 participants on-site and over 1400 joining remotely. This year, we are thrilled to return to a face-to-face congress and hope to welcome over 3500 attendees to the historic city of Athens.

The ESOT congress is an event like no other for the transplant community. It provides attendees with the opportunity to meet experts in the field, work together to make transplant access more equitable and improve education. The congress offers the chance to hear what really matters to patients, igniting collaboration, sharing best practices and debating ethical challenges. Coming together provides a platform for recognition, to award excellence and honour achievements through a variety of prestigious ESOT awards and ultimately, to inspire the next generation of transplant professionals.

ESOT is the leading international transplant society when it comes to innovation and cutting-edge technology, and our biennial congress is no exception. This year's meeting features a variety of session formats to stimulate interaction and fast-track learning. The programme is built on the principles of multidisciplinary team collaboration and offers a person-centric approach to transplant care. The dialogue between patients and healthcare professionals will be palpable throughout the congress, and we hope this will inspire the entire community to incorporate such collaboration into the heart of their practice.

ESOT is all about staying connected and, today, social media is a crucial communication channel in society. Social media provides a platform to inform, educate and connect the medical community in ways we could not previously have imagined.

The ability to communicate with professionals from all over the world at the touch of a button has transformed the way we exchange ideas and redefined the world of organ transplantation. The ESOT Social Media Ambassadors Team is an international group with members from various professional backgrounds. With a focus on connecting the transplant community through social channels, the team shares news about ESOT's educational activities, unites professionals with patients and highlights the latest scientific insights in the field.

We recognise the importance of the widespread use of social media platforms throughout the event to ensure the benefits of the congress are experienced across the world. We will be covering ESOT Congress 2023 on social media and encourage everyone to join the conversation by sharing their favourite scientific insights and social moments via our hashtags, #ESOTcongress and #ESOTmoments, before, during and after this milestone event.

We look forward to seeing you in Athens!

Frank Dor
ESOT Council Member
ESOT Congress 2023 Social Media Ambassador Lead

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ESOTCongress

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ATHENS | 17-20 SEPTEMBER 2023

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#ESOTcongress

PRE-CONGRESS WEBINARS

Congress webinars

16 MAY
Cellular therapies and regulation – opportunities and hurdles
13:00 – 14:00 CEST

6 JUN
Vascularised composite allotransplantation – overcoming hurdles to clinical application
18:00 – 19:00 CEST

27 JUN
Machine perfusion series: From clinical trials to an established machine perfusion programme (liver perfusion)
18:00 – 18:45 CEST
Machine Perfusion

6 JUL
Machine perfusion series: From clinical trials to an established machine perfusion programme (kidney perfusion)
18:00 – 18:45 CEST
Machine Perfusion

18 JUL
Congress webinar – cardiothoracic
18:00 – 19:00 CEST

1 AUG
Machine perfusion series: From clinical trials to an established machine perfusion programme (cardiothoracic perfusion)
18:00 – 18:45 CEST
Machine Perfusion

31 AUG
Machine perfusion series: Making NRP routine in abdominal and thoracic organ donation
18:00 – 19:00 CEST
Machine Perfusion

#ESOTcongress

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ORIGINAL RESEARCH
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Lungs From Donors ≥70 Years of Age for Transplantation—Do Long-Term Outcomes Justify Their Use?

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Donor shortages have led transplant centers to extend their criteria for lung donors. Accepting lung donors ≥70 years of age has previously shown good short-term outcomes; however, no mid- and long-term outcome data on these extended criteria donors has been published to date. In this study, all patients who underwent lung transplantation between 06/2010 and 12/2019 were included in the analysis, and the outcomes were compared between patients receiving organs from donors <70 years of age and patients transplanted with lungs from donors ≥70 years of age. Among the 1,168 lung-transplanted patients, 62 patients received lungs from donors ≥70 years of age. The recipient age of those receiving older organs was significantly higher, and they were more likely to suffer from obstructive lung disease. Older donors were exposed to significantly shorter periods of mechanical ventilation prior to donation, had higher Horowitz indices, and were less likely to have smoked. The postoperative time on mechanical ventilation, time on ICU, and total hospital stay were comparable. The overall survival as well as CLAD-free survival showed no differences between both groups in the follow-up period. Utilization of lungs from donors ≥70 years of age leads to excellent mid- and long-term results that are similar to organs from younger donors when the organs from older donors are carefully preselected.

Keywords: lung transplantation, extended criteria donor lungs, marginal donor lungs, old donor lungs, lung donor characteristics

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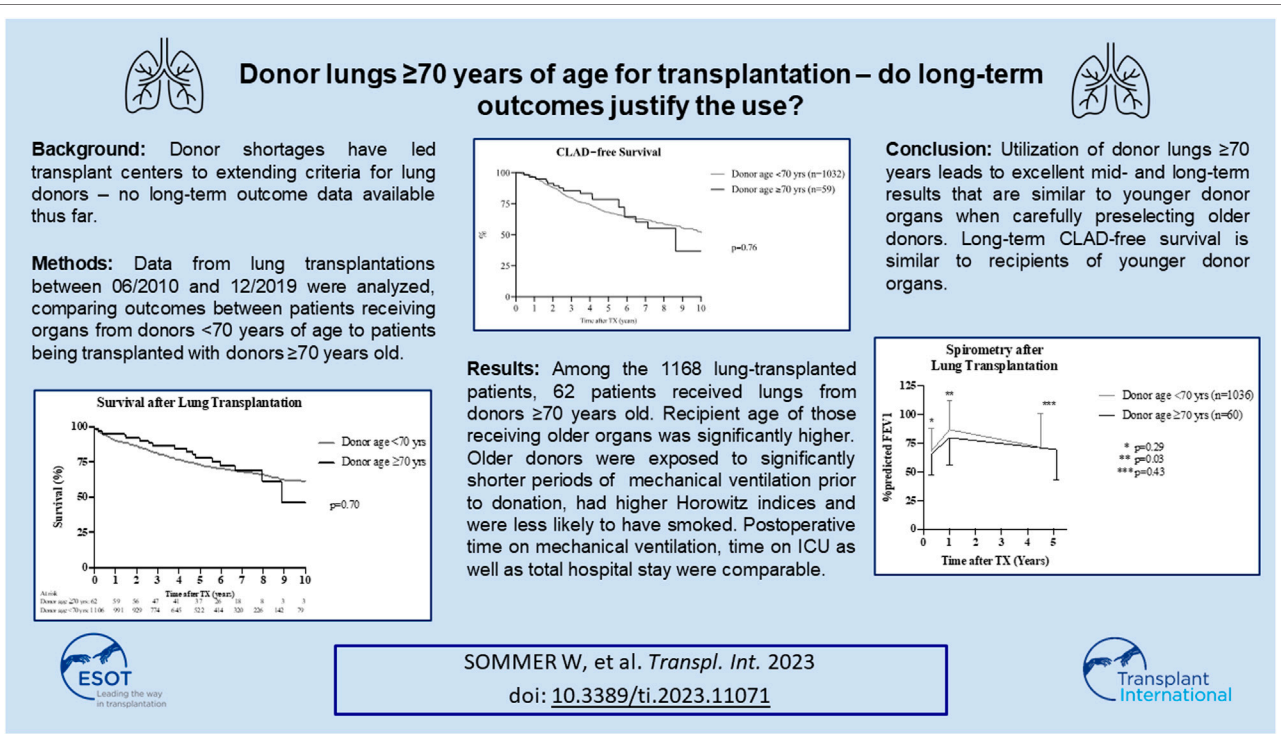
Abbreviations: BMI, body mass index; CLAD, chronic lung allograft dysfunction; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ET, Eurotransplant; FEV1, forced expiratory pressure in 1 second; LAS, lung allocation score; ICU, intensive care unit; ISHLT, International Society for Heart and Lung Transplantation; LAS, lung allocation score; PGD, primary graft dysfunction; UNOS, united network for organ sharing.



GRAPHICAL ABSTRACT |

INTRODUCTION

Given the known global shortage of ideal suitable donor organs for lung transplantation, obtaining more organs from the existing donor pool has been one tool used to optimize patient care in end-stage lung disease. As a result, utilization of non-ideal donor lungs from "extended-criteria" donors has become clinical routine in large lung transplant programs (1–4).

The lung donor age has steadily increased in Europe over the past number of years, with a reported median donor age of 51 years in 2018. In contrast, the median lung donor age in North America remains much lower at approximately 33 years for the past decade (5). Given these substantial geographic differences, countries with older organ donors are confronted with extended criteria organ offers on a daily basis in order to provide optimized patient care.

The impact of donor age on lung transplant outcomes and the clinical feasibility have been reviewed by multiple transplant centers in the past, with conflicting conclusions. More recent analyses have shown that an advanced donor age of >55 years does not appear to have a negative impact on recipient survival, especially in older recipients (6–9), whereas earlier analyses tended to show survival disadvantages in candidates receiving lungs from older donors (10, 11).

We have previously described outcomes using donor lungs from donors ≥70 years, finding no early survival disadvantage for up to 3 years after transplantation (7). Spirometry results in this early analysis indicated better results for recipients with an obstructive underlying disease pattern prior to transplantation, as compared to restrictive pulmonary disease.

However, longer-term follow-up of these "extended-criteria" donor organs has not yet been reported. The aim of this study is, therefore, to summarize the long-term follow-up of recipients of donor lungs from donors aged 70 and older in comparison to recipients of donor organs from donors younger than 70 years of age.

PATIENTS AND METHODS

Patient Groups

All patients who underwent lung transplantation between 06/2010 and 12/2019 at Hannover Medical School were included in the retrospective analysis. Lung recipients were divided in two groups: patients transplanted with lungs from donors <70 years and patients transplanted with lungs from donors ≥70 years. Outcome parameters, including pre-, peri-, and postoperative clinical parameters, as well as recipient overall survival and freedom from chronic lung allograft dysfunction (CLAD) were recorded and compared between the two groups.

All patients provided written informed consent for data utilization for scientific purposes at the time of listing for transplantation.

Variable Definition

The primary composite outcome, graft survival, was defined as patient and graft survival and included patient mortality and the

need for retransplantation. Primary graft dysfunction (PGD) was defined according to current International Society for Heart Lung Transplantation (ISHLT) guidelines (12).

Graft function was evaluated at regular outpatient visits and included surveillance biopsies as well as home spirometry testing. Predicted FEV1 was calculated for each recipient utilizing the formula FEV1 = race*((0.0395*height)−(0.025*age)−2.6). Since all recipients are Caucasian in the analyzed cohorts, 'race' was substituted by "1" in the formula. The measured FEV1 was then expressed as the %predicted FEV1.

CLAD was defined following current ISHLT guidelines as a persistent decline of FEV1 ≥20% from baseline in the absence of other conditions causing pulmonary impairment (13).

Donor Management

All donor organs were offered to our center by Eurotransplant. Within the regular LAS-based allocation process, organs were allocated for a specifc recipient, whereas organs in the rescue allocation process were accepted by the center and the recipient was chosen by the transplant center. Organ assessment and preservation were the same for lungs of donors <70 and of donors ≥70 years of age. Following endobronchial as well as macroscopic assessment of the donor lung during procurement, the donor organ was accepted by a surgical team from our center. Organs with irreversible macroscopic signs of parenchymal alterations such as emphysema were not accepted.

Recipient Management

Recipient management at our institution has been previously reported and did not differ between groups (14). All recipient characteristics were recorded as previously reported and spirometry results were included after discharge following the initial hospital stay, 1 year after transplantation, and during the last follow-up visit at the outpatient clinic. Calculation of recipient-specific %predicted FEV1 was performed as previously reported (7). The clinical routine in our program includes, if hemodynamically necessary, intraoperative extracorporeal support using veno-arterial extracorporeal membrane oxygenation (ECMO) instead of conventional cardiopulmonary bypass (CPB). CPB is only used if additional cardiac surgery is performed, which is technically not feasible with ECMO (e.g., atrial septal defect closure). It should be noted that, as per our centre's protocol, recipients with an underlying diagnosis of primary pulmonary hypertension received postoperative prolonged veno-arterial ECMO treatment for left ventricular remodeling as a planned treatment strategy (15).

Statistics

Retrospective analysis of all parameters was performed using GraphPad Prism, Version 8.0 (San Diego, Ca, USA). Multivariate analysis was performed using SPSS 28.0.1.1 (IBM, Armonk, NY, USA).Variables are summarized as percentages, mean ± standard deviation (SD), or median (interquartile range, IQR). A Mann–Whitney *U* test was performed to test differences between continuous variables. Outcome-free survivals were calculated using the Kaplan-Meier method and were compared by using a log-rank test. p values < 0.05 were considered statistically significant.

RESULTS

Patient Groups

A total of 1,168 patients underwent lung transplantation at Hannover Medical School between 06/2010 and 12/2019, of which 62 (5.3%) recipients received allografts from donors ≥70 years of age and the remaining 1,106 (94.7%) patients allografts from donors <70 years of age. The median follow-up was 8.9 years.

Recipient Characteristics

Patients who received lungs from donors ≥70 years of age were significantly older compared to recipients of organs from donors <70 years of age (median (IQR) 57 (54; 62) vs. 51 (36; 58) years of age; $p < 0.0001$). The body mass index of recipients who received organs from older donors was slightly higher than recipients of organs from younger donors (**Table 1**).

The distribution of transplant indications differed significantly between both groups. Organs from older donors were more likely to be offered to candidates suffering from chronic obstructive pulmonary disease (COPD) (40.3% vs. 27.6%, $p = 0.04$). In contrast, candidates with cystic fibrosis were more often transplanted with organs from younger donors (20.9% vs. 4.8%; $p = 0.003$). Lung retransplantation for CLAD was performed solely with organs from donors aged <70 years ($p = 0.05$) (**Table 1**).

The median lung allocation score (LAS; $p = 0.18$) and time on the waiting list ($p = 0.56$) showed no significant difference between groups.

Regarding the preoperative risk profile, no differences in the need for preoperative mechanical ventilation (3.2% vs. 3.3%; $p < 0.99$), preoperative ICU treatment (8.1% vs. 10.2%; $p = 0.67$), or preoperative ECMO (6.6% vs. 8.1%; $p = 0.79$) were observed (**Table 1**).

Donor Characteristics

The median donor age in the ≥70 years of age group was 73 years of age (71; 75) vs. 47 years of age (34; 56) in the <70 years of age group, with a similar gender distribution between both groups ($p = 0.19$). Older donors had significantly shorter exposure to mechanical ventilation prior to procurement (3 (2; 4) vs. 4 (2; 7) days; $p = 0.0007$) but showed a higher Eurotransplant donor score compared to younger organ donors (8.7 ± 1.1 vs. 7.9 ± 1.6; $p < 0.0001$) (16). The oxygenation capacity (PaO_2 at 100% FiO_2, mmHg) of donors aged ≥70 years was higher compared to donors <70 years of age (412.5 (356; −469.5) vs. 384.0 (316; −448); $p = 0.01$). Additionally, older donors were less likely to have a smoking history compared to younger organ donors (12.9% vs. 42.1%; $p < 0.0001$). No organ donors aged ≥70 years of age showed signs of pulmonary contusion or aspiration (**Table 2**).

TABLE 1 | Recipient preoperative characteristics.

	Donor <70 years of age (*n* = 1,106)	Donor ≥70 years of age (*n* = 62)	*p*-value
Age (median; IQR)	51 (36; 58)	57 (54; 62)	<0.0001
Female (%)	48.2	53.2	0.51
BMI (mean ± SD)	22.1 ± 4.3	23.1 ± 3.6	0.04
Underlying Disease (n; %)			
Emphysema	305; 27.6	25; 40.3	0.04
Fibrosis	350; 31.6	25; 40.3	0.16
Cystic fibrosis	231; 20.9	3; 4.8	0.003
Primary pulmonary hypertension	68; 6.1	3; 4.8	0.79
Re-transplant for CLAD	74; 6.7	-	0.05
Sarcoidosis	37; 3.3	4; 6.5	0.27
Other	41; 3.7	2; 3.2	0.84
Lung allocation score (median; IQR)	36 (33; 42.5)	34.9 (32.5; 39.3)	0.18
Time on waiting list (days) (mean ± SD)	220.2 ± 454.7	175.4 ± 296.1	0.56
Pulmonary artery pressure (mean ± SD)	27.3 ± 14.2	27.6 ± 12.8	0.42
Preop mechanical ventilation (n; %)	36; 3.3	2; 3.2	>0.99
Preop intensive care unit (n; %)	113; 10.2	5; 8.1	0.67
Preop ECMO (n; %)	5; 8.1	73; 6.6	0.79

BMI, body mass index; CLAD, chronic lung allograft dysfunction; ECMO, extracorporeal membrane oxygenation.

Intraoperative Characteristics

The majority of lung transplantations were performed as bilateral minimally-invasive surgeries, with no differences between groups. The need for extracorporeal support did not differ between groups (32.2% vs. 26.6% $p = 0.38$). Notably, the majority of patients requiring extracorporeal support intraoperatively were put on veno-arterial ECMO. Cardiopulmonary bypass was only used in a minority of cases, in which additional cardiac surgery was performed (2.1% vs. 1.6%; $p = 0.80$). The cold ischemic times of the first ($p = 0.29$) and second implanted lung ($p = 0.91$) did not differ between groups (**Table 3**).

Postoperative Characteristics

The rates of postoperative ECMO were similar in both cohorts (9.7% vs. 9.4%; $p = 0.94$). The majority of these ECMO treatments resulted from our centre's protocol for postoperative remodeling of the left ventricle in patients with severe pulmonary arterial hypertension (6.5% vs. 7.6%; $p = 0.81$) (15).

The primary graft dysfunction (PGD) score grade 3 at 24 h ($p = 0.99$), 48 h ($p = 0.60$) and 72 h ($p = 0.94$) after transplantation did not differ between groups.

Postoperative characteristics, including mechanical ventilation ($p = 0.68$), intensive care stay ($p = 0.65$), and total hospital stay times ($p = 0.58$), did not differ between groups (**Table 3**).

Survival

No differences in overall survival were observed between cohorts ($p = 0.71$) (**Figure 1A**), as measured at 1, 3, and 5 years ($p = 0.21$; $p = 0.28$; and $p = 0.34$) (**Table 3**). Patients who received lungs from donors aged ≥70 years showed no survival difference with respect to their underlying disease as compared to recipients of organs from younger donors in the same disease cohort (**Figures 1B, C**).

Chronic Lung Allograft Dysfunction

The incidence of CLAD did not differ between groups (**Figure 2A**). CLAD-free survival in recipients of organs from donors ≥70 years of age as compared to recipients of organs from donors <70 years after 3 and 5 years were 85.5% vs. 79.7% and 78.5% vs. 68.1%, respectively. Stratification of graft survival in patients transplanted for COPD and pulmonary fibrosis according to donor ages of <70 or >70 years did not differ between groups (**Figures 2B, C**).

Postoperative Spirometry Results

FEV1 (%predicted) did not differ between groups at discharge (63.2% (52.2; 78.4) vs. 66.4% (55; 80.5); $p = 0.29$) (**Figure 3A**). One year after lung transplantation, recipients of organs from donors <70 years of age showed a significantly higher FEV1 (%predicted) as compared to recipients of lungs from donors aged ≥70 years (76.8% (63; 93.2) vs. 86.0% (70; 104); $p = 0.03$). This significant difference between both cohorts diminished in the following years after lung transplantation, showing similar %predicted FEV1 values at the last outpatient follow-up visit (70.5% (53; 87.3) vs. 73.3% (50; 94); $p = 0.43$) (**Figure 3A**). Stratification of FEV1 in patients with COPD and pulmonary fibrosis according to donor ages of <70 or ≥70 years did not show any difference between groups (**Figures 3B, C**).

Donor Age Is Not a Risk Factor for Mortality or CLAD Development

In multivariable Cox regression analysis, which included multiple recipient- and donor-specific variables as well as procedure intraoperative variables (**Table 4**), donor age was not a risk factor for recipient mortality ($p = 0.50$) or the development of CLAD ($p = 0.67$) (**Table 5**).

Risk factors associated with recipient mortality included recipient age ($p = 0.008$), intraoperative utilization of ECMO ($p < 0.001$), and ischemic time of the first lung ($p = 0.006$). A donor history of smoking was identified as a risk factor for the diagnosis of CLAD ($p = 0.001$) (**Table 5**).

TABLE 2 | Donor characteristics.

	Donor <70 years of age (*n* = 1,106)	Donor ≥70 years of age (*n* = 62)	*p*-value
Age (years) (median; IQR)	47 (34; 56)	73 (71; 75)	<0.0001
Female (n; %)	559; 50.5	37; 59.7	0.19
BMI (mean ± SD)	25.7 ± 5.0	26.2 ± 2.9	0.10
Time on mechanical ventilation (days) (median; IQR)	4 (2; 7)	3 (2; 4)	0.0007
ET donor score (mean ± SD)	7.9 ± 1.6	8.7 ± 1.1	<0.0001
PaO_2 (FiO_2 1.0) (median; IQR)	384.0 (316; 448)	412.5 (356; 469.5)	0.01
History of smoking (n; %)	465; 42.1	8; 12.9	<0.0001
Contusion (n; %)	106; 9.6	-	0.009
Aspiration (n; %)	70; 6.3	-	0.04
Use of *ex vivo* lung perfusion (n; %)	65; 5.9	4; 6.5	0.85

BMI, body mass index; ET donor score: Eurotransplant donor score.

TABLE 3 | Recipient intra- and postoperative characteristics.

	Donor <70 years of age (*n* = 1,106)	Donor ≥70 years of age (*n* = 62)	*p*-value
Minimally-invasive (n; %)	1,034; 93.5	56; 90.3	0.43
Bilateral lung transplantation (n; %)	1,075; 97.2	61; 98.4	0.72
Intraoperative use of cardiopulmonary bypass (n; %)	23; 2.1	1; 1.6	0.80
Intraoperative use of ECMO (n; %)	294; 26.6	20; 32.3	0.38
Ischemic time; first side (min) (mean ± SD)	414 ± 122.1	396.3 ± 122.9	0.29
Ischemic time; second side (min) (mean ± SD)	527.9 ± 129.5	526.6 ± 135.7	0.91
ECMO postoperative (n; %)	104; 9.4	6; 9.7	0.94
ECMO postoperative per protocol[a] (n; %)	84; 7.6	4; 6.5	0.81
PGD score @24h (mean ± SD)	0.51 ± 0.91	0.53 ± 0.95	0.99
PGD score @48h (mean ± SD)	0.51 ± 0.90	0.55 ± 0.92	0.60
PGD score @72h (mean ± SD)	0.46 ± 0.85	0.50 ± 0.94	0.94
PGD 2 or 3 @72h (n; %)	146; 13.2	9; 14.5	0.84
Postoperative new dialysis (n; %)	99; 8.9	5; 8.1	0.83
Dialysis at discharge (n; %)	56; 5.1	2; 3.2	0.58
Mechanical ventilation postop (days) (median; IQR)	1 (1; 1)	1 (1; 1)	0.68
ICU stay (days) (median; IQR)	2 (1; 5)	2 (1; 4.5)	0.65
Total hospital stay (days) (median; IQR)	23 (21; 31)	23 (21; 32.5)	0.58
1-year survival (%)	90.2	95.1	0.21
3-year survival (%)	80.9	86.4	0.28
5-year survival (%)	73.2	77.8	0.34

[a]*Centre's protocol for postoperative ECMO in pulmonary arterial hypertension.*
ECMO, extracorporeal membrane oxygenation; PGD, primary graft dysfunction; ISHLT PGD score; ICU, intensive care unit.

DISCUSSION

Over the past two decades, discordance between the consistently high number of candidates awaiting lung transplantation and the number of available donor organs has led experienced transplant centers toward accepting "extended-criteria" donor organs in order to reduce waiting list mortality (3, 4). Questions remain however, regarding the limits of acceptability, as to what degree "extended-criteria" donor lungs can be used for transplantation without compromising recipient outcomes. Retrospective analyses have already demonstrated no adverse outcomes when using donor lungs with acute pulmonary embolism (17, 18) impaired oxygenation (19, 20), or contusion (21). Regarding donor age, multiple analyses have shown good results for lungs from donors >55 years of age (22, 23) however, the upper donor age limit in lung transplantation remains under discussion.

As per our program policy, donor offers are not declined solely because of advanced donor age, but such offers were targeted toward older recipients where possible in the allocation process. Organs from older donors, with additional risk factors such as a relevant history of smoking, severe infiltrates, contusion, or parenchymal alterations, were usually rejected outright upon offer or by an experienced surgeon at procurement. Since the majority of lungs from donors aged ≥70 years were accepted in the rescue allocation process, recipient selection for these organs was performed by our transplant center. Careful recipient selection was also undertaken with regards to anticipated intra- and postoperative risks and retransplantation as well as younger candidates were excluded. Through this combination of donor and recipient selection, utilization of organs from donors aged ≥70 years has facilitated meaningful mid- and long-term outcomes that were comparable to those seen in recipients of organs from younger donors. Both cohorts demonstrated statistically insignificant 1-, 3-, and 5-year survival differences, with recipients of organs from donors aged <70 years showing non-inferior survival rates (1-year: 95.1% vs. 90.2%; 3-year: 86.4%

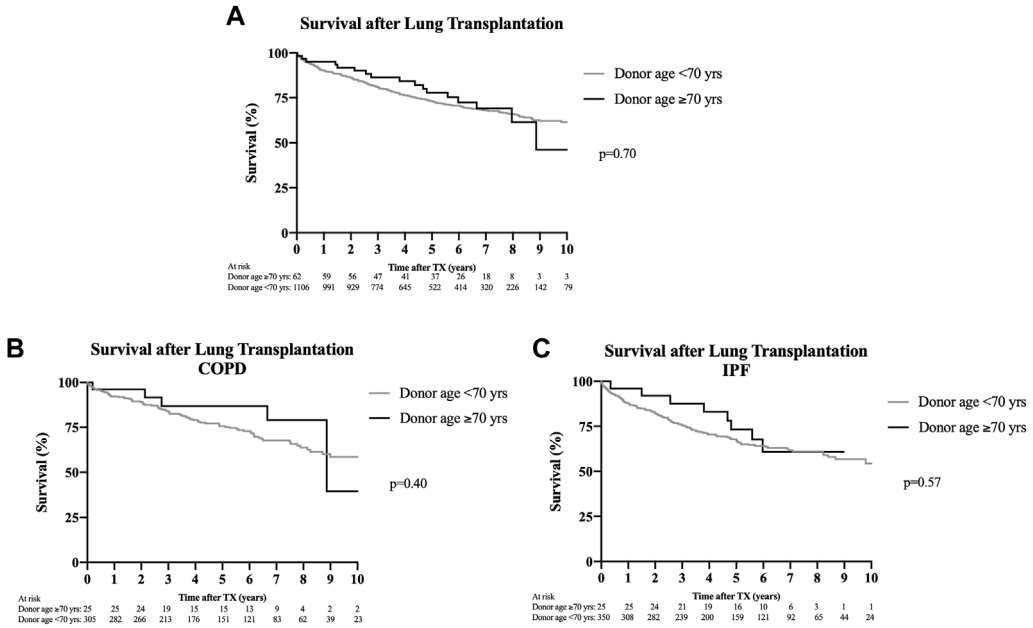


FIGURE 1 | Survival after lung transplantation. Kaplan-Meier analyses. **(A)** Overall survival between recipients who received organs from donors aged ≥70 years and recipients of organs from donors aged <70 years, showing no significant difference (p = 0.70) up to 10 years after lung transplantation. **(B)** Stratification of posttransplant survival in patients with COPD as transplant indication differentiating according to donors aged ≥70 and <70 years. No significant difference in survival up to 10 years after transplantation was detectable (p = 0.40). **(C)** Stratification of posttransplant survival in patients with idiopathic pulmonary fibrosis according to donors aged ≥70 or <70 years. No survival difference up to 10 years after transplantation was noticeable (p = 0.57).

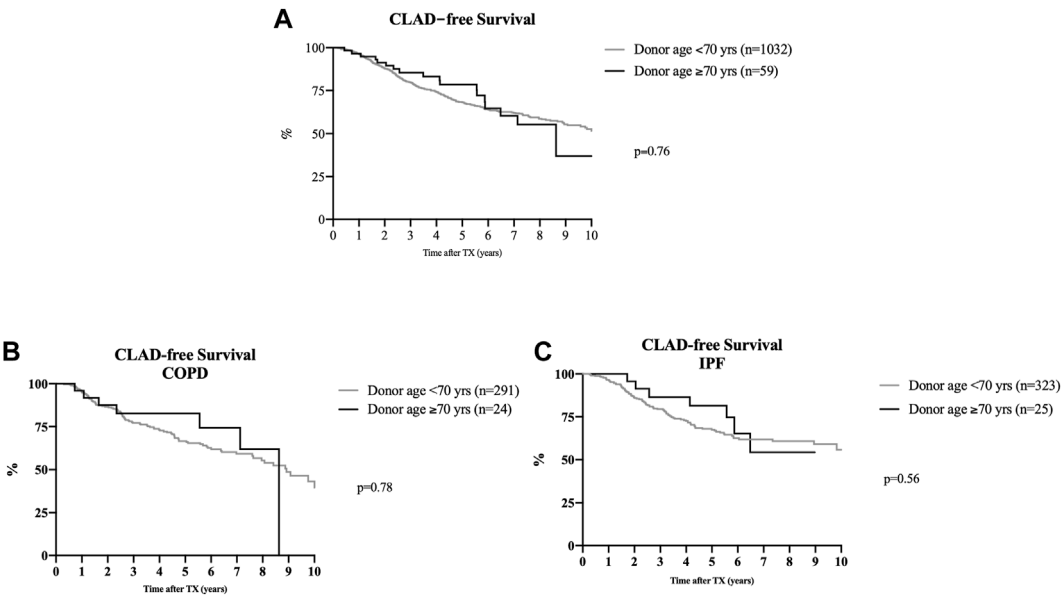


FIGURE 2 | CLAD-free survival after lung transplantation. Kaplan-Meier analyses. **(A)** Overall CLAD-free survival following lung transplantation utilizing organs from donors aged ≥70 years or >70 years, showing no difference between both groups (p = 0.76) within the first 10 years after transplantation. **(B)**: Stratification of CLAD-free survival in patients with COPD who received a lung transplantation from donors either ≥70 or <70 years of age. Donor age had no impact on the development of CLAD (p = 0.78). **(C)** Stratification of CLAD-free survival in patients with idiopathic pulmonary fibrosis who underwent lung transplantation with organs from donors aged ≥70 or <70 years of age. The incidence of CLAD was similar in both groups (p = 0.56).

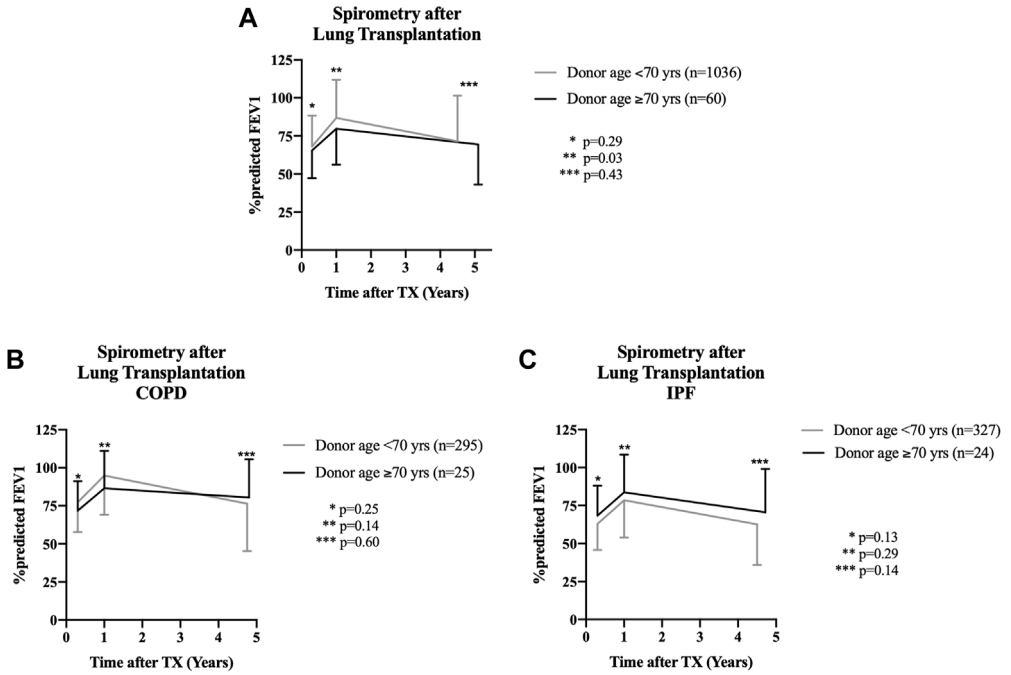


FIGURE 3 | Spirometry results for recipients after lung transplantation. Values are shown as mean ± standard deviation of the %predicted FEV1 at teh time of discharge from initial hospital stay (1st value), at 1 year after transplantation (2nd value), and at last follow-up in the outpatient clinic (3rd value). **(A)** Comparison of recipients of organs from donors aged ≥70 years with outcomes of patients who received lungs from donors aged <70 years. No functional spirometry difference was found at the time of discharge from the hospital ($p = 0.29$), but recipients of organs from donors <70 years of age showed a statistically significant better %predicted FEV1 at 1 year following transplantation ($p = 0.03$). This difference was no longer detectable at last follow-up after a median of 4.5 years (<70 years of age cohort) and 5.1 years (≥70 years of age cohort) ($p = 0.43$). **(B)** Sub-analysis of patients with the underlying disease COPD. No functional differences in spirometry results was detectable throughout the entire follow-up period when comparing donors aged ≥70 years and <70 years of age. **(C)**: Sub-analysis of patients with idiopathic pulmonary fibrosis undergoing lung transplantation with organs from donors aged ≥70 or <70 years of age. No difference in spirometry results was detectable within the first 5 years after transplantation for both cohorts.

vs. 80.9%; 5-year: 77.8% vs. 73.1%), which for all time points lie above ISHLT reported averages (24).

These findings are in contrast to existing analyses of the UNOS database, which identified a 2.14 fold increased risk in 1-year mortality in recipients of lungs from donors aged ≥65 years (25). This report however, did not include information on "recipient-related" risks that may have contributed to impaired early survival. We would argue that this again underlines the importance of cautious recipient selection for lungs from older donors. Another important aspect in managing all forms of "extended-criteria" donor organs may well be center volume and the inherent level of experience with marginal donor organs as well as recipient matching. Registry analyses usually comprise both entities and do not differentiate results between large- and low-volume centers. Given the previously reported negative impact of low center volume on lung transplant outcome, these results may well be further aggravated in the field of "extended-criteria" donor organs (26, 27).

The physiological differences in the characteristics of advanced age lungs that may influence outcomes, either negatively or indeed positively after transplantation, remain unknown. By selecting organs with no or little smoking history and with careful visual inspection of parenchymal alterations such as bullae or rarefication, moderate or severe age-related obstructive pulmonary disease may be excluded. Temporary disconnection of the ventilator when inspecting the organ in the donor should be advocated, to assess the capacity of the organ to collapse as an important indicator of possible airway obstruction. Similarly, an elevated precapillary pulmonary artery pressure can be quickly excluded invasively within the procurement setting. Applying these measures routinely during the acceptance process of lungs from older donors may assist in achieving similar functional outcomes, with both cohorts showing comparable spirometry results during long-term follow-up. It should be noted that we previously found lower spirometry results in the first postoperative year in patients with pulmonary fibrosis who received organs from donors ≥70 years of age as compared to recipients with an obstructive underlying pulmonary disease pattern (7). This finding was not detectable in longer follow-up data in this larger cohort, showing comparable %predicted FEV1 courses in the individual disease cohorts. Most likely, increased patient numbers led to these results.

Although of critical importance, graft function is however only one consideration. Concerns continue to be expressed

TABLE 4 | Variables included in multivariable Cox Regression Analysis.

Variables
Donor age ≥70 years
Recipient data
Age
Female sex
BMI recipient
Emphysema
Fibrosis
Cystic fibrosis
Primary pulmonary hypertension
Re-transplant for CLAD
Sarcoidosis
Other
Lung allocation sore
Time on waiting list
Pulmonary artery pressure
Preoperative mechanical ventilation
Preoperative Intensive Care Unit
Preoperative ECMO
Donor data
Female sex
BMI
Time on mechanical ventilation
PaO_2 (FiO_2 = 1.0)
History of smoking
Contusion
Aspiration
Intraoperative data
Minimal invasive access
Cardiopulmonary bypass
ECMO
Ischemic time first side
Ischemic time second side

CLAD, chronic lung allograft dysfunction; ECMO, extracorporeal membrane oxygenation; FiO_2, Fraction of inspired oxygen; BMI, body-mass index.

TABLE 5 | Multivariable cox regression analysis.

Variable	Multivariable		
Mortality (*n* = 341)	**HR**	**95% CI**	***p*-value**
Donor age ≥70 years	0.826	0.475–1.438	0.50
Recipient age	1.014	1.004–1.025	0.008
Intraoperative ECMO	1.706	1.286–2.264	<0.001
First lung ischemic time	1.002	1.000–1.003	0.006
CLAD Incidence (*n* = 352)			
Donor age ≥70 years	1.130	0.65–1.964	0.67
History of smoking	1.527	1.180–1.977	0.001

ECMO, extracorporeal membrane oxygenation; CLAD, chronic lung allograft dysfunction; CI, confidence interval; HR, hazard ratio.

regarding the utilization of advanced age donor lungs and the potentially higher risk of transferring malignant tumors to recipients. While understandable, little corroborating data supporting this argument exists. The underlying concerns are not entirely organ-specific, and would be considered similarly legitimate in abdominal organ transplantation, where older donors have been used regularly for decades. Despite this, donor-derived malignant tumor transmission remains an extremely rare event in solid organ transplantation (28–30). Age does appear to increase risk, and, as a consequence, additional measures such as routine computer tomography imaging of potential donors ≥65 years of age prior to organ donation may attenuate the risk of utilizing organs with cancer suspicious structures.

Regarding candidate considerations, lung transplantation in selected older recipients have been performed in high volume transplant centers with acceptable outcomes. However, most received lungs from donors aged <40 years (31). Analogous to the Eurotransplant senior program for kidney transplantation established in 1999 (32), an 'advanced age' focused donor-recipient matching program for lung transplantation could potentially assist in providing adequate patient outcomes whilst fully utilizing the existing donor pool. Given that donor lung utilization in donors aged ≥65 years remains <3% in the United States and low within Eurotransplant associated countries (33), such a program may benefit older patients with obstructive pulmonary disease pattern, who usually have minimal perioperative risk factors but also low lung allocation scores and limited probability of receiving a timely transplantation in the regular allocation process. Moreover, senior recipients show no survival impairment when receiving lungs from donors aged ≥60, making this approach clinically relevant (34, 35). This finding is in line with our findings, which show that donor age is not a risk factor for recipient mortality or the development of CLAD. This is especially important, since enrolment in such age-restricted programs requires informed consent of the candidate.

LIMITATIONS

The dataset comprises the known limitations of a single-center retrospective analysis. The overall number of analyzed transplantations using donors aged ≥70 years remains low as compared to larger registry analyses; however, in contrast to those, more detailed follow-up information, including spirometry results as well CLAD incidence, were available.

CONCLUSION

In conclusion, the utilization of lungs from donors ≥70 years of age presents a feasible option, especially for advanced age recipients, facilitating comparable early-, mid-, and long-term outcomes regarding survival, CLAD development, and spirometry as compared to transplantations utilizing organs from donors younger than 70 years of age. These results can be achieved by carefully selecting both suitable donors as well as recipients.

DATA AVAILABILITY STATEMENT

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

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

Participated in research design: WS, GW, and FI. Participated in the writing of the paper: WS, MG, GW, and FI. Participated in data acquisition: WS, KA, MF, AS, KF, PY, MA, IT, CK, JS, GW, and FI. Participated in data analysis: WS, MA, IT, MG, AH, TW, CK, JS, GW, and FI.

CONFLICT OF INTEREST

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

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ORIGINAL RESEARCH
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A Pilot Single-Blinded, Randomized, Controlled Trial Comparing BNT162b2 vs. JNJ-78436735 Vaccine as the Third Dose After Two Doses of BNT162b2 Vaccine in Solid Organ Transplant Recipients

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Solid Organ Transplant (SOT) recipients are at significant higher risk for COVID-19 and due to immunosuppressive medication, the immunogenicity after vaccination is suboptimal. In the previous studies, booster method showed significant benefit in this population. In the current study, we compared using a mix-and-match method vs. same vaccine as a third dose in SOT recipients. This was a patient-blinded, single center, randomized controlled trial comparing BNT162b2 vs. JNJ-78436735 vaccine as the third dose after two doses of BNT162b2 vaccine. We included adult SOT recipients with functional graft who had received two doses of BNT162b2 vaccine. Participants were randomly assigned to receive either BNT162b2 or JNJ-78436735 in one-to-one ratio. Primary outcome was SARS-CoV-2 IgG positivity at 1 month after the third dose. Sixty SOT recipients, including 36 kidney, 12 liver, 2 lung, 3 heart, and 5 combined transplants, were enrolled, and 57 recipients were analyzed per protocol. There were no statistically significant differences between the two vaccine protocols for IgG positivity (83.3% vs. 85.2% for BNT162b2 and JNJ-78436735, respectively, p = 0.85, Odds Ratio 0.95, 95% Confidence Interval 0.23–4.00). Comparison of the geometric mean titer demonstrated a higher trend with BNT162b2 (p = 0.09). In this pilot randomized controlled trial comparing mix and match

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Abbreviations: COVID-19, Coronavirus disease 2019; GMT, Geometric mean titer; RBD, Receptor binding domain; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SOT, Solid Organ Transplant.

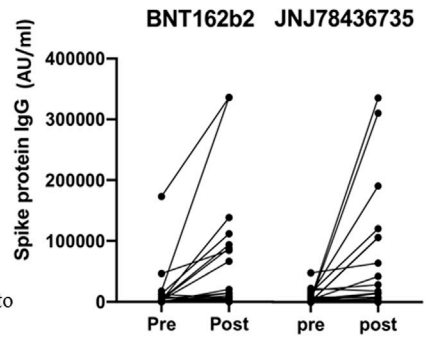
method vs. uniform vaccination in SOT recipients, both vaccines were safely used. Since this was a small sample sized study, there was no statistically significant difference in immunogenicity; though, the mix and match method showed relatively lower geometric mean titer, as compared to uniform vaccine. Further studies need to be conducted to determine duration of this immunogenicity.

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT05047640?term=20210641&draw=2&rank=1, identifier 20210641.

Keywords: COVID-19, solid organ transplant, vaccine, booster, randomized controlled trial

A Pilot Single-Blinded, Randomized, controlled trial comparing BNT162b2 vs JNJ-78436735 vaccine as the third dose after two doses of BNT162b2 vaccine in Solid Organ Transplant Recipients

- Patient-blinded, single center, randomized controlled trial comparing BNT162b2 vs JNJ-78436735 vaccine as the third dose after two doses of BNT162b2 vaccine
- Adult SOT recipients with functional graft
- 60 (36 kidney, 12 liver, 2 lung, 3 heart, and 5 combined) transplants reicipients were enrolled.
- IgG positivity; BNT162b2(83.3%) vs JNJ-78436735 (85.2%) (p=0.85).
- Geometric mean titer demonstrated a higher trend with BNT162b2 (p=0.09).
- The mix and match method showed relatively lower geometric mean titer, as compared to uniform vaccine.



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GRAPHICAL ABSTRACT |

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as the etiology behind the coronavirus disease 2019 (COVID-19) worldwide pandemic, has resulted in significant mortality rates worldwide. Solid organ transplant (SOT) recipients, not unexpectantly, are more likely to experience poor outcomes after SARS-CoV-2 infection including higher hospital admission rates and increase mortality (1). In this context, there is an urgent need to provide robust protection in this vulnerable population in addition to standard preventive strategies including wearing mask and hand hygiene.

Other than the natural immunological response against infections, vaccination and monoclonal antibody therapy are the other pathways available to augment the immune systems response to this infection. The United States Food and Drug Administration provided emergency use authorization for ticagevimab/cilgavimab as primary prophylaxis in high-risk patients such as immunocompromised recipients including SOT recipients (2). However, as different variants of concern including Omicron have emerged, the efficacy of some of the monoclonal antibody product has been challenged (3, 4). Thus, the importance of vaccination in this population continues to be a foundation of an effective preventive strategy.

Although the high efficacy of COVID-19 vaccines is well documented in the general population (5), the immunogenicity and efficacy of SARS-CoV-2 vaccination is suboptimal in SOT recipients, something that has been seen in with other vaccines (6). There have been several attempts to improve vaccine efficacy and/or immunogenicity in this vulnerable population, especially with boosted doses. A randomized controlled trial comparing placebo vs. other mRNA vaccine as a third dose study demonstrated significant benefit

(7). Furthermore, while this study was being conducted, the addition of a fourth dose has shown to have been beneficial (8), leading to the recommendation of a second booster in the immunosuppressed population. Even with the boosted dose strategy, reports of breakthrough infection in SOT recipients with COVID-19 exist (9).

We hypothesized that the mix and match method, i.e., using the different type of vaccine as a booster, would provide higher immunogenicity in SOT recipients. However, there are two studies comparing the mix and match method vs. uniform method in SOT recipients: one multicenter prospective, non-randomized, study and one randomized controlled trial (10, 11). The former vaccine series of Schwaighofer et.al. cohort differed from our study by utilizing various vaccines such as mRNA-1273 and BNT162b2 prior to administration of the third dose of AD26COVS1(10). Chiang et.al. conducted a prospective observation study, which cannot avoid selection bias (11). To study this concept more carefully, we conducted a single center randomized controlled trial comparing BNT162b2 (mRNA vaccine) vs. JNJ-78436735 (viral vector) as a third dose after completion of two doses of BNT162b2 vaccine in SOT recipients.

PATIENTS AND METHODS

Patient Selection and Study Design

This was a patient-blinded, superiority, randomized controlled trial, conducted at the Miami Transplant Institute, Jackson Health System, Miami, Florida, USA. The Miami Transplant Institute is one of the biggest SOT centers in North America, providing comprehensive care to all SOT recipients.

We included SOT recipients with a functional graft, whose age was 18 years and older at the time of enrollment. Inclusion for enrollment consisted of recipients with a minimum of 1 month post-transplant and having received two doses of BNT162b2 vaccine. Of note, the prior vaccines could have been administered any time pre or post transplantation. The third dose should have been given at least 28 days from the second dose of BNT162b2 vaccination and at least 1-month post-transplant. Exclusion criteria included any significant side effects due to previous SARS-CoV-2 vaccination, people unable to consent, receipt of more than or equal to three doses of SARS-CoV-2 vaccination, pregnancy and patients who previously received monoclonal antibody treatment that are specifically directed against the spike protein for SARS-CoV-2 such as Bamlanivimab plus Etesevimab, Casirivimab plus Imdevimab, and Sotrovimab at any time prior to the trial. Of note, at the time of enrollment, Ticagevimab/Cilgavimab was not available in USA.

This study was approved by local research ethics board and was given NCT05047640.

Blinding, Unblinding, Randomization and Follow up

After obtaining written informed consent, adult SOT recipients were randomized in one to one ratio to receive either BNT162b2 vs. JNJ-78436735. BNT16b2 uses nucleoside-modified mRNA encoding the viral spike glycoprotein for SARS-CoV-2 as an ingredient. On the other hand, JNJ-78436735 uses recombinant, replication-incompetent Adenovirus 26 vector, encoding a stabilized variant of SARS-CoV-2 spike protein, as an ingredient. A randomization schedule was created electronically and simple randomization was performed. The participants' blood specimens were collected to analyze anti-spike protein SARS-CoV-2 IgG. The patients were contacted by phone at day 3 and 7 post vaccination to monitor for adverse events. Follow-up blood test was planned between 21 and 35 days after the third dose of the vaccine to measure anti-spike protein SARS-CoV-2 IgG. We measured IgG titer to the SARS-CoV-2 spike protein receptor binding domain using enzyme-linked immunosorbent assay as described elsewhere (12). Briefly, the SARS-CoV-2 enzyme-linked immunosorbent assays were performed following a 2-step enzyme-linked immunosorbent assay protocol and results were interpreted in accordance with the manufacturer's cutoff calculations. Anti-spike protein SARS-CoV-2 IgG was reported as receptor binding domain (RBD) (13). At that time, we also questioned the adverse events. The vaccine given at the time of enrollment was unblinded at the time of follow up blood test to the participant. However, if an emergency ensued, the vaccine could be unblinded immediately for the patient and caring team.

Of note, this study was not observer blinded. However, the laboratory members were not notified of the randomization results.

Statistical Analysis and Sample Size Calculation

The primary outcome of the study was anti-spike protein SARS-CoV-2 IgG positivity after 28 (21–35) days of the booster dose with either vaccine. Secondary outcomes included side effect, graft rejection, and SARS-CoV-2 infection. The follow-up period of the current study was 28 (21–35) days, up to the follow-up blood collection. We set alfa of 0.05 and beta of 0.2. For pre-specified outcome analysis, based on our hypothesis, we compared IgG positivity between two vaccines. As an ancillary analysis, we tried to identify the risk factors to develop or not to develop IgG positivity in this cohort. We assumed the anti-spike protein SARS-CoV-2 IgG positivity in JNJ-78436735 as 80% and BNT162b2 as 60% (7). The number of subjects required for this analysis was 93 per each arm, or a total of 186. We assumed 5%–10% of patients would be lost to follow-up. Therefore, we planned to enroll 200 patients in total, to achieve statistical significance per protocol sample.

Demographics were analyzed using descriptive statistics. Pre- and post-vaccination anti-spike protein SARS-CoV-2 IgG titers were compared using Wilcoxon rank-sum test. Univariate analyses were performed to determine significant factors affecting seroconversion using chi-squared or Fisher's exact test for categorical variables and Mann–Whitney U for continuous variables. For multivariate analysis, we planned to construct a model using variables whose p-value were less than 0.2 on univariate analysis. Multivariate analysis was performed using logistic regression with stepwise backward elimination. Statistical significance was defined as a p-value of less than 0.05. Statistical analysis was performed using SPSS version 26.0 (Chicago) and GraphPad Prism version 8.0 (La Jolla, CA, USA).

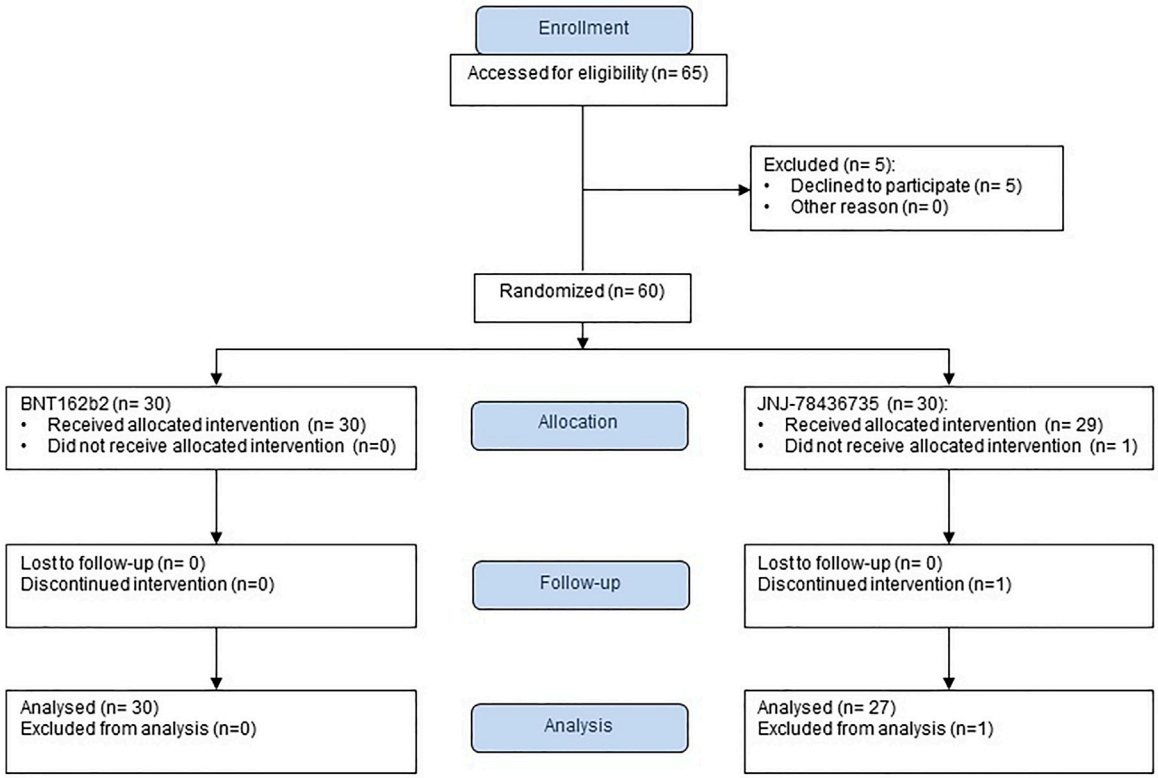

FIGURE 1 | Study flow chart.

TABLE 1 | Patient characteristics at enrollment.

Characteristic	All (n = 58)	BNT162b2 (n = 30)	JNJ-78436735 (n = 28)
Age, median (range)	57.5 (26–79)	59.5 (27–76)	54.5 (26–79)
Male sex (%)	38 (65.5)	21 (70)	17 (60.7)
Time from transplantation to vaccination (months), median (interquartile range)	11.5 (3–27)	10.7 (4.7–38.4)	12.5 (2.8–25.7)
Within 1 year of transplantation (%)	30 (51.7)	16 (53.3)	14 (50.0)
History of documented COVID-19(%)	7 (12.1)	4 (13.3)	3 (10.7)
Receipt of Anti-thymocyte globulin[a] (%)	17 (29.3)	8 (26.6)	9 (32.1)
Recent Rejection (%)	14 (24.1)	7 (23.3)	7 (25.0)
Type of transplant (%)			
Kidney	36 (62.0)	19 (63.3)	17 (60.7)
Liver	12 (20.7)	3 (10)	9 (32.1)
Lung	2 (3.4)	2 (6.7)	0 (0)
Heart	3 (5.2)	3 (10.0)	0 (0)
Combined	5 (8.6)	3 (10.0)	2 (7.1)
Immunosuppression			
Prednisone (%)	25 (43.1)	14 (46.7)	11 (39.2)
Prednisone dose, mg/day, median (range)	5 (2.5–80)	5 (2.5–80)	7.5 (4–40)
Tacrolimus (%)	52 (89.7)	26 (86.7)	26 (92.9)
Mycophenolate mofetil/mycophenolate sodium (%)	46 (79.3)	25 (83.3)	21 (75.0)

[a]*Within 6 months prior to the third dose of vaccination.*

RESULTS

Patient Population

From September to December 2021, we enrolled 60 SOT recipients and 59 of them received a study vaccine as one patient withdrew after obtaining the consent, prior to vaccination (30 BNT162b2, 29 JNJ-78436735) (**Figure 1**). We could not enroll the number of recipients because the majority of them had already received the third dose. The termination was not due to the interim analysis. After enrollment, one patient

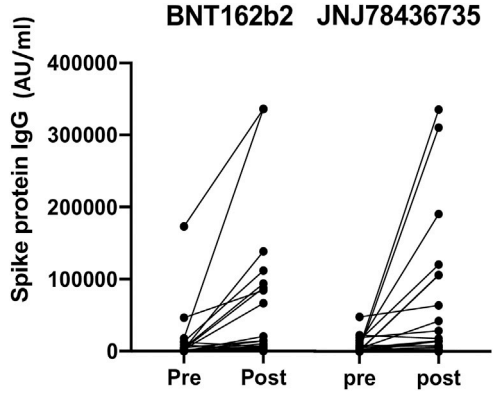

FIGURE 2 | Quantitative anti-spike protein IgG titer pre and post third dose of either BNT162b2 or JNJ78436735. Each dot represents each participant's IgG titer at pre or 1 month post third dose of vaccination.

TABLE 2 | Adverse Events after vaccination.

	BNT162b2 (n = 30)	JNJ- 78436735 (n = 28)
Local		
Arm Pain	8 (26.7)	6 (21.4)
Erythema	1 (3.3)	0 (0)
Any local reaction	9 (30.0)	6 (21.4)
Systemic		
Headache	3 (10.0)	2 (7.1)
Fatigue	5 (16.7)	2 (7.1)
Muscle aches/Joint pain	0 (0)	0 (0)
Gastrointestinal symptoms	0 (0)	0 (0)
Fever/Chills	1 (3)	1 (3.5)
Thrombosis	0 (0)	0 (0)
Any systemic reaction	7 (23)	5 (17)

declared that he had received monoclonal antibody, (resulting in the withdrawal of that participant (30 BNT162b2, 28 JNJ-78436735). Finally, we enrolled 36 kidney, 12 liver, 2 lung, 3 heart, and 5 combined. Baseline characteristics of 58 enrolled patients were shown in **Table 1**. The overall median time from transplant and the second dose of BNT162b2 to study vaccination was 10.7 [IQR] (4.7–38.4) and 7.8 (IQR 6.6–8.3) months, respectively. Of note, 20/58 (34.5%) of the recipients received the prior two doses prior to transplant. Only ethnicity was different between both groups ($p = 0.02$). Other demographic characteristics including type of transplant, presence of recent rejection, and immunosuppression at the time of vaccination were well balanced in the two groups.

Vaccine Immunogenicity

Of the 58 patients who were successfully vaccinated, one recipient that had received JNJ-78436735 was not included for the immunogenicity analysis due to acquiring SARS-CoV-2 infection prior to the second blood draw (**Figure 1**). The remainder of the recipients completed pre- and post-vaccination sera collection. Therefore, 57 patients were available for the immunogenicity analysis (30 BNT162b2, 27 JNJ-78436735) (**Figure 1**).

Post vaccination immunogenicity rates, which is the primary outcome, for BNT162b2 and JNJ-78436735 were 83.3% and 85.2% respectively ($p = 0.85$, Odds Ratio 0.95, 95% Confidence Interval 0.23–4.00).

The baseline anti-spike protein SARS-CoV-2 IgG positive rate was 36.9% among all cohort and there was no statistically significant difference between BNT162b2 and JNJ-78436735. Median quantitative SARS-CoV-2 IgG titers at the time of enrollment for BNT162b2 and JNJ-78436735 were 719 (range 11–173057) AU/mL and 2385 (range 101–48296) AU/mL, respectively.

Quantitative anti-spike protein SARS-CoV-2 IgG increased significantly post third dose vaccination compared to baseline ($p < 0.001$) in entire cohort (**Figure 2**).

Median geometric mean titer (GMT), analyzed as the absolute fold-increase of titer from pre- to post- third dose of the vaccination, for BNT162b2 and JNJ-78436735 was 9.51 (range 0.18–284.54) and 1.64 (range 0.24–170.2), respectively and there was a trend towards BNT162b2 showing higher response ($p = 0.09$).

When proceeding to analyze factors affecting vaccine IgG positivity after vaccination, we found in the univariate analysis that none of the variables could be identified as risk factors since all p values were greater than 0.2. Of note, we have analyzed age, gender, race, transplanted organ, duration between transplant and vaccination, recent rejection, usage of immunosuppressive medication including prednisone, tacrolimus, mycophenolate and anti-thymocyte globulin. Hence, we did not conduct multivariate analysis.

Vaccine Adverse Events

Vaccine-related adverse events were assessed in the 58 patients who received study vaccine (**Figure 1**). During follow-up, there were no statistically significant differences for local and systemic side effects in both groups (**Table 2**). The most common adverse event reported was localized injection site pain (14/58, 24.1%), which were seen within 7days after the vaccination. None of the 58 patients were diagnosed with new onset of rejection during the follow up. Mild SARS-CoV-2 infection was diagnosed in one patient at 31 days after JNJ-78436735 vaccination.

DISCUSSION

This was a randomized controlled trial comparing BNT162b2 vs. JNJ-78436735 as a third dose after completion of two doses of BNT162b2 in SOT recipients. Similar to previous randomized controlled trial (10) and non-randomized large observational study (11), these two vaccines were safely used in this population with similar immunogenicity as shown. Due to small sample size, not only the primary outcomes but also the secondary analysis, including risk factor analysis, may be inconclusive. However, although not statistically significant, we observed slightly higher immunogenicity following vaccination with mRNA vaccine.

At the time of our trial, there were two studies assessing the immunogenicity of mixing method in SOT recipients. One single center randomized controlled trial, conducted by Schwaighofer et al. (10), compared mRNA vaccine (either BNT162b2 or mRNA-1273) vs. Ad26COVS1 in 197 kidney transplant recipients with negative responses after two doses of mRNA vaccine. The positive antibody responses against SARS-CoV-2 spike protein after mRNA vaccine vs. Ad26COVS1 were 35% and 42%, respectively, not statistically significant. The other trial by Chiang et. al. concluded that mixing method did provide higher rate of seroconversion at 3- and 6-months post third dose vaccination in contrast to our study where GMT was higher in uniform method group. As a hypothesis, there might be an additive synergistic effect accompanying the administration of the same vaccine in contrast to the results seen using the mixing method. Of note, currently, JNJ-78436735 COVID-19 vaccine is authorized for adults only in certain limited situations due to risk of thrombosis with thrombocytopenia syndrome.

There are several limitations in this current study. Sample size was never achieved due to the challenges of persuading patients to possibly receive different vaccines based on randomization. Of note, the majority of our recipients had received the third dose at the time of enrollment. In addition, the prior vaccines could have been administered pre- or post transplantation; 34% of participants were vaccinated before transplant. Thus, we cannot conclude whether results are comparable between those vaccinated pre- and post-transplantation. In this study, we are limited to the use of surrogate marker, not the incidence itself. We included not only seronegative but also seropositive recipient at the time of the third dose vaccination in order to most accurately reflect our current population. We tried to address this limitation by calculating GMT. Lastly, our follow up consisted of 1 month duration making challenging to capture late occurring adverse events, along with concluding that IgG positivity 30 days post third vaccine dose properly reflect long term immunogenicity in transplant recipients. This warrants longer follow up for future studies.

In conclusion, we conducted a patient-blinded, randomized controlled trial comparing BNT162b2 vs. JNJ-78436735 vaccine for the third dose after two doses of BNT162b2 COVID-19 vaccines in SOT recipients. We found similar immunogenicity using both vaccination strategies. Even though the primary outcome was not achieved due to small sample size being underpowered, larger studies will need to be performed to draw conclusion. Further investigation is needed to understand the optimal method of COVID-19 vaccination in this vulnerable group of patients. Also, further studies need to be conducted to determine duration of this immunogenicity.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Human Subject Research Office at the University of Miami. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YN and GG designed the study. YN, EM, AM, and GG conceived the study. YN and SP analyzed the data. All the authors participated in the generation of the data and interpretation of results. YN and GG wrote the first version of the article. All the authors approved the final 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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ORIGINAL RESEARCH
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Simultaneous Heart-Kidney Transplant—Does Hospital Experience With Heart Transplant or Kidney Transplant Have a Greater Impact on Patient Outcomes?

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High institutional transplant volume is associated with improved outcomes in isolated heart and kidney transplant. The aim of this study was to assess trends and outcomes of simultaneous heart-kidney transplant (SHKT) nationally, as well as the impact of institutional heart and kidney transplant volume on survival. All adult patients who underwent SHKT between 2005–2019 were identified using the United Network for Organ Sharing (UNOS) database. Annual institutional volumes in single organ transplant were determined. Univariate and multivariable analyses were conducted to assess the impact of demographics, comorbidities, and institutional transplant volumes on 1-year survival. 1564 SHKT were identified, increasing from 54 in 2005 to 221 in 2019. In centers performing SHKT, median annual heart transplant volume was 35.0 (IQR 24.0–56.0) and median annual kidney transplant volume was 166.0 (IQR 89.5–224.0). One-year survival was 88.4%. In multivariable analysis, increasing heart transplant volume, but not kidney transplant volume, was associated with improved 1-year survival. Increasing donor age, dialysis requirement, ischemic times, and bilirubin were also independently associated with reduced 1-year survival. Based on this data, high-volume heart transplant centers may be better equipped with managing SHKT patients than high-volume kidney transplant centers.

Keywords: outcomes, kidney transplant, heart transplant, cardiac function, volume

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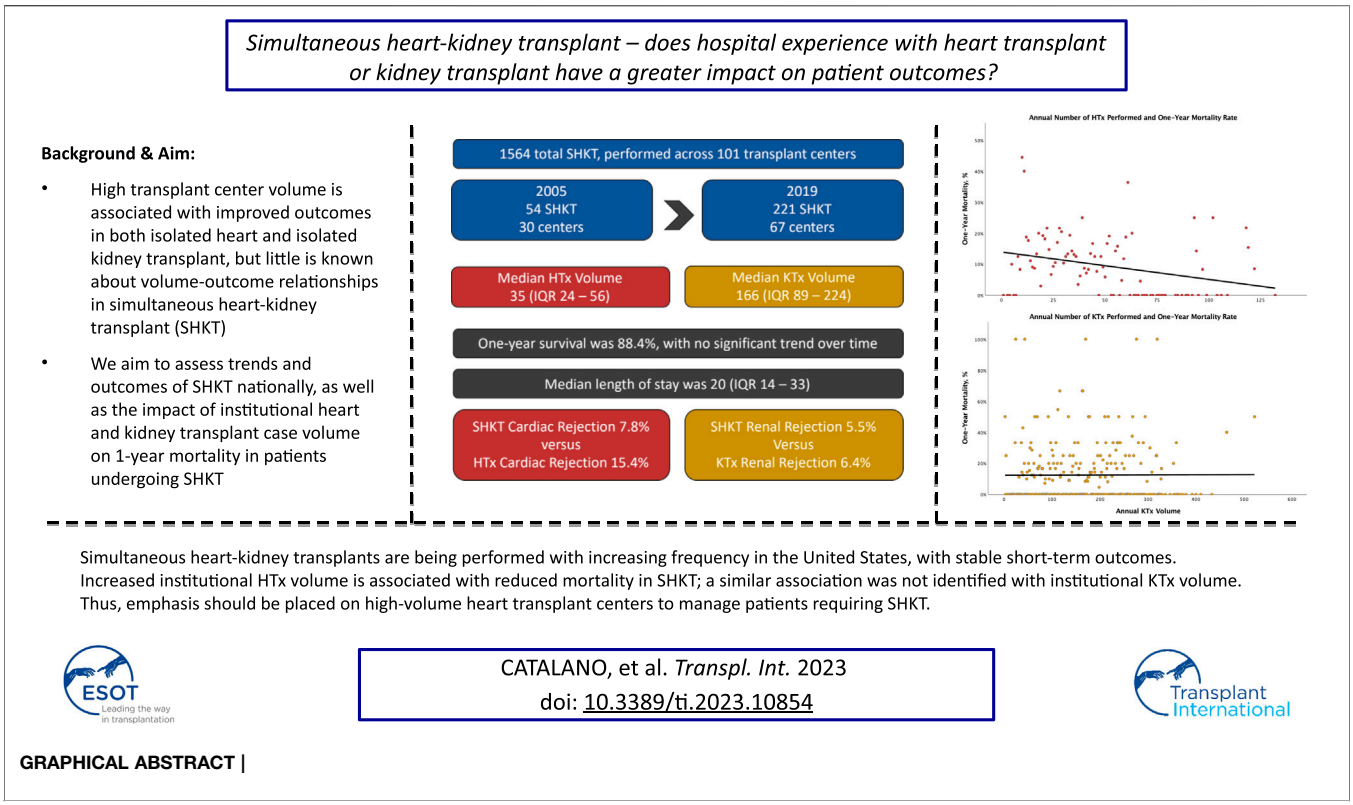
Abbreviations: ECMO, extracorporeal membrane oxygenation; HTx, heart transplant; IABP, intra-aortic balloon pump; KTx, kidney transplant; LVAD, left ventricular assist device; NDDRI, non-dialysis-dependent renal insufficiency; OR, odds-ratio; SHKT, simultaneous heart-kidney transplant; STAR, standard transplant analysis and research; UNOS, United Network for Organ Sharing.



GRAPHICAL ABSTRACT |

INTRODUCTION

Kidney disease and heart disease share common risk factors. Given these shared risk factors, as well as the renal impairment with abnormal hemodynamics associated with heart failure, end-stage heart and kidney disease frequently coexist. For that reason, as well as general overall improvement in organ transplant outcomes, there has been an increase in simultaneous heart-kidney transplant (SHKT) in the United States (1, 2). Small, single-center studies have demonstrated acceptable outcomes for this procedure (3–6), and large, national database studies have revealed improved outcomes relative to isolated heart transplant (HTx) in certain patient populations (1, 7–10). While a number of ethical and clinical questions remain regarding the utilization of SHKT (2, 11), its increasing utilization in the United States warrants further study. Specifically, it is important to assess which institutions may be best suited to care for this unique patient population.

Across surgical subspecialties, institutional experience with surgical procedures is associated with significantly improved clinical outcomes (12–15). This relationship has been demonstrated in both isolated HTx (16–23) and isolated kidney transplant (KTx) (24–28), as well as in lung and liver transplants (24, 29–32). However, little is known about the relationship between surgical volume and outcomes in SHKT.

The aim of this study was to evaluate contemporary trends and outcomes of SHKT nationally and to assess the impact of institutional HTx and KTx case volume on 1-year survival in patients undergoing SHKT.

MATERIALS AND METHODS

A retrospective analysis of the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) files was conducted for the years 2005–2019. This study was deemed exempt from review by an Institutional Review Board as the data provided by UNOS contains no patient identifiers.

In order to understand national trends in transplant volume, we first analyzed the total volume of isolated HTx, isolated KTx, and SHKT in adult patients (≥18 years old) performed in the United States each year. In order to avoid double-counting, SHKT patients were not included in our volume analysis of isolated HTx and KTx.

All adult patients who underwent SHKT were included in our analysis; patients undergoing sequential heart-kidney transplant were excluded. Patient-specific information collected included sex, age at transplant, body mass index (BMI), diabetes, total bilirubin at transplant, creatinine at transplant, and dialysis requirement at listing (as well as an indicator of hemodialysis *versus* peritoneal dialysis) and at transplant. Dialysis requirement was selected as the indicator of renal function to allow for more consistent comparison between patients—creatinine or eGFR measurements may vary significantly based on when drawn. The utilization of cardiovascular support at time of transplant, including extracorporeal membrane oxygenation (ECMO), intraaortic balloon pump (IABP), left-ventricular assist device (LVAD), and inotropic agents was also collected. These variables were utilized as primary indicators of global hemodynamic

compromise. Additionally, hemodynamics at time of transplant—including cardiac output, pulmonary artery pressures, and pulmonary capillary wedge pressures—were assessed; however, the use of quantitative measures of hemodynamics is limited given the possibility of transient fluctuations in these markers that may misrepresent the true overall hemodynamic picture based on when they were captured. Other variables included total days on waitlist, cardiac and renal ischemia time in hours, and age of heart donor.

Institutional experience in isolated heart transplant (HTx), isolated kidney transplant (KTx), and SHKT was assessed as the annual institutional transplant volume, by year. Thus, each institution is assigned a value for HTx volume, KTx volume, and SHKT volume for each year it participated in the dataset. This methodology was used in order to account for the dynamic changes in institutional experience over time, especially those that have recently opened and demonstrated rapid growth.

The primary outcome of interest was 1-year post-transplant survival. Secondary endpoints included length of stay, acute heart transplant rejection episodes requiring treatment within 1 year of transplant, and acute kidney rejection transplant episodes requiring treatment within 1 year of transplant. Length of stay was evaluated as the number of days from transplant to discharge or death. In evaluating 1-year post-transplant survival and rejection episodes requiring treatment, patients undergoing transplant in 2019 were excluded. This step was taken to avoid potential effects on survival of the COVID-19 pandemic in the year 2020.

In order to describe overall trends in utilization, the entire dataset was queried to identify all HTx and KTx over the selected timeframe, as well as changes over time. Trends were also assessed among the selected sample of SHKT. Next, descriptive analysis was conducted for the selected sample, including patient demographics, donor demographics, risk factors, organ ischemia time, and institutional experience. Each of these factors was also assessed as a predictor of 1-year survival in univariate and multivariable analysis. In univariate analysis, the Pearson chi-square test was used to analyze categorical variables, and Student's t-test was used to evaluate continuous variables. In multivariable analysis, binary logistic regressions were conducted, and odds-ratios (OR) and p-values are reported. Multivariable analysis was also conducted to assess predictors of secondary endpoints. Length of stay was assessed using multivariable linear regression, with coefficients and p-values reported. Acute transplant rejection episodes were assessed using binary logistic regression, with OR and p-values reported.

All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC). All P-values were 2-sided with a significance threshold of <0.05. A 95% confidence interval ($p < 0.05$) was defined as statistical significance for all analyses.

RESULTS

Trends in utilization of SHKT, HTx, and KTx are presented in **Figure 1**. Over the study period of 2005–2019, we identified 1564 SHKT, increasing from 54 procedures performed across 30 centers in 2005 to 221 procedures across 67 centers in 2019 (309.3% volume growth). While incidence of isolated HTx (1,841 in 2005, to 3,088 in 2019, 67.7% volume growth) and isolated KTx (16,489 in 2005, to 23,510 in 2019, 42.6% volume growth) also increased over the study period, the magnitude of growth was substantially lower. Utilization of SHKT increased from 2.9% of all heart transplants performed in 2005, to 7.2% in 2019. We observed a 1-year mortality of 11.5% for SHKT, with no significant change over time. Median length of stay was 20.0 days (IQR 14.0–33.0). Cardiac rejection episodes in the first-year post-transplant occurred in 7.8% of SHKT patients (*versus* 15.4% of isolated HTx), and kidney allograft rejection episodes in the first-year post-transplant occurred in 5.5% of SHKT patients (*versus* 6.4% of isolated KTx).

Baseline characteristics for patients undergoing SHKT and institutional transplant volume, and their association with 1-year survival, for the years 2005–2018, are presented in **Table 1**. Across the 1,343 patients, mean recipient age was 54.1 ± 11.5 years; mean donor age was 31.7 ± 11.4 years. Male patients made up 79.1% of the sample. There was no significant association between recipient age or sex and survival in univariate analysis; increasing donor age was associated with decreased survival ($p = 0.019$). Dialysis requirement was observed in 30.0% of patients at listing (including 27.0% of patients on hemodialysis and 3.0% of patients on peritoneal dialysis) and 38.2% of patients at time of transplant. Hemodialysis at listing trended towards an association with reduced survival ($p = 0.076$); any dialysis at transplant was associated with decreased survival ($p < 0.001$). Other patient and transplant factors associated with decreased survival on univariate analysis included elevated total bilirubin ($p < .001$), increased cardiac ischemia time ($p = 0.007$), and increased renal ischemia time ($p = 0.046$).

At the time of transplant, 603 (44.9%) patients were supported by inotropes, 275 (20.5%) were supported by an LVAD, 109 (8.1%) were supported by an IABP, and 17 (1.3%) were supported by ECMO. Utilization of inotropic or mechanical circulatory support was not associated with 1-year survival. While there was no significant association between mechanical circulatory support and survival, elevated pulmonary artery pressures and pulmonary capillary wedge pressures were associated with reduced 1-year survival (**Table 1**).

Median annual institutional HTx volume across the sample of institutions performing SHKT was 35.0 (IQR 24.0–56.0); median annual institutional KTx volume was 166.0 (IQR 89.5–224.0). Centers performing SHKT had greater annual experience with isolated HTx and KTx than centers which did not perform SHKT (**Figure 2**). In 2019, median HTx volume across all institutions was 23, compared to median HTx volume of 32 across institutions performing SHKT. Similarly, median KTx volume across all institutions was 70, compared to median KTx volume of 164 across institutions performing SHKT. On univariate analysis, transplant centers performing a higher volume of annual heart transplants had improved 1-year survial in their SHKT patients (annual volume of 44.2 ± 30.4 in patients who survived, vs. annual volume of 36.4 ± 24.2 in patients who died, $p = 0.002$). There was

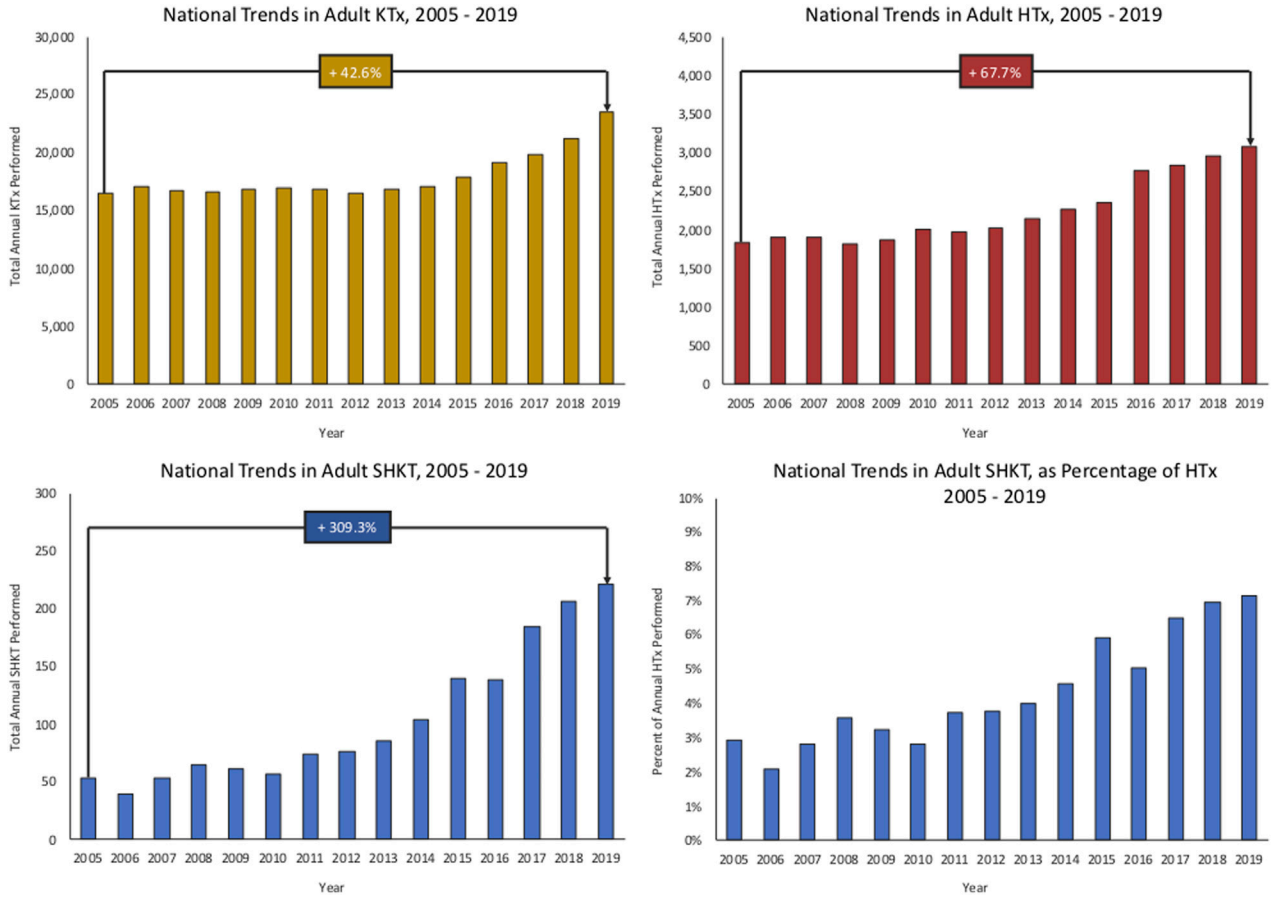


FIGURE 1 | National trends in adult isolated KTx, HTx, SHKT, and SHKT as a proportion of total HTx (2005–2019). HTx, heart transplant; KTx, kidney transplant; SHKT, simultaneous heart-kidney transplant.

no significant association between annual kidney transplant volume and survival (p = 0.121) (**Table 1**).

Multivariable analysis of factors associated with 1-year suvival in SHKT patients is shown in **Table 2**. Increased annual heart transplant volume remained associated with improved 1-year survival (OR 1.12 for every 10 heart transplants, p = 0.004). Other factors associated with decreased 1-year survival included increasing donor age, increasing recipient serum bilirubin, dialysis requirement at transplant, and increasing cardiac ischemia time. Annual kidney transplant volume was not associated with 1-year survival (p = 0.485).

Factors associated with prolonged length of stay after transplant in multivariable analysis included younger transplant recipient age, older heart donor age, higher recipient bilirubin, and longer renal ischemia time (**Table 3**). None of the assessed variables were associated with 1-year cardiac rejection episodes in multivariable analysis (**Table 3**). The presence of dialysis at transplant and reduced cardiac ischemia time was associated with increased risk of 1-year renal rejection episodes (**Table 3**).

DISCUSSION

Our study provides a contemporary assessment of the utilization and outcomes of SHKT, and is the first to assess the impact of institutional experience with HTx and KTx on SHKT outcomes. We identify a continued trend of increased SHKT utilization, increasing 309.3% over 14 years. We also observe a significant association between annual institutional HTx volume and 1-year survival in SHKT patients. A similar association between institutional KTx volume and SHKT outcomes was not observed. Further, we found that dialysis at transplant, increased donor age, increased bilirubin, and prolonged cardiac ischemia time are independently associated with reduced 1-year survival.

Our finding of increased utilization of SHKT, out-of-proportion to the increase in isolated HTx, is consistent with prior studies of SHKT in the United States. Karamlou et al., who assessed SHKT vs. isolated HTx in the United States from 2000–2010, found that national HTx volume increased 3.6% over time, while prevalence of SHKT increased 147% (1). Similarly, Melvinsdottir et al. found that, while staged heart-

TABLE 1 | Baseline characteristics as predictors of survival (2005–2018).

Variable	Total	Died	Survived	P-value
Total (%)	1,343	155 (11.5)	1,188 (88.5)	
Male Sex	1,062 (79.1)	123 (79.4)	939 (79.0)	0.927
Recipient Age, years	54.1 ± 11.5	54.3 ± 11.2	54.0 ± 11.6	0.763
Donor Age, years	31.7 ± 11.4	33.7 ± 11.5	31.4 ± 11.4	0.019
Recipient BMI	26.6 ± 4.9	27.3 ± 5.4	26.5 ± 4.8	0.062
Hemodynamics at Transplant				
Cardiac Output	4.9 ± 1.7	5.0 ± 1.8	4.9 ± 1.6	0.792
PA Systolic Pressure	43.9 ± 13.8	47.0 ± 13.6	43.5 ± 13.8	0.003
PA Diastolic Pressure	21.3 ± 7.9	23.3 ± 7.6	21.0 ± 7.9	0.001
Mean PA Pressure	29.9 ± 9.5	32.3 ± 9.1	29.6 ± 9.5	0.002
PCWP	19.8 ± 8.4	21.3 ± 7.7	19.6 ± 8.4	0.028
Dialysis at Listing				
Hemodialysis	362 (27.0)	51 (32.9)	311 (26.2)	0.076
Peritoneal Dialysis	40 (3.0)	6 (3.9)	34 (2.9)	0.487
Dialysis at Transplant	513 (38.2)	83 (53.5)	430 (36.2)	<0.001
Creatinine at Transplant	3.5 ± 2.6	4.0 ± 3.1	3.4 ± 2.5	0.019
Total Bilirubin, mg/dL	1.2 ± 3.4	2.1 ± 6.7	1.1 ± 2.7	<0.001
Waiting List Days	219.5 ± 351.9	199.3 ± 287.2	222.1 ± 359.6	0.448
Recipient Diabetes	580 (43.2)	72 (46.5)	508 (42.8)	0.382
ECMO at Transplant	17 (1.3)	4 (2.6)	13 (1.1)	0.119
IABP at Transplant	109 (8.1)	17 (11.0)	92 (7.7)	0.166
Inotropes at Transplant	603 (44.9)	61 (39.4)	542 (45.6)	0.140
LVAD at Transplant	275 (20.5)	30 (19.4)	245 (20.6)	0.712
Cardiac Ischemic Time, hours	3.1 ± 1.0	3.3 ± 1.1	3.1 ± 1.0	0.007
Kidney Ischemic Time, hours	14.6 ± 8.2	15.9 ± 8.5	14.4 ± 8.2	0.046
Annual HTx Volume	43.3 ± 29.8	36.4 ± 24.2	44.2 ± 30.4	0.002
Annual KTx Volume	162.8 ± 92.1	152.0 ± 90.4	164.2 ± 92.3	0.121

Pearson chi-square test was used for evaluation of categorical variables, with column percent in parentheses; Student's t-test was used for evaluation of continuous variables. BMI, body mass index; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; ECMO, extracorporeal membrane oxygenation; HTx, heart transplant; IABP, intraaortic balloon pump; KTx, kidney transplant; LVAD, left ventricular asssit device.

kidney transplant utilization has decreased from 1990–2016, SHKT utilization has increased (2). We demonstrate that this trend has continued, as SHKT as a proportion of total HTx has increased from 2.9% in 2005% to 7.2% in 2019. The increase in utilization has likely been influenced by evolving literature demonstrating acceptable outcomes of patients undergoing SHKT. In 1997, Laufer et al. retrospectively assessed the clinical and immunologic outcomes of six patients who underwent SHKT at their institution. With a mean follow-up of 32 months, they identified 100% survival, with no episodes of renal transplant rejection. Further, in a comparison to isolated HTx patients, there was no difference in rates of cardiac rejection (5). Hermsen et al., similarly, reviewed patient and graft survival across 19 SHKTs performed at their institution from 1987–2006, comparing outcomes to isolated HTx, isolated KTx, and staged heart-kidney transplant. They found no difference in patient or graft survival; further, they identified reduced rates of coronary allograft vasculopathy and increased time to graft rejection episodes in SHKT patients, suggesting an immunologic benefit to simultaneous organ transplantation (4). Our finding of reduced cardiac and kidney allograft rejection episodes for SHKT patients, as compared with isolated HTx and KTx, supports this suggested immunologic benefit. Grupper et al., in their 2017 study of 35 SHKT patients, identified survival rates of 97% at 6 months, 91% at 1 year, and 86% at 3 years (3). This 1-year mortality rate of 9% is comparable to our finding of 11.5% 1-year mortality nationally.

As utilization of SHKT continues to increase nationally, it is vital to understand if there are centers that may be better suited to care for this unique patient population. Based on the existence of a volume-outcome relationship in organ transplantation (16–32) and other surgical fields (12–15), our focus was on identifying whether experience with one or both components of this particular multi-organ transplant has an impact on outcomes. Our finding that increased annual HTx volume is associated with improved SHKT survival is consistent with our hypothesis of the existence of a volume-outcome relationship, and it is consistent with prior isolated HTx literature. In their study of isolated HTx in Korea, Nam et al. assessed outcomes in 833 adult transplants across 17 centers, identifying in-hospital mortality of 3.7% in high-volume centers (>20 HTx/year), 10.1% in medium-volume centers (10–20 HTx/year), and 18.6% in low-volume centers (<10 HTx/year). This difference persisted in evaluation of 10-year survival (19). Differences in short-term and long-term HTx patient and graft survival have also been demonstrated using UNOS in both congenital (17, 18) and general adult populations (16, 21–23). In order to understand why a volume-outcome relationship may exist in HTx, Arnaoutakis et al. assessed institutional volume as an effect modifier on the relationship between patient risk and survival. In their analysis, low-volume centers (<7 HTx/year) had increased mortality relative to medium-volume (7–15 HTx/year) and high-volume (>15 HTx/year) centers. However, the difference in mortality was primarily driven by outcomes in high-risk patients; the effect

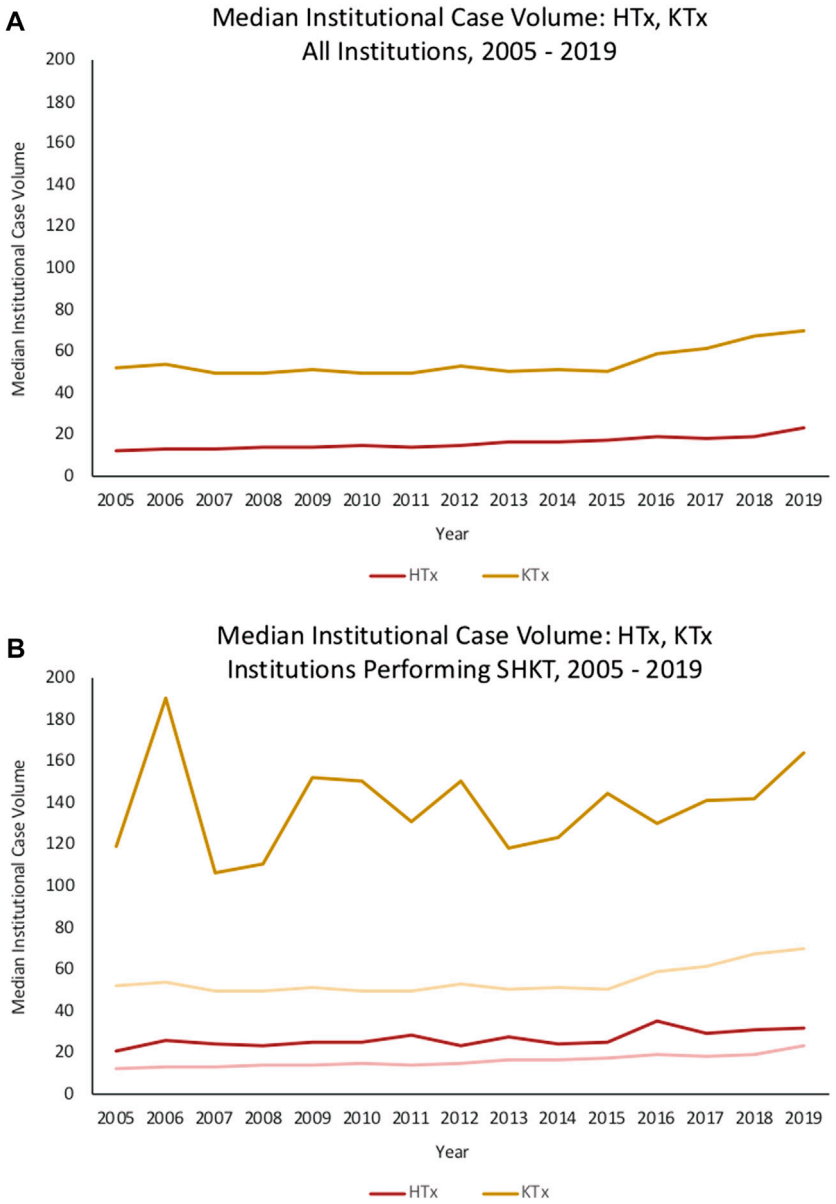


FIGURE 2 | Trends in median institutional case volume for HTx, KTx, and SHKT among **(A)** all institutions in the United States, 2005–2019, and **(B)** only institutions performing SHKT in the United States, 2005–2019. HTx, heart transplant; KTx, kidney transplant; SHKT, simultaneous heart-kidney transplant.

of center volume on outcomes in low-risk patients is minimal (16). This suggests that institutional experience in HTx may primarily play a role in caring for sicker, more complex patients. While we do not quantify risk in our study, SHKT patients tend to carry a greater burden of comorbidities than isolated HTx patients, potentially explaining why a volume-outcome relationship was observed. It is, indeed, possible that lower volume centers included in our sample were transplanting sicker patients; however, despite including comorbidities in our multivariable analysis, case volume remained a significant predictor of post-operative survival, suggesting that experience may be important across all risk groups. Another study that provides insight into the reason that experience in transplant affects outcomes is that by Kilic et al. In their study of isolated lung transplant, they found no association between center volume and occurrence of major post-operative complications. However, they found that in patients who do experience complications, risk of mortality is significantly greater at low-volume centers (29). This, similar to the results of our study, suggests that higher-volume institutions are better equipped to care for the most complex transplant patients.

In contrast to the HTx volume-outcome relationship, we observed no association between institutional isolated KTx experience and SHKT outcomes. This may be rationalized by

TABLE 2 | Multivariable predictors of 1-year survival in SHKT (2005–2018).

Variable	Odds ratio for mortality (95% CI)	p-value
Annual Heart Transplant Volume (+10)	1.12 (1.04–1.21)	0.004
Annual Kidney Transplant Volume (+10)	1.01 (0.99–1.03)	0.485
Recipient Male Sex	1.19 (0.75–1.88)	0.458
Recipient Age (+10)	0.89 (0.74–1.06)	0.221
Donor Age (+10)	0.83 (0.70–0.98)	0.031
Recipient BMI (+5)	0.87 (0.71–1.06)	0.187
Dialysis at Transplant	0.46 (0.31–0.68)	<0.001
Recipient Serum Bilirubin (+0.3)	0.93 (0.90–0.97)	<0.001
Total Days on Waiting List (+30)	1.01 (0.99–1.02)	0.537
Recipient Diabetes	1.08 (0.72–1.61)	0.690
ECMO at Transplant	0.46 (0.13–1.61)	0.228
Intraaortic Balloon Pump at Transplant	0.71 (0.38–1.33)	0.292
Inotropes at Transplant	1.19 (1.78–1.78)	0.370
Left Ventricular Assist Device at Transplant	1.17 (0.71–1.92)	0.534
Cardiac Ischemia Time (+1 h)	0.78 (0.66–0.92)	0.004
Kidney Ischemia Time (+10 h)	0.83 (0.68–1.02)	0.083

BMI, body mass index; ECMO, extracorporeal membrane oxygenation; SHKT, simultaneous heart-kindey transplant.

TABLE 3 | Multivariable predictors of LOS, 1-year HTx rejection, and 1-year KTx rejection (2005–2018).

Variable	LOS[a]		HTx rejection		KTx rejection	
	Coefficient	P	OR	P	OR	P
Annual HTx Volume (+10)	–0.5 (–1.2, 0.1)	0.119	0.95 (0.88, 1.03)	0.210	0.94 (0.85, 1.04)	0.210
Annual KTx Volume (+10)	–0.2 (–0.4, 0.0)	0.055	1.01 (0.99, 1.04)	0.239	1.01 (0.99, 1.04)	0.339
Recipient Male Sex	2.6 (–2.2, 7.3)	0.283	1.09 (0.64, 1.86)	0.750	0.96 (0.52, 1.77)	0.897
Recipient Age (+10)	–2.4 (–4.1, –0.7)	0.007	0.89 (0.74, 1.08)	0.246	0.83 (0.67, 1.04)	0.106
Donor Age (+10)	2.2 (0.4, 3.9)	0.014	1.01 (0.83, 1.22)	0.912	0.97 (0.77, 1.22)	0.793
Recipient BMI (+5)	0.2 (–1.8, 2.2)	0.828	0.92 (0.73, 1.16)	0.474	1.09 (0.84, 1.42)	0.506
Dialysis at Transplant	2.6 (–1.4, 6.6)	0.208	0.99 (0.64, 1.55)	0.976	2.19 (1.32, 3.65)	0.003
Recipient Bilirubin (+0.3)	0.6 (0.2, 1.1)	0.003	1.00 (0.96, 1.05)	0.878	1.00 (0.95, 1.05)	0.993
Days on Waiting List (+30)	–0.1 (–0.3, 0.1)	0.246	1.00 (0.98, 1.02)	0.937	1.02 (1.00, 1.03)	0.082
Recipient Diabetes	3.0 (–1.0, 7.0)	0.141	1.04 (0.66, 1.64)	0.864	1.18 (0.70, 2.02)	0.534
ECMO at Transplant	11.9 (–1.4, 25.3)	0.080	0.70 (0.09, 5.45)	0.733	0.98 (0.12, 7.95)	0.988
IABP at Transplant	–0.5 (–6.4, 5.5)	0.879	0.86 (0.38, 1.93)	0.712	0.57 (0.17, 1.87)	0.353
Inotropes at Transplant	–3.1 (–7.1, 0.9)	0.129	1.11 (0.71, 1.73)	0.646	1.58 (0.93, 2.66)	0.090
LVAD at Transplant	–1.5 (–6.7, 3.8)	0.581	0.79 (0.43, 1.45)	0.450	0.88 (0.43, 1.77)	0.711
HTx Ischemia (+1 h)	–0.5 (–2.4, 1.3)	0.582	1.00 (0.82, 1.22)	0.978	0.73 (0.56, 0.94)	0.016
KTx Ischemia (+10 h)	4.4 (2.1, 6.7)	<0.001	1.09 (0.86, 1.39)	0.461	0.78 (0.56, 1.10)	0.154

[a]*LOS analysis includes patients undergoing SHKT in 2005–2019; 1-year rejection episode analysis includes patients undergoing SHKT in 2005–2018.*
BMI, body mass index; ECMO, extracorporeal membrane oxygenation; HTx, heart transplant; IABP, intraaortic balloon pump; KTx, kidney transplant; LOS, length of stay; LVAD, left ventricular asssit device; OR, odds ratio.

the difference in expected short-term mortality in isolated HTx *versus* isolated KTx—given the substantially greater risk associated with the HTx component of the simultaneous procedure, it can be expected that strong experience with HTx drives outcomes in SHKT. Moreover, center selection bias may play a role. While median annual KTx volume across all institutions in the United States during our study period is approximately 60 KTx/year, the median annual KTx volume among the subset of institutions performing SHKT is 166 KTx/year. Thus, we are already selecting for relatively high-volume KTx institutions, which may explain why differences in volume have less of an impact on outcomes in our select population. The existing literature in isolated KTx also less consistently demonstrates the volume-outcome relationship observed in isolated HTx (28). Axelrod et al. identify a significantly increased risk of mortality and 1-year renal graft loss in isolated KTx at low-volume centers as compared to high-volume centers. On the other hand, Sonnenberg et al. found no association between KTx volume quartile (ranging from Q1 <66 KTx to Q4 >196 KTx) and 3-year graft or patient survival (33).

While we identified a volume-outcome relationship in patient survival, the same relationship was not observed between transplant center experience and 1-year cardiac and renal allograft rejection episodes. Interestingly, however, we did identify a higher rate of cardiac allograft rejection compared to renal allograft rejection among the population of SHKT patients (7.8% *versus* 5.5%); while it is challenging to ascertain

the cause of this difference, one likely explanation is the difference in identification of rejection episodes—while renal allograft may only be identified when clinical signs present, planned endomyocardial biopsies allow for the detection of subclinical rejection episodes. Another interesting finding in multivariable analysis was the significant association between cardiac ischemic time and renal allograft rejection, with prolonged cardiac ischemic time associated with lower rates of renal allograft rejection. Without knowing exactly when each renal allograft implantation began relative to cardiac allograft implantation, this is challenging to explain. However, a common critique of SHKT is that the hemodynamic instability and coagulopathy that occur immediately during and after heart transplant place the renal allograft at significant risk of dysfunction and early rejection. Thus, some advocate for a short period of hemodynamic recovery in the operating room prior to initiation of the renal allograft transplantation. It is, therefore, possible that reduced cardiac allograft ischemic time is associated with a more rapidly performed procedure overall, including rapid renal allograft implantation, greater early exposure of the renal allograft to hemodynamic instability, and greater risk of renal allograft compromise and early graft rejection.

In addition to understanding volume-outcome relationships, we also sought to identify comorbidities associated with 1-year survival. We found that dialysis-dependent patients undergoing SHKT have decreased 1-year survival and increased rates of renal allograft rejection relative to patients not requiring pre-transplant dialysis. Despite the increased risk identified, there is substantial literature that suggests that SHKT provides benefit relative to isolated HTx in patients with the most severe degrees of kidney dysfunction. For instance, Karamlou et al. compared 593 SHKT and 26,183 isolated HTx, assessing the impact of pre-operative renal function on benefit of SHKT relative to isolated HTx. They observed similar overall survival; however, when stratifying by eGFR quintiles, patients in the lowest quintile (eGFR <37 mL/min) undergoing isolated HTx had significantly worse survival than patients undergoing SHKT, suggesting a relative benefit of SHKT (1). The utilization of eGFR as a measure of renal function in UNOS studies is limited by the fact that it is based on a single creatinine measure, often that most proximal to the transplant date. Thus, other studies have attempted to expand upon the association between renal function and SHKT benefit by looking specifically at dialysis-dependence. Gill et al. assessed clinical outcomes in 263 SHKT patients relative to isolated HTx. Overall adjusted risk of death was found to be 44% lower with SHKT compared to isolated HTx, and this difference was driven by dialysis-dependent patients (8). Schaffer et al. compared outcomes of SHKT *versus* isolated HTx in patients with eGFR <50 mL/min, stratified by dialysis-dependence. Five-year posttransplant survival was improved in SHKT patients among dialysis-dependent patients (73% vs. 51%) as well as those with non-dialysis-dependent renal insufficiency (80% vs. 69%) (10). While kidney recovery for patients with non-dialysis-dependent renal insufficiency is possible following isolated HTx, these findings suggest that SHKT may provide a significant survival advantage in this patient population. Thus, while our results highlight that dialysis-dependence represents an independent risk factor for poor outcomes among SHKT patients, there exists strong evidence that SHKT remains beneficial as compared to isolated HTx in dialysis-dependent patients.

Our study is not without limitations. First, this is a retrospective study using a clinical database with inherent limitations. In the evaluation of a clinically complex patient population, nuances in pathology and management may not be captured by the database. Second, our study does not provide insight into why volume-outcome relationships are observed in SHKT. While we identify increased ischemic time as a predictor of decreased survival and high-volume centers are likely to have reduced ischemic times, further explanation is an important area of future study. Third, we do not include sequential heart-kidney transplant patients in our analysis; this is because the volume of sequential heart-kidney transplant is quite low in the United States, the patients undergoing sequential heart-kidney transplant are inherently different than SHKT patients (2), and this patient population has already been quite well described (2). Melvinsdottir et al. identify that sequential heart-kidney transplant may have improved outcomes relative to SHKT; however, they also show that sequential heart-kidney transplant volume in the United States is falling out of favor, with only 6 procedures performed in 2016 (2).

In summary, simultaneous heart-kidney transplants are being performed with increasing frequency in the United States, with stable short-term outcomes. Increased institutional HTx volume, but not KTx volume, is associated with improved 1-year survival in SHKT. Thus, emphasis should be placed on high-volume heart transplant centers to manage patients requiring SHKT.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study, available through the United Network for Organ Sharing (UNOS) and the Organ Procurement and Transplantation Network (OPTN), and they can be found here: https://optn.transplant.hrsa.gov/data/view-data-reports/request-data/.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MC conducted idea conception, data collection and initial analysis, manuscript drafting, and manuscript revision. SP conducted idea conception, manuscript drafting, and manuscript revision. KJ

conducted idea conception and manuscript revision. GS conducted idea conception and manuscript revision. AH conducted idea conception and manuscript revision. P-JY conducted idea conception, data collection and analysis, manuscript drafting, and manuscript revision.

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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Risk Stratification for Hepatitis B Virus Reactivation in Kidney Transplant Recipients With Resolved HBV Infection

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The prophylaxis strategy for hepatitis B virus (HBV) reactivation in kidney transplant recipients (KTRs) with resolved HBV infection remains unclear. In this hospital-based retrospective cohort study, consecutive KTRs with resolved HBV infection were screened from the years 2000 through 2020. After excluding confounding conditions, 212 and 45 patients were respectively recruited into Anti-HBs positive and Anti-HBs negative groups. Cumulative incidences of, and subdistribution hazard ratios (SHRs) for HBV reactivation were analyzed after adjusting the competing risk. During a median 8.3 (mean 8.4 ± 4.9) years of follow-up, the 10-year cumulative incidence of HBV reactivation was significantly higher in Anti-HBs negative group when compared to that in Anti-HBs positive group (15.2%, 95% CI: 3.6–26.7 vs. 1.3%, 95% CI: 0.0–3.0; $p < 0.001$). In multivariable regression analysis, absence of anti-HBs (SHR 14.2, 95% CI: 3.09–65.2; $p < 0.001$) and use of high-dose steroids, i.e., steroid dose ≥20 mg/day of prednisolone equivalent over 4 weeks (SHR 8.96, 95% CI: 1.05–76.2; $p = 0.045$) were independent risk factors related to HBV reactivation. Accordingly, the 10-year cumulative incidence of HBV reactivation occurring in patients with two, one and zero risk factors was 42.7% (95% CI: 0.0–87.1), 7.9% (95% CI: 1.2–14.7) and 0%, respectively ($p < 0.001$). In conclusion, the strategy of HBV antiviral prophylaxis may be defined according to the risk stratification.

Keywords: immunosuppression, renal transplantation, hepatitis B, reversion, antiviral therapy

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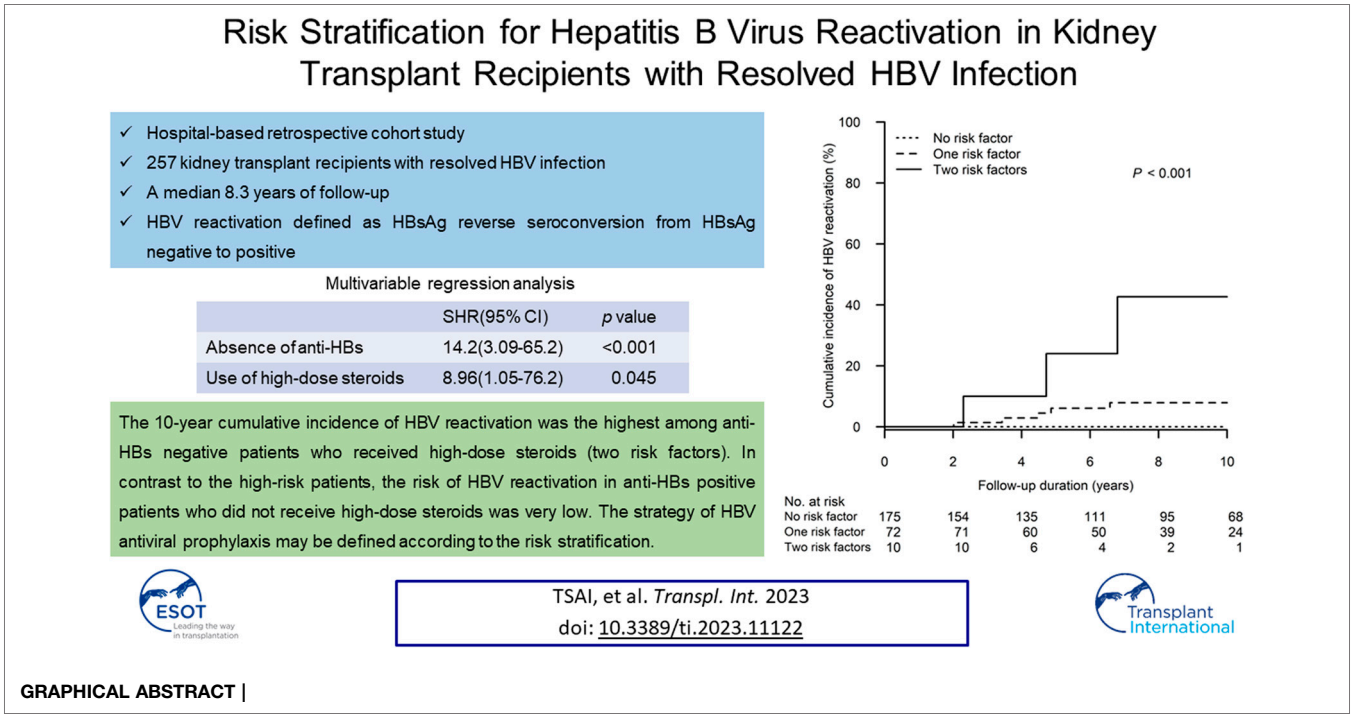
Abbreviations: ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; CI, confidence interval; DNA, deoxyribonucleic acid; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HLA, human leukocyte antigens; IQR, interquartile range; KTRs, kidney transplant recipients; MTP, methylprednisolone; NA, nucleos(t)ide analogue; SHR, subdistribution hazard ratio; ULN, upper limit of normal.



GRAPHICAL ABSTRACT |

INTRODUCTION

Kidney diseases are the leading cause of solid organ transplantation globally, with more than 100,000 patients receiving a kidney transplant per year (1). Although hepatitis B virus (HBV) infection may not directly involve the pathogenesis of kidney diseases, hepatitis B progression can be the major cause of either patient morbidity or mortality after kidney transplantation (2). In kidney transplant patients with chronic HBV infection, immunosuppressive therapy can result in rapid liver fibrosis progression, and patients may in turn die of liver-related complications (2, 3). In patients with resolved HBV infection, i.e., those with positive antibody to hepatitis B core antigen (anti-HBc) but negative hepatitis B surface antigen (HBsAg) in the blood, although the risk of hepatitis B progression is much lower than that in HBsAg-positive patients, HBV may still exist somewhere in the body; e.g., in the nucleus of hepatic cells (4). While the host immune system is suppressed, HBV replication may be reactivated, i.e., the reappearance of HBsAg and HBV deoxyribonucleic acid (DNA) in blood (5). Previous studies have reported that immunosuppressive chemotherapy could induce both severe hepatitis B flare and death in patients with resolved HBV infection (6–8), where nucleos(t)ide analogue (NA) therapy can be considered for patients in the high-risk stratification.

With a high risk of HBV reactivation and liver-related mortality in kidney transplant recipients (KTRs) with chronic HBV infection, i.e., positive HBsAg, life-long prophylactic NA therapy has been recommended in the practice guidelines (9–11). However, with a relatively lower risk of HBV reactivation, ranging from 2% to 9.6% in KTRs with resolved HBV infection (12–18), current guidelines only suggest regular follow-ups, rather than long-term NA therapy prophylaxis (10, 11). However, several clinical studies have observed that the risk of HBV reactivation may be particularly higher in patients with resolved HBV infection, but without antibody to HBsAg (anti-HBs) (6, 19). Although the absence of anti-HBs could be a risk factor for HBV reactivation in KTRs with resolved HBV infection, the role in which other risk factors may play remains largely unknown (12–18).

In previous studies of patients with resolved HBV infection, immunosuppressants could be seen as being strongly related to HBV reactivation (7, 20), however their role in KTRs has not yet been systemically investigated. For example, corticosteroids are commonly used as the backbone of immunosuppression therapy, with a dose ranging from an ultra-high dose of pulse therapy or a high dose of rejection therapy, to low-dose maintenance therapy (21); however, the association between steroid dosages and the risk of HBV reactivation remains unclear. For patients at a high risk of HBV reactivation, severe liver complications may be avoided or prevented. We therefore aimed to conduct a long-term cohort study to assess the timing and severity of HBV reactivation in KTRs with resolved HBV infection, as well as comprehensively analyze any possible risk factors which may be of concern.

PATIENTS AND METHODS

Study Design

This retrospective cohort study was conducted at Taichung Veterans General Hospital (VGHTC), a tertiary medical center

in central Taiwan. Any end-stage renal disease patient who had received kidney transplantation at VGHTC between 1st January 2000 and 31st December 2020 was recruited. The study subjects were followed up for clinical outcomes until 31st December of 2021. The medical records of the study subjects were retrieved for analysis. This study was approved by the Institutional Review Board of VGHTC (CE21059B).

Study Subjects

The patient selection process is shown in **Figure 1**. The inclusion criteria were as follows: 1) KTRs and 2) positive anti-HBc. The exclusion criteria were as follows: 1) positive HBsAg, 2) receiving long-term prophylactic NA therapy, 3) kidney graft failure within 3 months after transplantation, and 4) incomplete essential data. The study subjects were followed up for 10 years or until the dates of 1) HBV reactivation, 2) kidney graft failure, 3) patient mortality, 4) receiving of chemotherapy for a newly diagnosed malignancy, 5) loss follow-up, or 6) 31st December of 2020. According to the positivity of serum anti-HBs before kidney transplantation, patients were recruited into anti-HBs positive or anti-HBs negative group.

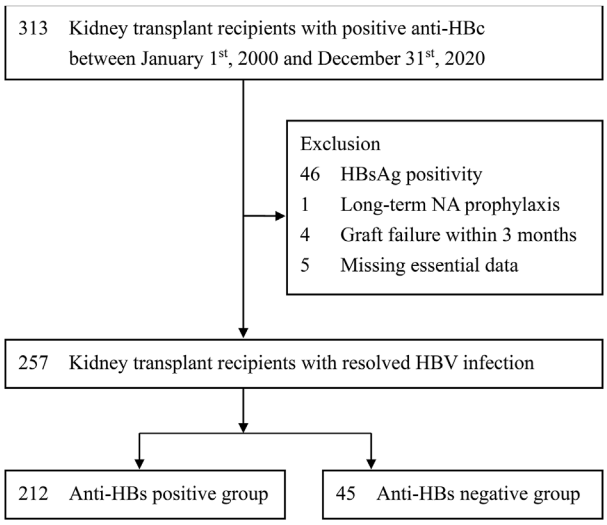


FIGURE 1 | Selection of study subjects. Anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to HBsAg; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide analogue.

HBV Reactivation and Hepatitis Flare

The primary endpoint was HBV reactivation, which was defined as HBsAg reverse seroconversion from HBsAg-negative to HBsAg-positive (10). According to the clinical practice routines in our hospital, periodical surveillance for HBV reactivation was performed after kidney transplantation, i.e., serum ALT every 3 months and serum HBsAg every 6–12 months. In addition, serum HBsAg and HBV DNA would be additionally checked if serum ALT was increased for at least twice the baseline level or above the upper limit of normal (ULN). The secondary endpoints included HBV-associated hepatitis in combination with HBV reactivation and hepatitis flare. Hepatitis flare is defined as alanine aminotransferase (ALT) increase >3 times baseline and >100 U/L (10). Other endpoint, including severe flare, was defined as hepatitis B flare (HBV DNA level >2,000 IU/mL and ALT > 5x the ULN) with jaundice (total bilirubin ≥2 mg/dL), and/or coagulopathy (prothrombin time prolongation ≥3 s) (22). The ULN of ALT was defined according to the updated American Association for the Study of Liver Diseases criteria (>25 U/L for females and >35 U/L for males) (10).

Risk Factors Assessment

The data including blood type ABO incompatibility and human leukocyte antigens (HLA) mismatch numbers were collected. Hepatitis C virus (HCV) co-infection in patients was defined as those who were hepatitis C antibody positive with a detected HCV viral load in their serum. We retrieved the immunosuppressants used during induction (rituximb, basiliximab, thymoglobulin and others), as well as the standard triple agents in maintenance (calcineurin inhibitor, mycophenolate mofetil and corticosteroids). The calcineurin inhibitors included cyclosporine and tacrolimus. The data on sirolimus or everolimus combination with the triple agents used in maintenance was also captured. Steroid therapy is a part of immunosuppressive regimens used for induction, maintenance and anti-rejection therapy. Detailed information regarding steroid therapy, including dosage and duration, was comprehensively obtained from medical records. We converted dosages of various steroid therapies into equivalent doses of prednisolone based on anti-inflammatory potency (23). The average steroid dose was defined as the total amount of steroid dosage used in maintenance divided by the sum of the days of steroid treatment. Peak steroid dose was defined as the maximal steroid dosage which persisted at least 4 weeks in maintenance. We set up three strata of peak steroid dose using prednisolone equivalents as rates of <10 mg/day, 10–19 mg/day and ≥20 mg/day (24). After kidney transplantation, allograft rejection development would be suspected as patients experienced a rising serum creatinine or worsening proteinuria. Acute rejection was defined by the presence of pathologic evidence seen on a kidney allograft biopsy (21). The data on rejection episodes and treatments were collected.

Statistical Analyses

Continuous variables were expressed in median with interquartile ranges (IQRs), while categorical variables were presented as both number and percentage. Continuous variables were compared by the Mann-Whitney U test, while categorical variables were compared through use of either the Chi-square test or Fisher's exact test. Cumulative incidence rates of HBV reactivation or hepatitis flare were calculated and compared by using a Fine-Gray method and Kaplan-Meier method, respectively (25). The differences in the full time-to-event distributions among the study groups were compared by a log-rank test. Renal graft failure or patient mortality before HBV reactivation was treated as a competing event. We further performed univariable analysis to identify any potential risk factors for HBV reactivation, with independent risk factors being

TABLE 1 | Baseline characteristics of study subjects.

	Positive anti-HBs *n* = 212	Negative anti-HBs *n* = 45	*p*-value
Age, years	49.0 (39.5–54.0)	51.5 (47.9–60.5)	0.008
Male, n (%)	112 (52.8)	26 (57.8)	0.660
HCV co-infection, n (%)	16 (7.5)	5 (11.1)	0.622
HBsAg-positive donor, n (%)	23 (10.8)	3 (6.7)	0.587
Positive Anti-HBs donor, n (%)	169 (79.7)	33 (73.3)	0.343
Donor source, n (%)			0.303
Living donor	96 (45.3)	16 (35.6)	
Deceased donor	116 (54.7)	29 (64.6)	
Prior history of renal transplant, n (%)	3 (1.4)	3 (6.7)	0.068
ABO-incompatibility, n (%)	30 (17.9)	7 (15.6)	0.870
HLA mismatch numbers	2 (0.3–3.0)	2 (0.0–3.0)	0.144
Induction therapy, n (%)			0.772
No	51 (26.0)	13 (29.5)	
Rituximab	11 (5.6)	1 (2.3)	
Basiliximab	107 (54.6)	23 (52.3)	
Thymoglobulin	27 (13.8)	7 (15.9)	
NA prophylaxis during induction, n (%)	16 (7.5)	5 (11.1)	0.622
Duration of NA prophylaxis, months	4.2 (0.9–6.5)	5.6 (0.9–7.1)	0.934
Maintenance immunosuppressants, n (%)[a]			0.886
Cyclosporine + MMF + steroids	30 (14.2)	6 (13.3)	
Tacrolimus + MMF + steroids	182 (85.8)	39 (86.7)	
Maintenance steroid[b]			
Average dose, mg/day	6.0 (5.2–7.5)	6.1 (5.1–8.3)	0.545
Peak dose[c]			0.748
<10 mg/day	77 (36.3)	15 (33.3)	
10–19 mg/day	98 (46.2)	20 (44.4)	
≥20 mg/day	37 (17.5)	10 (22.2)	
Sirolimus or everolimus combination, n (%)	96 (45.3)	13 (28.9)	0.064
Acute rejection episodes, n (%)			0.979
No	138 (65.1)	30 (66.7)	
Once	39 (18.4)	8 (17.8)	
≥2 episodes	35 (16.5)	7 (15.6)	
Treatment for acute rejection, n (%)			0.712
Rituximab	12 (16.2)	3 (20.0)	
Methylprednisolone pulse therapy	62 (83.8)	12 (80.0)	

[a]*Major immunosuppressants used in maintenance.*
[b]*Values represent prednisolone equivalents.*
[c]*Peak dose defined as the maximal steroid dosage which persisted ≥4 weeks in maintenance.*
Continuous variables are expressed in median (interquartile range).
Anti-HBs, antibody to HBsAg; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HLA, human leucocyte antigen; MMF, mycophenolate mofetil; NA, nucleos(t)ide analogue.

determined according to the results of multivariable regression analysis. Subdistribution hazard ratios (SHRs) were obtained in Cox proportional hazard models and adjusted on the basis of the subdistribution of the competing risk. The R-package "cmprsk" was used for the purpose of competing risks regression (26). A two-tailed $p < 0.05$ was considered statistically significant. We managed the data using SAS 9.3 software (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Study Subjects

As shown in **Figure 1**, after excluding those with confounding conditions, 257 patients were identified for final analysis. According to the positivity of serum anti-HBs, 212 and 45 patients were respectively recruited into anti-HBs positive and anti-HBs negative groups. As shown in **Table 1**, apart from age, nearly all the baseline patient characteristics do not reveal significant differences between the two study groups. The median age was younger in the anti-HBs positive group than that in the anti-HBs negative group (49.0 vs. 51.5 years). The proportions of other possible risk factors were not significantly different between the two study groups, including gender, HCV co-infection, HBsAg-positive donor, blood type ABO incompatible transplant, HLA mismatch, immunosuppressive regimens, short-term NA prophylaxis during induction, episodes of biopsy proven acute rejection, and treatment for acute rejection. Moreover, we also analyzed the details surrounding steroid use, including average steroid dose and peak steroid dose, which were also similar in the two study groups. The median follow-up duration was 8.3 (IQR, 4.4–11.9) years, with a mean

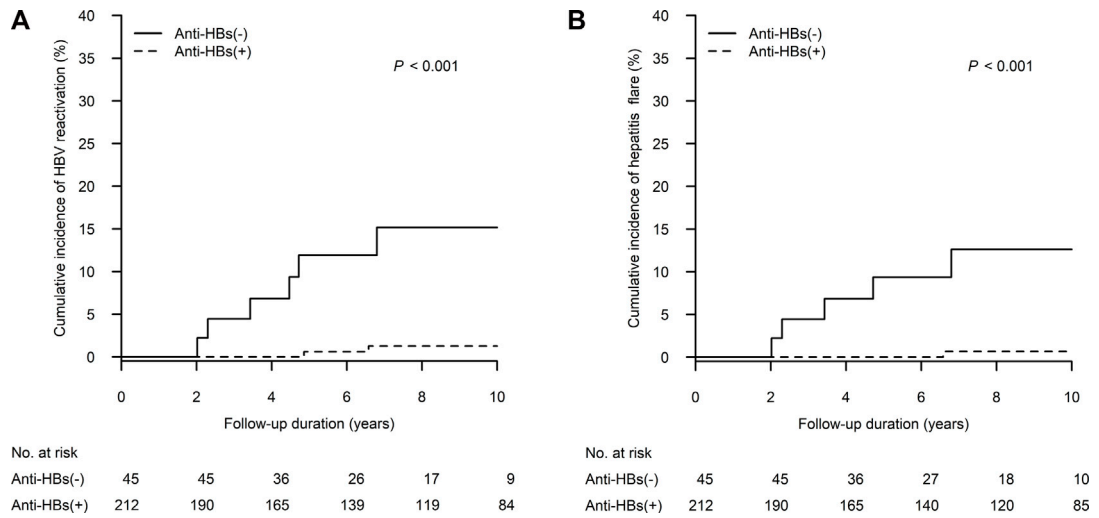


FIGURE 2 | The cumulative incidence of **(A)** HBV reactivation and **(B)** hepatitis flare was higher in patients without anti-HBs than in patients with anti-HBs in competing risks regression. Anti-HBs, antibody to hepatitis B surface antigen; HBV, hepatitis B virus.

TABLE 2 | Characteristics of the patients with HBV reactivation.

No.	Age (years)	Gender	Anti-HBs	Maintenance steroid[a]		Time to HBV reactivation		Data during HBV reactivation					NA therapy	HBsAg loss after NA therapy
				Avg. dose (mg/day)	Peak dose[b] (mg/day)	From transplant (months)	From peak steroid tapering (months)	Steroid dose[a] (mg/day)	HBV DNA (log IU/mL)	Bilirubin[c] (mg/dL)	ALT[c] (U/L)	HbeAg presence		
1	50	F	Neg.	5.6	5	41	5	5	6.20	1.1	118	Neg	LAM	Yes
2	39	M	Neg.	9.1	10	54	12	5	8.04	1.0	61	Pos.	ETV	No
3	59	M	Neg.	5.7	10	24	2	5	3.96	0.8	158	Neg	LAM	Yes
4	48	F	Pos.	7.1	20	79	12	5	7.95	1.7	151	Pos.	ETV	Yes
5	33	F	Pos.	7.9	30	58	1	20	5.96	0.4	52	Pos.	ETV	No
6	51	F	Neg.	7.2	30	82	10	5	6.87	1.1	812	Pos.	ETV	No
7	60	F	Neg.	10.4	20	28	14	5	8.23	0.6	119	Neg	ETV	No
8	48	F	Neg.	7.0	40	57	8	10	6.20	7.9	326	Neg	ETV	No

[a]*Values represent prednisolone equivalents.*

[b]*Peak dose defined as the maximal steroid dosage which persisted ≥4 weeks in maintenance.*

[c]*Peak level during HBV reactivation.*

ALT, alanine aminotransferase; Anti-HBs, antibody to HBsAg; DNA, deoxyribonucleic acid; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LAM, lamivudine; NA, nucleos(t)ide analogue.

duration of 8.4 ± 4.9 years (**Supplementary Figure S1**). The median follow-up duration was not significantly different in the two study groups. (anti-HBs positive vs. anti-HBs negative: 8.8 [IQR: 4.3–10.0] vs. 6.8 [IQR, 4.5–8.6] years; $p = 0.084$).

HBV Reactivation and Hepatitis Flare

As shown in **Figure 2A**, the 10-year cumulative incidence of HBV reactivation was significantly higher in the anti-HBs negative group when compared to that in the anti-HBs positive group (15.2%, 95% confidence interval [CI]: 3.6%–26.7% vs. 1.3%, 95% CI: 0.0–3.0; $p < 0.001$). **Table 2** presents the details of patients experiencing HBV reactivation: six in the anti-HBs negative group and two in the anti-HBs positive group. HBV reactivation happened during the period of 2–6 years after kidney transplant, and often appeared within 1 year after tapering steroid administration from its peak dose. Reappearance of HBsAg also combined with HBV DNA level >2,000 IU/mL and ALT elevation > 2x ULN in all of these patients. Moreover, five anti-HBs negative patients and one anti-HBs positive patient experienced hepatitis flare, which is defined as ALT increase >3 times baseline and >100 U/L (10). Eight patients who developed HBV reactivation were all hepatitis B e antigen (HBeAg) negative at baseline, and three with antibody to HBeAg. Four (4/8; 50%) patients became HBeAg positive during HBV reactivation.

Regarding HBV vaccination, among 47 patients were initially anti-HBs negative prior to kidney transplantation, 14 patients (14/47; 29.8%) received HBV vaccination: Two patients (2/14;

TABLE 3 | Subdistribution hazard ratio of risk factors for HBV reactivation in univariate and multivariate competing-risks regression.

	Univariable analysis			Multivariable Model 1			Multivariable Model 2		
	SHR	**95% CI**	***p*-value**	**SHR**	**95% CI**	***p*-value**	**SHR**	**95% CI**	***p*-value**
Anti-HBs Negative vs. Positive	14.3	(2.97–68.8)	<0.001	13.3	(2.75–64.4)	0.001	14.2	(3.09–65.2)	<0.001
Age per year	1.01	(0.96–1.06)	0.709						
Male vs. Female	0.30	(0.06–1.47)	0.138						
HCV co-infection	N/A[a]	-	-						
HBsAg-positive donor	1.13	(0.14–8.89)	0.904						
Positive Anti-HBs donor	0.53	(0.11–2.65)	0.442						
Living vs. Deceased donor	0.96	(0.23–3.99)	0.961						
Prior history of renal transplant	N/A[a]	-	-						
ABO-incompatibility	0.59	(0.12–2.88)	0.514						
HLA mismatch numbers	0.67	(0.40–1.12)	0.129						
Induction therapy									
No		*ref.*							
Rituximab	N/A[a]	-	-						
Others	2.64	(0.33–21.1)	0.361						
NA prophylaxis during induction	1.96	(0.25–15.2)	0.521						
Maintenance immunosuppressants									
Cyclosporine + MMF + steroids		*ref.*							
Tacrolimus + MMF + steroids	0.60	(0.12–2.93)	0.530						
Maintenance steroid[b]									
Average dose per mg/day	1.13	(1.04–1.23)	0.003	1.12	(1.02–1.23)	0.023			
Peak dose[c]									
<10 mg/day		*ref.*						*ref.*	
10–19 mg/day	1.39	(0.13–15.3)	0.788				1.50	(0.14–16.5)	0.741
≥20 mg/day	8.96	(1.05–76.2)	0.045				9.20	(1.06–79.8)	0.044
Combined sirolimus or everolimus	0.68	(0.16–2.83)	0.596						
Acute rejection episodes									
No rejection		*ref.*							
Once	0.57	(0.07–4.49)	0.589						
≥2 episodes	0.58	(0.07–4.66)	0.609						
Treatment for acute rejection									
No rejection		*ref.*							
Rituximab	N/A[a]	-	-						
MTP pulse therapy	0.71	(0.15–3.44)	0.675						

[a]*No HBV reactivation in patients with HCV co-infection, prior history of renal transplant and administration of rituximab. The associated effects of these factors could not be evaluated in the Cox proportional hazard model for HBV reactivation.*

[b]*Values represent prednisolone equivalents.*

[c]*Peak dose defined as the maximal steroid dosage which persisted ≥4 weeks in maintenance.*

Anti-HBs, antibody to HBsAg; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HLA, human leucocyte antigen; MMF, mycophenolate mofetil; MTP, methylprednisolone; NA, nucleos(t)ide analogue; N/A, not available; SHR, subdistribution hazard ratio.

14.3%) produced durable anti-HBs, and they were thus sorted into the anti-HBs positive group. Only one vaccinated patient (1/14; 7.1%), who failed to produce durable anti-HBs, experienced HBV reactivation after kidney transplantation. In univariable regression analysis for all the initially anti-HBs negative patients, HBV vaccination prior to transplantation was not significantly associated with a lower risk of HBV reactivation (SHR 0.61, 95% CI: 0.07–5.28; $p = 0.656$). The efficacy of HBV vaccination in preventing HBV reactivation might not be sufficiently evaluated due to the limited case numbers in this study.

The 10-year cumulative incidence of hepatitis flare was significantly higher in the anti-HBs negative group when compared to that in the anti-HBs positive group (12.6%, 95% CI: 1.9%–23.3% vs. 0.7%, 95% CI: 0.0–2.0; $p < 0.001$) (**Figure 2B**). Severe hepatitis flare, i.e., jaundice and ALT > 5x ULN (1), was noted in one anti-HBs negative patient. All patients diagnosed with HBV reactivation received NA therapy within 1 month after HBsAg seroreversion. Fortunately, no patient died of hepatic failure. After NA therapy, three patients (37.5%) experienced HBsAg loss again thereafter (1.2, 4 and 8.7 years after their HBV reactivation episodes).

The Risk Factors of HBV Reactivation

As shown in **Table 3**, in univariable regression analysis, a negative anti-HBs status (SHR 14.3, 95% CI: 2.97–68.8; $p < 0.001$), increased average steroid daily dose (SHR 1.13 per mg of prednisolone equivalent, 95% CI: 1.04–1.23; $p = 0.003$), and a peak steroid dose ≥20 mg/day of prednisolone equivalent (SHR 8.96, 95% CI: 1.05–76.2; $p = 0.045$) were associated with the occurrence of HBV reactivation. The peak dose was defined as the maximal steroid dosage which persisted ≥4 weeks in maintenance. Furthermore, in multivariable regression analysis (Model 1), both a negative anti-HBs status (SHR 13.3, 95% CI: 2.75–64.4; $p = 0.001$) and increased average steroid daily dose (SHR 1.12 per mg of prednisolone equivalent, 95% CI: 1.02–1.23; $p = 0.023$) were significantly associated with the development of HBV reactivation. In

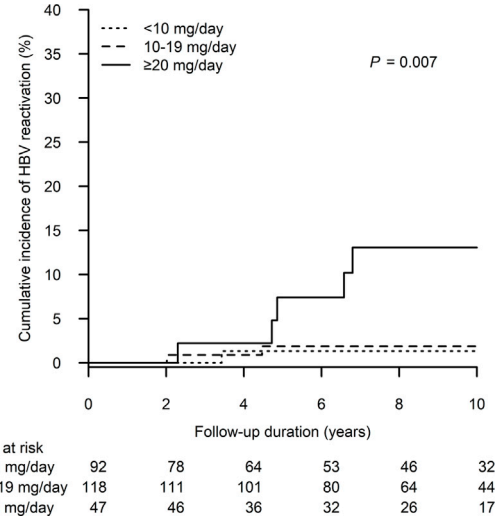


FIGURE 3 | The cumulative incidence of HBV reactivation after kidney transplant according to different peak daily doses of prednisolone, or equivalent. HBV, hepatitis B virus.

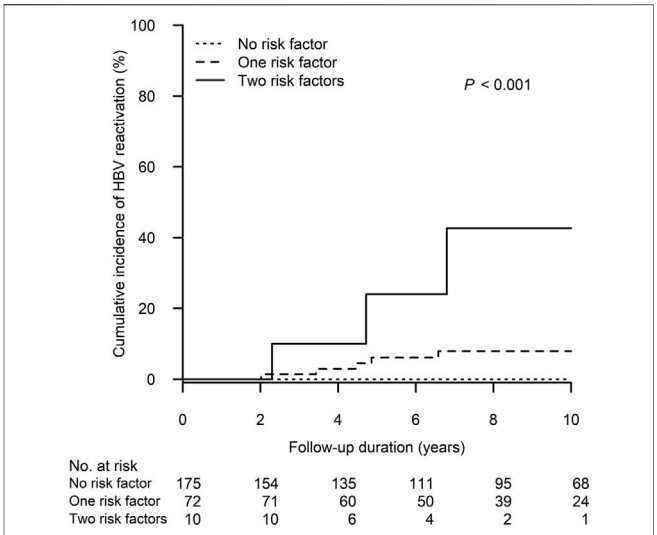


FIGURE 4 | The cumulative incidence of HBV reactivation after kidney transplant in the patient groups stratified by the risk factors of HBV reactivation. The two risk factors are defined as follows (1): absence of baseline serum anti-HBs and (2) high-dose steroids, i.e., a peak steroid dose ≥20 mg/day of prednisolone equivalent which persisted ≥4 weeks in maintenance. HBV, hepatitis B virus.

addition, as shown in Model 2, a negative anti-HBs status (SHR 14.2, 95% CI: 3.09–65.2; $p < 0.001$) and a peak steroid dose ≥20 mg/day of prednisolone equivalent (SHR 9.20, 95% CI: 1.06–79.8; $p = 0.044$) remained the independent risk factors for HBV reactivation.

Figure 3 shows the cumulative incidence of HBV reactivation in the patient groups receiving different peak steroid doses (<10, 10–19 and ≥20 mg/day of prednisolone equivalent for 4 weeks). The 10-year cumulative incidence of HBV reactivation was highest in patients who received high-dose steroids (≥20 vs. 10–19 vs. < 10 mg/day: 13.1%, 95% CI: 2.1%–24.0% vs. 1.9%, 95% CI: 0.0%–4.4% vs. 1.3%, 95% CI: 0.0–4.0, $p = 0.007$). Moreover, as demonstrated in **Figure 4**, we performed a risk stratification based on the independent risk factors of HBV reactivation, i.e., absence of baseline serum anti-HBs and high-dose steroids, and the 10-year cumulative incidence of HBV reactivation occurring in patients with two, one and zero risk factors was 42.7% (95% CI: 0.0–87.1), 7.9% (95% CI: 1.2–14.7) and 0%, respectively ($p < 0.001$).

DISCUSSION

Although HBV reactivation in 1%–10% of cases can be classified as moderate risk (24), the prophylaxis strategy for HBV reactivation in KTRs with resolved HBV infection remains unclear in the current practice guidelines. In the present study, we comprehensively collected the data on immunosuppressants and analyzed the dosages and durations of corticosteroid use. This cohort study is able to provide evidence that the absence of anti-HBs and high-dose steroid use (≥20 mg/day of prednisolone equivalent ≥4 weeks in maintenance) were both independent risk factors associated with HBV reactivation. The cumulative incidence of HBV reactivation will be the highest (>40%) among anti-HBs negative patients who received high-dose steroids, in which case antiviral therapy prophylaxis should be mandatory. In contrast to the high-risk patients, the risk of HBV reactivation in anti-HBs positive patients who did not receive high-dose steroids is very low (0%), therefore a long-term antiviral therapy prophylaxis may be waived. In these low-risk patients, a strategy involving periodic surveillance for HBV reactivation, such as HBsAg testing, may be more cost-effective than NA therapy prophylaxis. The findings of this study may provide an effective and cost-saving strategy in the use of antiviral prophylaxis, which should be valuable to both clinicians and patients.

Similar to the findings in previous studies for KTRs with resolved HBV infection, our study also demonstrates that the absence of baseline serum anti-HBs is a strong risk factor of HBsAg seroreversion after kidney transplantation (12–14). However, other risk factors may be also involved in HBV reactivation (13–15). Although the presence of anti-HBs lowered HBV reactivation risk, the risk is not totally eliminated. For patients with only one risk factor of HBV reactivation, i.e., positive anti-HBs patients who will receive high-dose steroids or negative anti-HBs patients who do not need to use high-dose steroids in this study, NA therapy prophylaxis or close monitoring for HBV reactivation should be considered. However, which strategy is more cost-effective needs further investigated. In addition, the other risk factors found in other similar studies (13–15), including age, ABO-incompatibility, rituximab use, and acute rejection, were not significantly related to HBV reactivation in this study, and their effects should be further clarified in the future studies.

To the best of our knowledge, our cohort is the first study designed to evaluate the effects of steroid therapy on the risk of HBV reactivation in KTRs with resolved HBV infection. Corticosteroids are the most widely used immunosuppressive agents, and a daily

dose above 20 mg for longer than 2 weeks of prednisolone, or its equivalent, is generally considered to induce significant immunosuppression (27). HBV reactivation with active viral replication maybe occur when the host is immune suppressed (5). A systemic review suggested that steroid therapy longer than 4 weeks at a moderate (10–20 mg/day of prednisolone equivalent) or high-dose (>20 mg/day of prednisolone equivalent) may lead to HBV reactivation in 1%–10% of patients resolved HBV infection (24). In a cohort study involving rheumatic patients with resolved HBV infection, individuals experiencing HBsAg seroreversion had been exposed to a daily dose of prednisolone over 20 mg (7). Our analysis demonstrates that receiving a peak steroid dose ≥20 mg/day of prednisolone equivalent ≥4 weeks in maintenance had a major impact on risk of HBV reactivation. In addition, most HBsAg seroreversion and hepatitis flare occurred within 1 year after the tapering off of steroid administration from its peak dose. Host immune may rebound and hepatitis may develop after the withdrawal of immunosuppressants. Therefore, close surveillance of liver biochemistries, HBsAg status and HBV DNA remains essential while steroids are given in a decremental fashion. On the other hand, episodes of methylprednisolone (MTP) pulse therapy for acute rejection did not associate with HBV reactivation. Similar to our previous study for rheumatic patients with resolved HBV infection, maintained high dose oral steroid therapy, rather than short-term ultra-high dose MTP pulse therapy, increased the risk of HBV reactivation (28).

Several commonly used immunosuppressants, such as rituximab, have been evaluated for their HBV reactivation risk in previous studies, but the results remain conflicting (13–16). In studies mainly for hematologic malignancy patients receiving multi-course high-dose rituximab during chemotherapy, rituximab could lead to HBV reactivation in more than 10% of patients with resolved HBV infection (24). However, only a single-dose rituximab may be used for KTRs during induction or acute rejection. In two Japanese studies for KTRs with resolved HBV infection, rituximab was not related to an increased HBV reactivation risk (15, 16). In contrast to two Korean studies, rituximab was identified as a risk factor related to HBV reactivation, and patients might die of hepatic failure (13, 14). In the present study, the case number of rituximab users was limited (12 cases during induction and 15 cases for acute rejection), and HBV reactivation was not found during the follow-up period. However, due to the potentially fatal outcome and long-term effect reported in previous studies, careful surveillance for rituximab users remains required.

While there is insufficient evidence to recommend long-term antiviral prophylaxis for KTRs with resolved HBV infection, a limited duration of NA prophylaxis during the period of induction therapy with intensified immunosuppression may be an alternative option (10). However, the consensus regarding short-term NA prophylaxis has not been made in our hospital. Moreover, NA prophylaxis for KTRs with resolved HBV infection was not reimbursed by the National Health Insurance in Taiwan during the study period, therefore only a minority of KTRs received short-term NA prophylaxis during induction out of pocket. However, NA prophylaxis during induction was not significantly associated with HBV reactivation in our analysis.

Several limitations should be acknowledged with regards to this study. First, this is a retrospective study conducted in a transplant referral center, and some data were not completely collected, such as serum HBV DNA prior to transplantation, serum anti-HBc in donors, and the duration between resolving HBV infection and transplantation. However, the prevalence rate of occult HBV infection in patients with resolved HBV infection was low (29), and no HBV DNA was detected in our limited data. In addition, a Korean study reported that a positive anti-HBc in kidney donors was not related to HBV reactivation (14). With a high prevalence of anti-HBs positivity in Taiwanese donors, we believe that the effect of anti-HBc in donors should be insignificant in our study. A well-designed prospective study should be helpful to address the effects of these factors. Second, the incidence of HBsAg seroreversion may have been underestimated in this retrospective study. In patients without positive HBsAg, HBsAg and HBV DNA are usually performed when hepatitis has been suspected. However, our study demonstrates an increased risk not only for HBV reactivation but also for hepatitis flare; therefore, the conclusion of this study should be convincing. Third, the efficacy of long-term NA prophylaxis for kidney transplant patients with resolved HBV infection remains unclear. Although this study may stratify HBV-resolved patients in high risk of HBV reactivation, i.e., absence of anti-HBs and high-dose steroid maintenance, antiviral therapy prophylaxis cannot be directly recommended. A prospective study involving long-term NA prophylaxis versus periodic surveillance as controls would be valuable towards investigating both the risk of HBV reactivation and whether long-term NA prophylaxis could benefit liver and renal outcome.

In conclusion, the absence of baseline serum anti-HBs and the use of high-dose steroids may result in a higher risk of HBV reactivation in KTRs with resolved HBV infection, and the strategy of antiviral therapy prophylaxis may be defined according to the risk stratification for HBV reactivation.

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 authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Taichung Veterans General Hospital (CE21059B). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

H-JT, C-HC, M-JW, S-SY, Y-HH, Y-ZC, H-RC, and T-YL participated in study design and the performance of the research. H-JT, C-HC, S-SY, Y-HH, Y-ZC, H-RC, and T-YL collected and analyzed data.

H-JT, H-RC, and T-YL participated in writing the manuscript. C-HC, M-JW, S-SY, Y-HH, Y-ZC, H-RC, and T-YL participated in results interpretation and critical review of the manuscript.

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CONFLICT OF INTEREST

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

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2023.11122/full#supplementary-material

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ORIGINAL RESEARCH
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Understanding Health-Related Quality of Life in Kidney Transplant Recipients: The Role of Symptom Experience and Illness Perceptions

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The purpose of our article is to investigate the impact of symptom experience on health related quality of life (HRQOL) in kidney transplant recipients (KTRs) and whether illness perceptions mediated this impact. Symptom experience, illness perceptions, and HRQOL were measured at transplantation and 6 weeks after transplantation in KTRs in an ongoing Dutch cohort study. Multivariable linear regression models were used for the analysis. 90 KTRs were analyzed. Fatigue and lack of energy were the most prevalent and burdensome symptoms at transplantation. Mental HRQOL at 6 weeks after transplantation was comparable to that of the general Dutch population (mean [standard deviation, SD]: 49.9 [10.7]) versus 50.2 [9.2]), while physical HRQOL was significantly lower (38.9 [9.1] versus 50.6 [9.2]). Experiencing more symptoms was associated with lower physical and mental HRQOL, and the corresponding HRQOL reduced by −0.15 (95%CI, −0.31; 0.02) and −0.23 (95%CI, −0.42; −0.04) with each additional symptom. The identified mediation effect suggests that worse symptom experiences could cause more unhelpful illness perceptions and consequently lead to lower HRQOL. Illness perceptions may explain the negative impact of symptom experience on HRQOL. Future studies at later stages after kidney transplantation are needed to further explore the mediation effect of illness perceptions and guide clinical practice to improve HRQOL.

Keywords: kidney transplantation, adult, illness perceptions, health related quality of life, symptom experience

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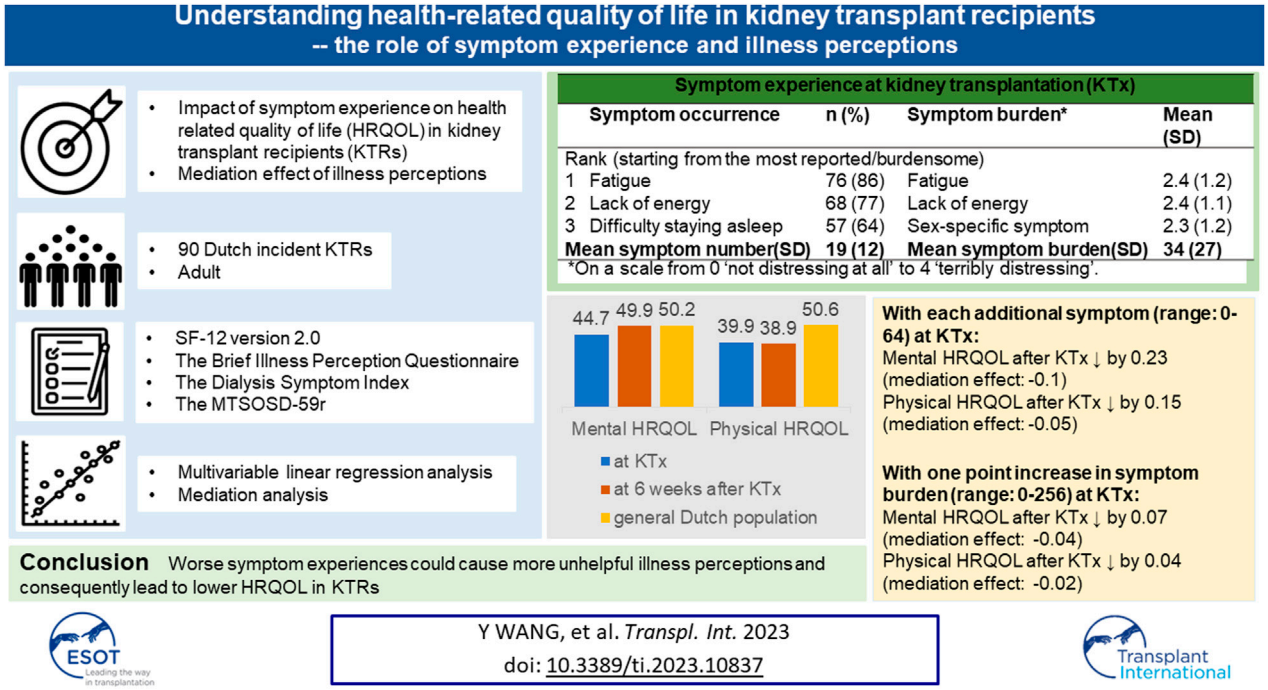
Abbreviations: B-IPQ, the brief illness perception questionnaire; CI, confidence interval; CKD, chronic kidney disease; CSM, Leventhal's common-sense model of self-regulation; DSI, dialysis symptom index; HRQOL, health-related quality of life; KTRs, kidney transplant recipients; LUMC, Leiden University Medical Center; MCS, mental component summary; MUMC, Maastricht University Medical Center; MTSOSD-59r, the modified transplant symptom occurrence and symptom distress scale-59 items revised; PCS, physical component summary; PKD, primary kidney disease; POSITIVE, the Patient-reported Outcomes In kidney Transplant recipients: Input of Valuable Endpoints Study; PROMs, patient-reported outcome measures; SES, socioeconomic status; SD, standard deviation; SF-12, the 12-item short-from health survey; STROBE, the strengthening the reporting of observational studies in epidemiology guideline.



GRAPHICAL ABSTRACT |

INTRODUCTION

In patients with kidney failure, previous studies have shown the benefits of kidney transplantation regarding survival and health-related quality of life (HRQOL) compared to dialysis (1, 2). However, HRQOL after kidney transplantation is lower than that of the general population and healthy controls (1), which suggests room for further improvement. Therefore, it is of clinical interest to explore the risk factors for suboptimal post-transplant HRQOL and identify interventional targets for better health outcomes after kidney transplantation.

One potential risk factor for decreased HRQOL in kidney transplant recipients (KTRs) is the symptom experience, which comprises symptom occurrence and symptom burden. KTRs can experience a large number of symptoms and a high symptom burden due to their primary kidney disease (PKD) and the immunosuppresive treatment after kidney transplantation (3, 4). In patients with advanced chronic kidney disease (CKD) not receiving renal replacement therapy or on dialysis patients, existing evidence suggests an impact of the number of symptoms on HRQOL (5, 6). Previous studies in patients with other chronic conditions support these results and also found an association between high symptom burden and poor HRQOL (7, 8). Following Leventhal's Common-Sense Model (CSM) of self-regulation, we hypothesize that the following mechanism could explain this association between symptom experience and HRQOL: symptoms are perceived as a health threat by patients, who then form cognitive and emotional illness beliefs and expectations about these health threats; these so-called "illness perceptions" shape patient's behavioral and cognitive adjustment to managing their illness (i.e., coping strategy such as adherence to treatment and seeking support) which consequently contribute to health outcomes (**Supplementary Figure S1**) (9–11). Presumably, this could mean that the impact of symptom experience on HRQOL is mediated *via* illness perceptions. Previous research has indeed revealed associations between illness perceptions and various health outcomes (e.g., decline in kidney function and HRQOL) in patients with advanced CKD not receiving renal replacement therapy, dialysis patients and KTRs(12–16). However, to our knowledge, the mediation effect of illness perceptions between symptom experience and HRQOL has not yet been studied in CKD populations (including KTRs).

Therefore, our study explored the effect of symptom experience (i.e., symptom occurrence and burden) at transplantation on HRQOL 6 weeks after transplantation in Dutch incident KTRs (i.e., recently transplanted KTRs in relation to the study) and analyzed whether illness perceptions mediated this effect. Past research has shown that unhelpful illness perceptions are modifiable (17, 18), and hence, it is of clinical interest to understand whether illness perceptions can be a potential interventional target to alleviate the impact of symptom experience on HRQOL, especially in cases where effective treatments for symptoms are lacking.

PATIENTS AND METHODS

The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline was used to guide the reporting of this study (19).

Study Design and Participants

The Patient-reported OutcomeS In kidney Transplant recipients: Input of Valuable Endpoints (POSITIVE) study is an ongoing multicenter cohort study to map patient-reported outcomes (PROs) in Dutch incident KTRs (20). The study was initiated in Leiden University Medical Center (LUMC) in April 2019 and hereafter joined by Maastricht University Medical Center (MUMC) from January 2021 onwards. A signed informed consent form was obtained prior to participation from all participating KTRs. The POSITIVE study was approved by the institutional review board for non-WMO research (i.e., research not subjected to the Medical Research Involving Human Subjects Act) in both centers and complied with the national guidelines for medical scientific research (21). This specific analysis using the POSITIVE data was also approved by the scientific committee of the Clinical Epidemiology Department in LUMC. Patients were invited to participate in this study if they were admitted for kidney transplantation and: 1) were older than 18 years, 2) had no cognitive impairment as determined by patients' medical history or healthcare professionals' opinion, and 3) had sufficient understanding of the Dutch language to complete the questionnaires. The invited patients received information about the study's aim, procedure, and confidentiality; an informed consent form; and a baseline questionnaire. After providing informed consent, patients filled in the first questionnaire during their hospitalization for kidney transplantation. Afterwards, the KTRs received the questionnaires at 6 weeks, 3 months, 6 months, 1 year, and 2 years after kidney transplantation. For the follow-up measurement, an invitation email was sent to patients 1 week before the scheduled time point to fill out the questionnaire and a reminder email was sent if no response was received. The PROs of interest included: HRQOL, symptom experience (i.e., occurrence and burden), and illness perceptions. The estimated average time to finish the questionnaire was approximately 20 min. As the follow-up of the POSITIVE study is still ongoing, this analysis only used the available PROs collected at transplantation (T0) and 6 weeks after kidney transplantation (T1).

HRQOL

Generic HRQOL was measured using the 12-item Short-Form Health Survey version 2 (SF-12 v2), from which the physical component summary (PCS) score and the mental component summary (MCS) score were derived, indicating physical and mental HRQOL, respectively. PCS consists of four domains, namely,: physical functioning, physical role functioning, bodily pain, and general health; and MCS consists of the following four domains: vitality, social role functioning, emotional role functioning, and mental health. The SF-12 v2 has a recall time of 1 week (22). Following the SF-12 scoring algorithm and to facilitate interpretation and comparison with other studies, norm-based scoring was applied using standardization to the US population with a mean of 50 and a standard deviation of 10, with higher scores indicating better HRQOL (23).

Symptom Experience (Occurrence and Burden)

Symptom occurrence and burden were measured using the combination of two questionnaires: Dialysis Symptom Index (DSI) (24) and Modified Transplant Symptom Occurrence and Symptom Distress Scale-59 Items Revised (MTSOSD-59r) (4) to cover both CKD-related and immunosuppressants-related symptoms. The DSI was selected as this questionnaire is—like the SF-12—part of routine Dutch dialysis care and the patient-reported outcome measures (PROMs) registry in nephrology care, hereby facilitating comparison across treatment modalities and different stages of CKD (20, 25). Moreover, previous research supports using the DSI in KTRs (26). As there is a considerable overlap between the DSI and the MTSOSD-59r, we chose to only keep the treatment-related symptoms from the MTSOSD-59r (i.e., Immunosuppression-related side effect). After removing duplicate items, sixty-one symptoms were left in the combined questionnaire, comprising 30 DSI-items and 31 MTSOSD-59r-items, with an open-ended question to add 3 additional symptoms. The occurrence of each symptom was measured using binary response options ("yes" and "no") and a "total number of symptoms" sum score (range: 0–64) was calculated. The burden of each symptom was measured using a 5-point scale ranging from 0 "not distressing at all" to 4 "terribly distressing." A "total symptom burden" sum score (range:0–256) was calculated by adding up the response from all items. The recall time of this combined questionnaire is 1 week.

Illness Perceptions

The following eight illness perceptions were measured using single items on a 0-to-10 response scale using the Brief Illness Perception Questionnaire (Brief-IPQ): consequences, timeline, personal control, treatment control, illness identity, concern, illness coherence, and emotional response (27). Like other studies (14), we omitted illness perception "cause" as the cause of kidney disease is very heterogeneous. We recoded the scores for three illness perceptions (i.e., personal control, treatment control, and illness coherence) to facilitate interpretation so that a higher score always indicated stronger negative illness perceptions. Following the B-IPQ instructions, we calculated an overall score for illness perceptions by adding up the scores of all eight perceptions, resulting in a "total illness perceptions score" ranging from 0 "patients perceive their kidney disease as a benign condition" to 80 "patients perceive their kidney disease as a threatening condition" (28, 29). The Cronbach's alpha value of the total illness perceptions score in our study population was 0.7, indicating a good and sufficient internal consistency to use this total illness perceptions score (22).

Covariates

Patients' demographic and clinical characteristics at transplantation were retrieved from their medical records, including age at transplantation, sex, socioeconomic status (SES), PKD, comorbidities, and donor type. The SES of study participants was obtained by linking the four digits of their postcode with the latest SES scores reported by the

Netherlands Institute for Social Research. The postcode was considered a proxy of patients SES covering income, educational background and position in the labor market (30). PKD included four categories following the European Renal Association codes: glomerulonephritis, diabetes mellitus, hypertension or renal vascular disease, and other PKDs (31). Comorbidities were defined based on a history of cardiovascular events, cerebrovascular events, and diabetes mellitus. Donor type included living and deceased donors.

Statistical Analysis

Continuous variables were presented as mean with standard deviation (SD) or median with interquartile range (IQR) depending on their distribution. Categorical variables were presented as counts (percentages). This analysis used symptom experience (i.e., occurrence and burden) measured at T0 and illness perceptions and HRQOL measured at T1 to achieve a temporal sequence of the variables being studied. Patients who responded at T0 and T1 were included in the analysis. HRQOL scores at T1 were calculated and compared to HRQOL at T0 and HRQOL of the general Dutch population (32). The means of the number of symptoms and symptom burden were calculated. A "top 10" list of symptoms in terms of occurrence and burden was presented to describe the symptom experience in the study population at transplantation.

Multivariable linear regression analysis was used to test the impact of symptom occurrence and symptom burden on both physical and mental HRQOL separately and also to conduct the mediation analysis while adjusting for potential baseline confounders. The hypothesized exposure-outcome, exposure-mediator, and mediator-outcome confounders were structured using Directed Acyclic Graphs (**Supplementary Figure S2**) and included: age, sex, SES, PKD, donor type, and comorbidities. The mediation analysis was conducted using "the product method" with the total illness perceptions score as a mediator (33). The indirect effect, also called the mediation effect, was calculated by multiplying the beta-coefficient (β1) of symptom occurrence or symptom burden when regressing the total illness perceptions score on symptom occurrence or symptom burden, and the beta-coefficient (β2) of the total illness perceptions score when regressing the physical or mental HRQOL on the total illness perceptions score; the total effect equals the sum of the direct effect (β3) and indirect effect (β1*β2) and refers to the impact of symptom occurrence or burden on physical or mental HRQOL (**Figure 1**) (33). Bootstrapping method was used to calculate the 95% confidence interval (CI) of the mediation effect using the PROCESS macro for SPSS software (34). The exposure-mediator interaction was checked for the mediation analysis.

Missing values were considered missing at random and were imputed with 10-folds multiple imputation (35). The mediation effects in each imputed dataset were pooled using the package "miWQS" following Rubin's rule in R version 3.6.1. Given the relatively high percentages of missing values in comorbidities and the relatively small sample size, we conducted our main analysis with and without including comorbidities in the multivariable models.

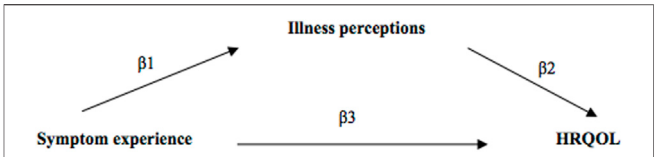


FIGURE 1 | Hypothesized pathways of the mediation effect of illness perceptions between symptom experience and HRQOL.

To test the robustness of our results, we conducted two sensitivity analyses: a complete case analysis and analyses with symptom experience measured using the DSI-items and the remaining MTSOSD-59R-items as patients may not have immunosuppressant-related symptoms at transplantation. Finally, baseline characteristics of study participants and non-participants were tabulated to explore the representativeness of our study population. We used SPSS software version 25.0. (IBM, Armonk, NY, United Sates) for all analyses if not indicated otherwise. Statistical significance was determined by a p-value <0.05 or when the 95% CI did not contain the null-effect value of "zero."

RESULTS

Patient Characteristics

Of the 156 KTRs included in our study at transplantation (T0), 90 KTRs (58%) responded at 6 weeks after kidney transplantation (T1) and were included in the main analysis. One patient deceased before the measurement at T1, and 65 (42%) patients did not respond to the follow-up questionnaires (**Figure 2**). The average time (SD) between the measurement at T0 and T1 was 5.6 (1.9) weeks. The clinical and demographic characteristics of the study population are presented in **Table 1**. Our population had an average age of 52.5 years (SD, 13.8), 36% were female, 66% received a living donor kidney transplantation, and glomerulonephritis was the most common PKD. Compared to the responders at 6 weeks, non-responders were more likely to have a deceased donor, diabetes mellitus as PKD or comorbidity, and a history of cardiovascular events (**Table 1**). The participants and non-participants of the study were similar in the following characeristics: age, sex and donor type. Compared to participants, more non-participants had a low SES and diabetes mellitus as PKD and comorbidity (**Supplementary Table S1**).

Symptom Experience at Kidney Transplantation

The mean number of symptoms (SD) reported by KTRs at T0 was 19 (12) on a 0–64 scale, and the mean symptom burden (SD) was 34 (27) on a 0–256 scale. **Table 2** shows the 10 most frequently reported and the most burdensome symptoms. The two ranks had an overlap in the following symptoms: fatigue, lack of energy, difficulty falling asleep, difficulty staying asleep, and decreased appetite. Sex-specific symptoms (i.e., erection problem in males and menstrual problem in females) and difficulty becoming

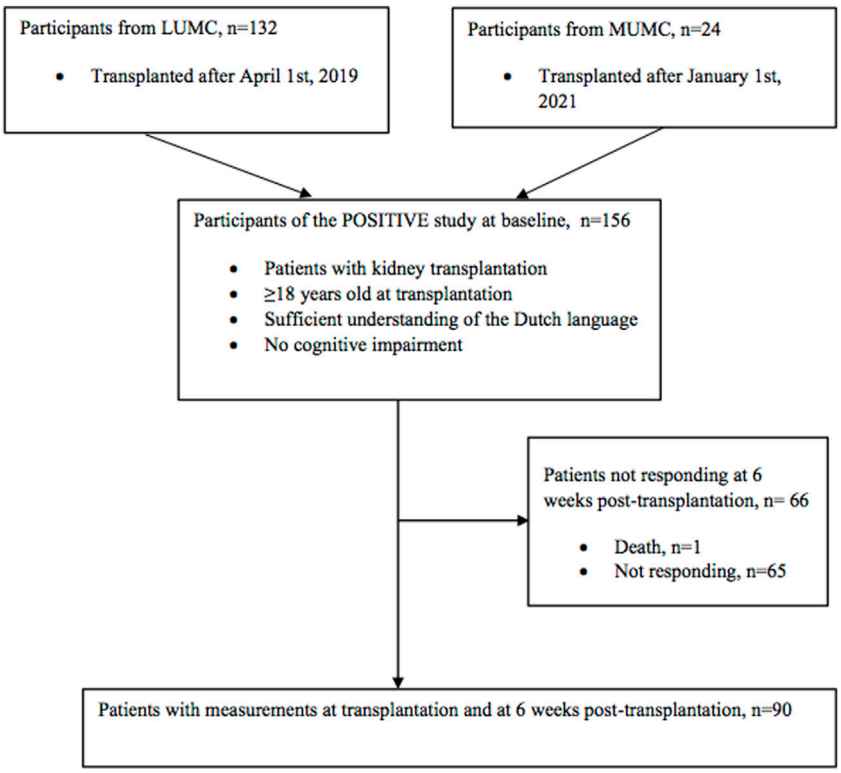


FIGURE 2 | Flow chart of the study population.

sexually aroused had a lower rank in occurrence but were considered very burdensome. **Supplementary Figure S3** shows the occurrence and the mean burden of individual symptoms at T0.

HRQOL at 6 Weeks After Kidney Transplantation

KTRs at T2 reported a mental HRQOL (mean [SD]; 49.9 [10.7]) which was significantly higher than at T0 (44.7 [10.7]) and similar to the general Dutch population (50.2 [9.2]). Physical HRQOL (38.9 [9.1]) was similar to that reported at T0 (39.9 [9.6]) but significantly lower than the general Dutch population (50.6 [9.2]) (**Table 3**) (32). Scores of the HRQOL-domains *general health*, *vitality*, and *mental health* increased on average by 8.0 (13.0), 6.0(12.9), and 4.1 (12.7) compared to the scores at T0, indicating better general health, more energy, and less mental distress in KTRs at T1; the score for *bodily pain* reduced by −5.2 (11.9), indicating a larger influence of bodily pain on routine activities at T1. No significant changes were found in the other four HRQOL-domains (i.e., *physical function*, *role physical*, *social functioning*, and *role emotional*).

Illness Perceptions at 6 Weeks After Kidney Transplantation

The individual and total mean (SD) illness perceptions scores reported by KTRs at T1 are shown in **Table 4**. Individual illness perceptions scores were measured on a scale from 0-to-10 (27). The study population reported a good understanding of their kidney disease (*illness coherence*; 1.9 [2.0]). They considered their kidney disease a chronic condition (*timeline*; 7.6 [3.4]) that negatively influences their life (*consequence*; 6.2 [3.0]). They reported a moderate level of worrying (*concern*; 4.8 [2.8]) and emotional distress due to their kidney disease (*emotional response*; 3.2 [2.7]). They believed that a moderate amount of symptoms can be attributed to their kidney disease (*illness identity*; 4.5 [2.9]), and they believed to a great extent that the treatment they receive (e.g., kidney transplantation) can effectively control their kidney disease (*treatment control*; 1.8 [2.2]), but to a lesser extent that they can control the disease themselves (*personal control*; 3.8 [2.5]). The mean total illness perceptions score (SD) was 34.1 (12.3) on a scale from 0-to-80, indicating that patients perceived their kidney disease as a threatening condition at a moderate level.

Impact of Symptom Experience on HRQOL After Kidney Transplantation

Table 5 presents the impact of KTRs' symptom experience at T0 on their physical and mental HRQOL at T1 (i.e., total effect) and the mediation effect of illness perceptions (i.e., indirect effect). The unadjusted analyses showed that mental and physical HRQOL reduced by −0.17 (95%CI: −0.33, −0.01) and −0.24 (95%CI: −0.42, −0.05) with each additional

TABLE 1 | Clinical and demographic characteristics of the study population.

Characteristics	T0 (*n* = 156)	Responders at T1 (*n* = 90)	Non-responders at T1 (*n* = 66)
Mean age (SD)	53.3 (13.5)	52.5 (13.8)	54.3 (13.0)
Female, n (%)	56 (36)	32 (36)	24 (36)
SES, n (%)			
Low	25 (16)	14 (16)	11 (17)
Middle	103 (66)	61 (68)	42 (64)
High	26 (17)	15 (17)	11 (17)
Primary kidney disease, n (%)			
Diabetes mellitus	29 (19)	15 (17)	14 (21)
Glomerulonephritis	36 (23)	23 (26)	13 (18)
Renal vascular disease	18 (12)	12 (13)	6 (9)
Other diseases	71 (46)	40 (44)	31 (47)
Donor type, n (%)			
Living donor	89 (57)	59 (66)	30 (46)
Deceased donor	65 (42)	31 (34)	34 (52)
Comorbidities, n (%)[a]			
Diabetes mellitus	18 (12)	8 (9)	10 (15)
Cardiovascular event	24 (15)	7 (8)	17 (26)
Cerebrovascular event	8 (5)	5 (6)	3 (5)

[a]*Missing values: diabetes mellitus, cardiovascular event, cerebrovascular event (baseline: 37.8%, 32.1%, 32.1%; responders: 36.7%, 33.3%, 33.3%.; non-responders: 39.4%, 30.3%, 30.3%). Non-responders had 2% missing values in age, SES, primary kidney disease and donor type. Abbreviations: SES, socioeconomic status; SD, standard deviation.*

TABLE 2 | Symptom experience (symptom occurrence and symptom burden) of the study population at T0 (*n* = 90).

	Symptom occurrence	n (%)	Symptom burden	Mean (SD)
Rank (starting from the most reported/burdensome)				
1	Fatigue	76 (86)	Fatigue	2.4 (1.2)
2	Lack of energy	68 (77)	Lack of energy	2.4 (1.1)
3	Difficulty staying asleep	57 (64)	Sex-specific symptom[a]	2.3 (1.2)
4	Increased urge to urinate at night	56 (63)	Difficulty falling asleep	2.2 (1.1)
5	Difficulty falling asleep	47 (53)	Decreased appetite	2.2 (1.2)
6	Decreased appetite	42 (47)	Sweat more	2.1 (1.2)
7	Flatulence	42 (47)	Difficulty staying asleep	2.0 (1.1)
8	Memory problems	42 (47)	Muscle weakness	2.0 (0.9)
9	Difficulty concentrating	41 (47)	Restless legs	2.0 (1.0)
10	Dry skin	41 (46)	Difficulty becoming sexually aroused	2.0 (1.1)
Total score, mean (SD)		19 (12)	Total score, mean(SD)	34 (27)

[a]*Erection problem in males and menstrual problem in females. Five patients with more than 5 missing values in their symptom checklist were excluded from the descriptive statistics in the table. Abbreviations: SD, standard deviation.*

symptom, respectively. After adjusting for potential baseline confounders with and without comorbidities, the decline in mental HRQOL with each additional symptom remained statistically significant and was −0.23 (95%CI: −0.42, −0.04) and −0.24 (95%CI: −0.42, −0.05), respectively. The unadjusted and adjusted analysis showed a statistically insignificant decrease in mental and physical HRQOL with an increase in symptom burden.

Mediation Effect of Illness Perceptions

The unadjusted mediation effect of illness perceptions was −0.07 (95%CI: −0.13, −0.01) between the number of symptoms and physical HRQOL; −0.14 (95%CI: −0.25, −0.04) between the number of symptoms and mental HRQOL; −0.03 (95%CI: −0.05, −0.003) between symptom burden and physical HRQOL; and −0.06 (95% CI: −0.10, −0.01) between symptom burden and physical HRQOL (**Table 5**). The negative mediation effects indicate corresponding reductions in HRQOL due to the increased strength of negative illness perceptions following each additional symptom or each point increase in symptom burden score. After adjustment with or without comorbidities, β-coefficients remained similar or slightly changed; the 95%CI became broader than the unadjusted results with the upper confidence limit larger than but close to the no-effect value of "zero."

Sensitivity Analysis

Results from the complete case analysis (*n* = 87) and the analyses with symptom experience measured using the DSI-items and the rest of the items, supported results from the main analysis (**Supplementary Tables S2–S4**).

TABLE 3 | HRQOL at T0 and T1 in comparison to the Dutch general population.

HRQOL score[a]	At T0 (*n* = 82)	At T1 (*n* = 89)	Dutch GP (*n* = 2013) (32)	Mean difference between different time points or groups					
				T1-T0	*p*-value[b]	Dutch GP-T0	*p*-value[c]	Dutch GP- T1	*p*-value[c]
PF	41.0 (11.3)	40.2 (10.9)	—	–0.6 (12.0)	0.63	—	—	—	—
RP	36.2 (10.1)	36.3 (8.7)	—	0.1 (10.6)	0.92	—	—	—	—
BP	49.6 (10.5)	44.1 (11.4)	—	–5.2 (11.9)	<0.001	—	—	—	—
GH	36.6 (11.1)	44.6 (10.3)	—	8.0 (13.3)	<0.001	—	—	—	—
VT	43.7 (10.4)	49.5 (10.9)	—	6.0 (12.9)	<0.001	—	—	—	—
SF	38.6 (13.9)	40.5 (12.2)	—	2.1 (16.5)	0.25	—	—	—	—
RE	40.4 (12.8)	42.7 (11.5)	—	2.7 (14.0)	0.08	—	—	—	—
MH	48.7 (10.7)	52.5 (10.5)	—	4.1 (12.7)	0.01	—	—	—	—
PCS	39.9 (9.6)	38.9 (9.1)	50.6 (9.2)	−1.2 (9.5)	0.28	10.7 (1.0)	<0.001	11.7 (1.0)	<0.001
MCS	44.7 (10.7)	49.9 (10.7)	50.2 (9.2)	5.7 (12.5)	<0.001	5.5 (1.0)	<0.001	0.3 (1.0)	0.76

Abbreviations: BP, bodily pain; GH, general health; GP, general population; KT, kidney transplantation; MCS, mental component scale; MH, mental health; PCS, physical component scale; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; VT, vitality.

[a]*All HRQOL scores and their mean differences were reported as mean and standard deviation.*

[b]*The p-value was calculated using paired sample t-test, and 82 patients without missing values in the 12-item Short Form Survey at KT and 6 weeks after KT were included for this comparison.*

[c]*The p-value was calculated using independent sample t-test.*

TABLE 4 | Illness perceptions of the study population at T1 (*n* = 90).

Illness perception	Mean (SD)	A higher score indicates patients believe to a greater extent that…
Consequences	6.2 (3.0)	their kidney disease has more negative consequences upon their life
Timeline	7.6 (3.4)	their kidney disease lasts for a longer time
Personal control	3.8 (2.5)	their kidney disease cannot be effectively controlled by themselves
Treatment control	1.8 (2.2)	their kidney disease cannot be effectively controlled by their treatment
Illness identity	4.5 (2.9)	their kidney disease causes more symptoms
Concern	4.8 (2.8)	their kidney disease causes greater worries about their health
Illness coherence	1.9 (2.0)	they do not understand their kidney disease
Emotional response	3.6 (2.7)	their kidney disease causes more emotional distress
Total score[a]	34.1 (12.3)	their kidney disease is a more threatening condition

[a]*Total score was measured on a 0-to-80 scale and the domain scores on a 0-to-10 scale. One patient with missing values in the illness perception questionnaire was excluded from the descriptive statistics. Abbreviations: SD, standard deviation.*

DISCUSSION

Our study showed a considerable number of symptoms and a moderate level of symptom burden at transplantation in Dutch KTRs. Mental HRQOL 6 weeks after kidney transplantation was higher than HRQOL at transplantation and became comparable to HRQOL in the general Dutch population, whereas physical HRQOL remained unchanged compared to HRQOL at transplantation and was significantly lower than HRQOL in the general Dutch population. The number of symptoms had a significant effect on mental HRQOL and a borderline significant effect on physical HRQOL, while the effect of symptom burden on HRQOL was small and not significant. Furthermore, our results suggest that illness perceptions mediate the effects of symptom experience on both mental and physical HRQOL in KTRs in the short term after kidney transplantation.

Our study population experienced, on average, nineteen out of sixty-four symptoms at transplantation. The number of symptoms in our study is larger than seven out of twenty-six detected by a study in prevalent KTRs in the UK (3) and ten out of thirty in Dutch dialysis patients (25). The proportions of symptoms reported by patients could be considered similar in the three studies, suggesting that these patient groups may experience a comparable number of symptoms. However, no solid conclusion can be drawn as different questionnaires were used. Notably, the most frequently experienced symptoms in our study were similar to those from the previous studies, with the top three being identical, namely,: fatigue, lack of energy, and sleep problems (3, 25). Fatigue and lack of energy were also the most burdensome symptoms in our study population, as well as prevalent KTRs in the UK (3).

KTRs in our study had similar mental HRQOL but lower physical HRQOL at 6 weeks after transplantation than the general Dutch population (32). Previous studies have reported similar results in KTRs (36, 37). KTRs 6 weeks after transplantation had similar physical HRQOL and improved mental HRQOL than themselves at transplantation. The stable physical HRQOL can be a trade-off between improved general health and increased impact of bodily pain on daily activities that is most likely due to the recent surgical procedure. The improved mental HRQOL in our study population was a result of the improvement in the domains *vitality* and *mental health* after transplantation, suggesting that KTRs became more energetic and had less mental distress. Previous studies echo this finding showing

TABLE 5 | Impact of symptom experience at T0 on HRQOL at T1 and the mediation effect of illness perception (n = 90).

	Estimates	Crude β (95%CI)	*p*-value	Adjusted β (95%CI)[a]	*p*-value	Adjusted β (95%CI)[b]	*p*-value
Number of symptoms and HRQOL							
PCS	Total effect[c]	−0.17 (−0.33, −0.01)	0.04	−0.16 (−0.32, 0.01)	0.06	−0.15 (−0.31, 0.02)	0.09
	Direct effect	−0.10 (−0.26, 0.06)	0.20	−0.08 (−0.24, 0.09)	0.35	−0.09 (−0.26, 0.07)	0.27
	Indirect effect	−0.07 (−0.13, −0.01)		−0.06 (−0.13, 0.003)		−0.05 (−0.12, 0.01)	
MCS	Total effect	−0.24 (−0.42, −0.05)	0.01	−0.24 (−0.42, −0.05)	0.01	−0.23 (−0.42, −0.04)	0.02
	Direct effect	−0.10 (−0.26, 0.07)	0.25	−0.13 (−0.28, 0.03)	0.12	−0.13 (−0.19, 0.03)	0.11
	Indirect effect	−0.14 (−0.25, −0.04)		−0.11 (−0.22, 0.004)		−0.10 (−0.21, 0.01)	
Symptom burden and HRQOL							
PCS	Total effect	−0.06 (−0.12, 0.02)	0.12	−0.05 (−0.12, 0.02)	0.19	−0.04 (−0.12, 0.03)	0.26
	Direct effect	−0.03 (−0.10, 0.04)	0.44	−0.02 (−0.09, 0.05)	0.50	−0.02 (−0.09, 0.05)	0.56
	Indirect effect	−0.03 (−0.05, −0.003)		−0.03 (−0.05, 0.002)		−0.02 (−0.05, 0.01)	
MCS	Total effect	−0.07 (−0.15, 0.01)	0.08	−0.07 (−0.15, 0.01)	0.10	−0.07 (−0.15, 0.02)	0.11
	Direct effect	−0.02 (−0.09, 0.05)	0.63	−0.02 (−0.09, 0.04)	0.49	−0.03 (−0.10, 0.04)	0.45
	Indirect effect	−0.06 (−0.10, −0.01)		−0.04 (−0.09, 0.003)		−0.04 (−0.08, 0.04)	

The p-values of the interaction term between symptom experience and illness perceptions ranged from 0.13 to 0.98. Abbreviations: CI, confidence interval; HRQOL, health-related quality of life; MCS, mental component scale; PCS, physical component scale; RR, risk ratio; SD, standard deviation.

[a]*The adjusted variables include age, sex, SES, primary kidney disease, and donor type.*

[b]*The adjusted variables include age, sex, SES, primary kidney disease donor type, and comorbidities.*

[c]*The total effect is the sum of the direct and indirect effects.*

more physical activities and less depressive symptoms in KTRs than dialysis patients (38, 39).

Our study population believed to a moderate extent that their kidney disease is a threatening condition. Specifically, patients believed to a great extent that they understand their kidney disease and that their treatment can control their kidney disease. However, patients also believed to a great extent that their kidney disease has many negative consequences upon their lives. The separate illness perceptions scores in our study population are comparable to those in another Dutch KTRs cohort, except for *illness identity*: our study population reported a higher score, indicating that patients attributed more symptoms to their kidney disease (40). This difference could be explained by the different time after kidney transplantation when the measurements were conducted and the 14% more KTRs with deceased donors in our study population who are more likely to have comorbidities (40, 41).

Our analysis indicates that the number of symptoms impacted HRQOL in KTRs. This finding is in accordance with results from a previous study in Dutch CKD patients prior to kidney replacement therapy, showing lower HRQOL in patients with more symptoms(5). The impact on HRQOL with each increment in symptom burden score was statistically insignificant, which is most likely due to our small sample size. Furthermore, our analysis revealed mediation effects of illness perceptions with 0 being the upper limit of its 95% CI after adjustment without comorbidities. Based on literature (42) and the significant mediation effects in the complete case analysis consisting 97% of the study population (**Supplementary Table S2**), our results could indicate that worse symptom experience (i.e., more symptoms or a higher symptom burden) at transplantation leads to unhelpful illness perceptions, which consequently leads to lower HRQOL after kidney transplantation. A previous study found the same mechanism in Dutch patients with irritable bowel syndrome (43). After adjusting for comorbidities, the mediation effects remained similar or became slightly smaller. However, the 95% CI became wider due to our relatively small sample size and the large percentage of missing values in comorbidities despite being imputed. Future studies with a larger sample size are necessary to confirm our findings.

Our results suggest the potential benefit of active symptom management among KTRs regarding HRQOL. Actively treating symptoms requires structural identification of patients' symptom experience. Studies have shown positive results of clinically implementing symptom-checklists for this purpose (25, 44). Moreover, our findings support the use of Leventhal's CSM of self-regulation (9) to explain the impact of symptom experience on HRQOL in KTRs and suggest the potential of illness perceptions as interventional targets to reduce the impact of symptom experience on HRQOL. Please note that we measured HRQOL 6 weeks after transplantation; patients' HRQOL during the first 6 weeks could be influenced by many other factors (e.g., surgery-related complications or withdrawal of dialysis), which could diminish the impact of symptom experience at transplantation on HRQOL 6 weeks after transplantation. Despite the relatively small impact of symptom experience on HRQOL detected in our analysis, our results suggest a mediation effect of illness perceptions, and we speculate that the impact is larger in KTRs at a more stable stage for the reason mentioned above. Therefore, modifying unhelpful illness perceptions could potentially alleviate the negative influence of symptom experience in HRQOL to a greater extent in stable patients. Furthermore, unhelpful illness perceptions are common and identified as important risk factors for health outcomes among patients in different CKD stages, including HRQOL, kidney function, or graft function (12, 14, 15). Moreover, past research has shown that unhelpful illness perceptions are modifiable by means of psycho-educational support strategies and can lead to improved coping behaviors and health outcomes (17, 18, 45). Future studies

in KTRs are needed to: 1) further explore the role of illness perceptions in the relationship between symptom experience and HRQOL at a stable stage to provide further information for clinical practice, 2) explore the mediation effect of individual illness perceptions to provide more precise intervention targets, and 3) explore whether support strategies targeting unhelpful perceptions indeed lead to improved outcomes.

Our study has several strengths. First, our study generates new insights into patient-reported outcomes shortly after kidney transplantation. Second, our study is the first to explore the potential mechanism of the impact of symptom experience on HRQOL in KTRs and herein examine the potential of modifying illness perceptions in order to improve impaired HRQOL due to symptoms. Third, our longitudinal study is more appropriate to evaluate the influence of symptom experience on HRQOL than a cross-sectional study. Our study also has limitations. First, as mentioned above, a number of factors can influence patients' HRQOL shortly after transplantation, and the impact of symptom experience at transplantation on HRQOL may not be dominant. Data with regard to surgery-related complications and lifestyle change (e.g., dialysis withdrawal) may be collected in future study to better explain the HRQOL change in this period. Nevertheless, we detected a significant impact of symptom number on HRQOL. However, our sample size was most likely insufficient to detect the relatively small effect of symptom burden on HRQOL. Please note that the symptom burden score ranges from 0 to 256, which still has the potential to influence HRQOL largely despite a small effect of one increment in symptom burden score on HRQOL. Second, the percentage of non-responders at 6 weeks after kidney transplantation was relatively high (42.3%), which could influence the representativeness of our study population or introduce selection bias. The non-responders in our study were older and had more often diabetes as PKD, more comorbidities, and more often deceased donors. Finally, this observational study cannot prove causality. In addition, due to the limited sample size, we did not adjust all factors that were suggestive of patient's health at transplantation, such as time on dialysis or preemptive transplantation or not. Instead, donor type was adjusted and considered a proxy for these factors, which could cause residual confounding.

In conclusion, symptom experience at transplantation can influence HRQOL shortly after kidney transplantation, and this influence is partially mediated by patients' illness perceptions, suggesting the potential benefit of active symptom management and modifying patients' unhelpful perceptions in optimizing post-transplant HRQOL. Future studies in KTRs at different stages after kidney transplantation are needed to confirm our findings.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the data are collected for this specific study. Requests to access the datasets should be directed to FD, f.w.dekker@lumc.nl.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by institutional review board for non-WMO research of Leiden University Medical Center and Maastricht University Medical Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YW: concept/design, analysis, interpretation, and drafting article; PV: concept/design, data collection, interpretation, and critical review of the article; MH: concept/design, data collection, interpretation, and critical review of the article; FD: concept/design, analysis, interpretation, critical review of the article and supervision; AD: concept/design, data collection, interpretation, critical review of the article and supervision; YM: concept/design, analysis, interpretation, critical review of the article, and supervision.

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CONFLICT OF INTEREST

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

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2023.10837/full#supplementary-material

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BRIEF RESEARCH REPORT
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Application Effectiveness of Segment IV Portal Vein Reconstruction for Early Postoperative Liver Function Recovery in Split Liver Transplantation

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The objective of this study was to investigate the significance of portal vein reconstruction in segment IV of the liver on early postoperative liver function recovery in split liver transplantation. The clinical data of patients of right trilobe split liver transplantation in our center were analyzed and divided into two groups, including a group without portal vein reconstruction and a group with portal vein reconstruction. Clinical data of alanine aminotransferase (ALT), aspartate transaminase (AST), albumin (ALB), creatinine (Cr), total bilirubin (TB), alkaline phosphatase (ALP), gamma-glutamyl Transferase (GGT), lactic acid (Lac), and international normalized ratio (INR) levels were analyzed. The technique of segment IV portal vein reconstruction is beneficial to the early postoperative recovery of liver function. Statistically, there was no significant effect of portal vein reconstruction in the IV segment of the liver on the recovery of liver function within 1 week after split liver transplantation. There was no significant difference in survival rate between the control group and reconstruction group over the 6 months follow-up period after surgery.

Keywords: liver transplantation, donors, split, liver function, portal reconstruction

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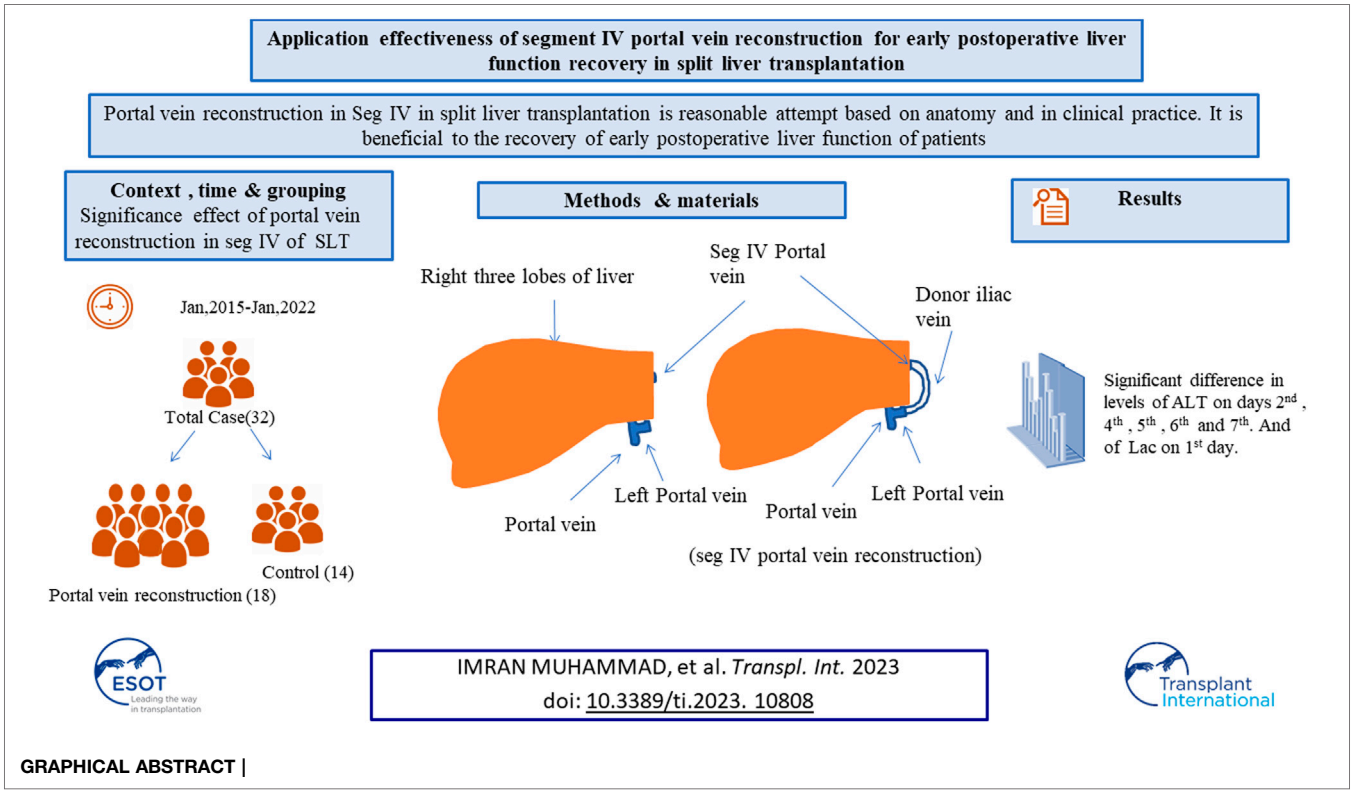
Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; Cr, creatinine; DBD, donation after brainstem death; GGT, gamma-glutamyl transferase; GRWR, graft weight/recipient weight; ICU, intensive care unit; INR, international normalized ratio; Lac, lactic acid; MELD, model for end-stage liver disease; TB, total bilirubin.



GRAPHICAL ABSTRACT |

INTRODUCTION

Since the first liver transplant was performed, with the continuous advancement of surgical techniques, extensive development, and clinical application of various new immunosuppressants, liver transplantation has become the most effective means of treating various end-stage liver diseases (1). Successful transplantation of a reduced volume liver to children, and right/left hemi-split liver transplantation performed on two adults have also been documented in the literature (2, 3). Expanding the source of donor livers has always been a major problem to be solved. According to statistics, the development of split liver transplantation can increase the number of donor livers, so it has become an important way for experts in the field of liver transplantation to solve the shortage of donor livers (4). In split liver transplantation, one donor liver is transplanted to two recipients, thereby expanding the source of donor livers.

There is no statistically significant difference in the graft and recipient survival rates at 1 year for those who have had whole liver transplantation and those who have undergone adult split liver transplantation (5, 6). In experienced transplantation institutions, split liver transplantation has a similar impact to whole liver transplantation, and its survival rate is comparable (7–9). The selection of donors and recipients is critical to the success of split liver transplantation. The ideal donor for splitting is someone who is young, has normal liver enzymes, hemodynamically stable, has no history of liver illness, and has a brief hospital stay (10, 11). Different donor splitting criteria have been suggested in previous studies, and they differ across nations and transplant institutions (12, 13).

A team disclosed two separate *in situ* split techniques for the fabrication of split grafts acceptable for two adult patients. In order to enhance the arterial supply to segment IV, they retain the common portal vein and the common hepatic duct with the right graft and the celiac axis with the left graft (14, 15). Another group released an evaluation, this time they described distinct anatomic situations following dissection of the portal subdivisions to segment IV, exposing the left hilar plate beneath the left portal vein, and surgery of the biliary ducts from segments II and III for traditional split liver transplantation (16).

In our center, the donor iliac blood vessels are used to bridge the partial segment IV portal vein branches that have been severed, thereby preserving the portal vein blood supply of the segment IV liver, ensuring functional liver volume, and improving the transplant rate of split liver transplantation. Our center's exploration of portal vein reconstruction in segment IV liver for split liver transplantation is a reasonable attempt based on anatomy, and it is beneficial in clinical practice to the recovery of early postoperative liver function of patients.

PATIENTS AND METHODS

This was a single center study, and after the necessary approval, the medical records of all patients who underwent split liver

transplant were obtained. During the study from January 2015 to January 2022, a total of 32 cases of split liver transplant were obtained in which right trefoil hepatic portal vein reconstruction was carried out in 18 cases, and non-reconstruction of hepatic portal vein segment IV made up 14 cases and the general information of patients is shown in **Table 1**. In split liver transplantation, blood vessel splitting and distribution are the key to the success or failure of the operation. The choice of middle hepatic vein during left and right liver splitting is determined according to the situation of the two recipients before operation. Our center has made a series of improvements to the *invivo* split liver transplantation technology, especially the intraoperative vascular reconstruction. This mainly includes reconstruction of the segment IV portal vein after left lateral lobe and right trilobe splitting, left and right half liver splitting, reconstruction of middle hepatic vein after splitting, and formation of posterior vena cava and portal vein after splitting. The vascular materials required for reconstruction mainly come from donor iliac vessels and all of above discussed procedures are shown in **Figures 1A–D**.

Donor and Recipient Criteria

Recipients received right hemihepatic and right trilobular liver transplantation in our center if they met the following inclusion criteria: 1) Indications for liver transplantation with no contraindications; 2) preoperative Model for end-stage liver disease (MELD) score <30 points(17); 3) Graft weight/recipient weight (GRWR) ≥ 1.2% in adult recipients and 2%–4% in pediatric recipients (18); 4) No history of multiple abdominal surgeries and the donor also needed to have met the Milan recommendation criteria (19). The donor selection criteria included: 1) age <55 years; 2) hemodynamically stable, no need for high dose escalation maintenance with antidepressants (dopamine ≤5 mg/kg·min, dobutamine ≤10 mg/kg·min, no epinephrine or norepinephrine); 3) Intensive care unit (ICU) Hospitalization days <5 days; 4) aspartate transaminase (AST) and alanine aminotransferase (ALT) values lower than two times the normal value; 5) no fatty liver manifestations under the naked eye, if liver biopsy is performed, fatty infiltration moisture <20%; 6) Serum sodium <155 mmol/L. All donor livers which were cardiac-death organ donations were signed by immediate family members, and organ donation consent was given. All recipients signed the patient's informed consent approved by the hospital ethics committee, in line with medical ethics regulations.

Grouping and Observation Metrics

Of 32 patients, those who did not undergo portal vein reconstruction were included in the control group, consisting of 14 cases in total, and the 18 patients who underwent portal vein reconstruction were included in the reconstruction group. From the first to seventh days after the operation, ALT, AST, albumin (ALB), creatinine (Cr), total bilirubin (TB), alkaline phosphatase (ALP), gamma-glutamyl Transferase (GGT), lactic acid (Lac), and international normalized ratio (INR) level data were collected to analyze the significance of portal vein reconstruction of donor liver segment IV in patients with early postoperative liver function recovery.

Statistical Methods

STATA statistical software was used for data processing, normally distributed measurement data were expressed as mean ± standard deviation, and *t*-test was used for independent samples. The reconstruction group was compared with the control group. Data with a *p*-value of less than 0.05 were considered statistically significant.

TABLE 1 | General information of control and reconstruction group.

	Control	Reconstruction	t/x2	*p*-value
Male	5	10	—	—
Female	9	8	—	—
Total	14	18	—	—
Age (Mean)Yrs	50.0 ± 12.48	50.66 ± 14.45	–0.667	0.8918
Height	162.57 ± 9.13	167.22 ± 7.90	0.1333	–4.651
Weight	57.28 ± 13.04	64.27 ± 9.55	–6.992*	0.0901
BMI	21.38 ± 3.25	22.93 ± 2.52	–1.548	0.1458
MELD Score (Points)†	16.42 ± 8.38	10.84 ± 6.62	5.584**	0.0475
Intraoperative conditions				
Weight of graft	1207.28 ± 267.69	1238.55 ± 198.14	31.270	0.7066
ALT/g	0.472 ± 0.276	0.413 ± 0.242	–0.059	0.5227
AST/g	0.714 ± 0.421	0.723 ± 0.354	0.009	0.9481
Operation time (min)	677.85 ± 122.65	603.611 ± 85.40	74.246*	0.0546
Anhepatic time (min)	52.21 ± 13.26	54.333 ± 16.60	–2.119	0.7071
Cold ischemia (min)	300.14 ± 21.46	302.50 ± 47.15	–2.357	0.8878
Blood transfusion RBC(U)	12.64 ± 5.57	9.05 ± 3.83	3.587*	0.0575
Postoperative recovery				
ICU (days)	4.78 ± 1.57	4.66 ± 1.64	0.119	0.8376
Postoperative hospital stay	36.28 ± 19.18	32.38 ± 7.88	3.897	0.4394

*** , ** and * shows the level of significance at 1%, 5% and 10%, respectively.

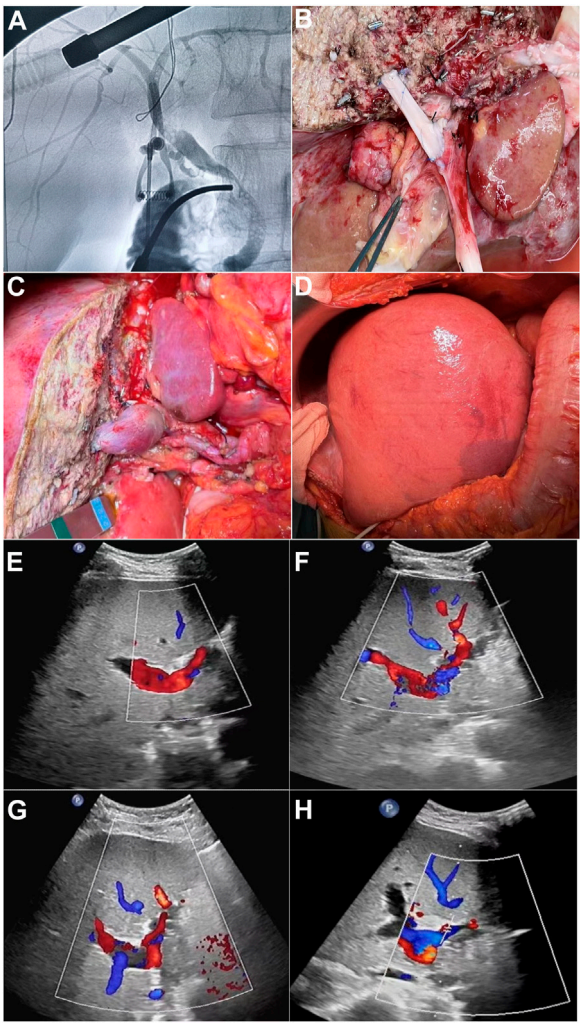


FIGURE 1 | (A) Pre-splitting cholangiography of liver parenchyma. **(B)** Segment IV portal vein reconstruction before blood flow. **(C)** Segment IV portal vein reconstruction after blood flow. **(D)** After surgery/portal vein reconstruction, right three lobes. **(E–H)** Postoperative ultrasound images of segment IV portal vein bridging vessels of days 1, 3, 5, and 7, respectively.

RESULTS

Comparison of Postoperative Data of Recipients in the Reconstruction and Control Groups

There was a statistically significant difference between the control and reconstruction groups in the levels of ALT on days 2, 4, 5, 6, and 7 after surgery, and in the levels of Lac on day 1 after surgery, but there was no statistically significant difference in AST, ALB, Cr, TB, ALP, GGT, and INR as determined by a comparison of data which is shown in **Table 2**.

Significance of Portal Vein Reconstruction of Donor Liver Segment IV on Early Postoperative Liver Function Recovery

Judging from the recovery of various indicators of the recipients in the two groups after surgery, the recovery of liver function in the reconstruction group was significantly better than that in the control group. No serious bleeding, biliary fistula, or other complications occurred in the two groups of recipients after operation. In the control group, 14 recipients did not undergo segment IV hepatic portal vein reconstruction, and the segment IV liver was insufficiently perfused. Ultrasonography indicated that segment IV liver atrophy and necrosis occurred earlier, and early postoperative liver function recovery was poor. The postoperative ultrasound of the 18 recipients in the reconstruction group showed blood flow through the reconstructed vessels of the portal vein in the recipients within 1 week after surgery, the speed of IV segment liver atrophy was significantly slower than that of the control group, and the postoperative liver function recovered faster. It can be seen that intraoperative reconstruction of the portal vein of the donor liver segment IV can effectively reduce the damage of hepatocytes, preserve more functional liver tissue, and promote the early postoperative liver function recovery of patients, thereby improving the prognosis of patients and restoring blood recirculation, which is shown in **Figures 1E–H**.

Survival Analysis

We compared the 6-month data to calculate the survival rate between these two groups.

The 6-month rate in the Control group and Reconstruction group was [85.7% vs. 94.4%] with an overall 90.6% rate of survival. There was no significant difference in survival rate between these two groups is shown in the **Figure 2**.

DISCUSSION

The development of split liver transplant was prompted by a lack of organs and rising morbidity on waiting lists. The gap between organ supply and recipient demand has never been wider than it is today. This has rekindled interest in expanding the use of traditional adult/pediatric split liver transplant and adult/adult split liver transplant. At centers that routinely use these techniques, split liver transplant applied to pediatric recipients offers good results, with considerable decreases in pediatric wait times, wait-list morbidity, and living-donation utilization, according to a decade of experience with left lateral segment grafts (20, 21). Split liver transplantation, as the most difficult liver transplantation technology, comprehensively embodies this feature from the preoperative evaluation of the general conditions of donors and recipients, to the distribution of blood vessels including hepatic artery, portal vein, inferior vena cava, and hepatic vein and biliary tract. The splitting of

TABLE 2 | Postoperative data comparison.

	Control	Value	Reconstruction	Value	t/x2	*p*-value
Postoperative ALT comparison (U/L)						
ALT1	14	942.50 ± 574.05	18	741.94 ± 235.13	200.556	0.1875
ALT2	14	759.42 ± 502.56	18	546.83 ± 149.02	212.595*	0.0980
ALT3	14	495.42 ± 292.19	18	374.88 ± 161.88	120.540	0.1478
ALT4	14	353.69 ± 196.94	18	240.88 ± 79.73	112.803**	0.0434
ALT5	14	231.92 ± 128.51	18	145.33 ± 73.50	86.595**	0.0226
ALT6	14	186.41 ± 101.71	18	106.16 ± 66.38	80.250**	0.0136
ALT7	14	117.46 ± 50.02	18	80.83 ± 55.75	36.628*	0.0785
Postoperative Lac comparison (mmol/L)						
Lac1	14	2.00 ± 1.36	18	3.17 ± 1.21	−1.163**	0.0194
Lac2	14	1.32 ± 0.55	18	1.40 ± 0.56	−0.071	0.7257
Lac3	14	1.26 ± 0.47	18	1.18 ± 0.59	0.078	0.6979
Lac4	14	1.26 ± 0.57	18	1.27 ± 0.55	−0.013	0.9513
Lac5	14	1.41 ± 0.76	18	1.31 ± 0.54	0.104	0.8152
Lac6	14	0.92 ± 0.36	18	1.28 ± 0.58	−0.358	0.3908
Lac7	14	1.40 ± 0.65	18	1.11 ± 0.71	0.286	0.4891
Postoperative AST comparison (U/L)						
AST1	14	1125.07 ± 1075.57	18	885.33 ± 405.62	239.738	0.3899
AST2	14	549.57 ± 374.29	18	443.33 ± 218.22	106.238	0.3221
AST3	14	241.42 ± 157.11	18	224.77 ± 128.40	16.651	0.7436
AST4	14	146.76 ± 93.67	18	126.33 ± 79.69	20.436	0.5206
AST5	14	100.28 ± 90.25	18	95.44 ± 84.26	4.841	0.8768
AST6	14	91.58 ± 80.57	18	69.16 ± 46.03	22.417	0.2820
AST7	14	71.69 ± 60.55	18	63.77 ± 34.10	7.915	0.6554
Postoperative ALB comparison (U/L)						
ALB1	14	40.22 ± 6.45	18	42.87 ± 6.09	−2.655	0.2616
ALB2	14	41.44 ± 4.59	18	41.22 ± 5.52	0.218	0.9091
ALB3	14	38.30 ± 8.16	18	39.27 ± 5.74	−0.972	0.7064
ALB4	14	38.83 ± 5.29	18	39.43 ± 5.82	−0.606	0.7842
ALB5	14	37.96 ± 6.40	18	40.11 ± 6.23	−2.142	0.3738
ALB6	14	35.49 ± 8.07	18	38.55 ± 5.28	−3.065	0.2211
ALB7	14	36.25 ± 8.72	18	37.16 ± 5.30	−0.907	0.7321
Postoperative ALP comparison (U/L)						
ALP1	14	90.54 ± 48.89	18	97.938 ± 53.24	−7.392	0.7308
ALP 2	14	143.09 ± 109.84	18	102.688 ± 57.20	40.403	0.3828
ALP 3	14	153.18 ± 133.19	18	101.063 ± 44.78	52.119	0.2289
ALP 4	14	177.30 ± 176.76	18	100.063 ± 39.37	77.238	0.1408
ALP 5	14	151.63 ± 121.61	18	100.267 ± 35.31	51.370	0.2310
ALP 6	14	138.55 ± 100.92	18	107.533 ± 44.02	31.022	0.3223
ALP 7	14	121.63 ± 70.58	18	110.333 ± 44.27	11.303	0.6507
Postoperative GGT comparison (U/L)						
GGT1	14	108.25 ± 138.24	18	53.063 ± 34.46	55.188	0.1655
GGT 2	14	84.18 ± 48.12	18	60.125 ± 34.69	24.057	0.1839
GGT 3	14	94.72 ± 48.91	18	65.563 ± 33.07	29.165	0.1263
GGT 4	14	114.50 ± 61.18	18	76.063 ± 37.58	38.438	0.1339
GGT 5	14	112.45 ± 50.36	18	87.933 ± 44.86	24.521	0.2637
GGT 6	14	113.33 ± 47.13	18	97.267 ± 49.50	16.067	0.4285
GGT 7	14	102.36 ± 36.74	18	106.733 ± 58.78	−4.370	0.8287
Postoperative Cr comparison (mmol/L)						
Cr1	14	93.91 ± 31.28	18	79.82 ± 27.80	14.082	0.1885
Cr2	14	80.55 ± 25.96	18	81.95 ± 26.62	−1.398	0.8826
Cr3	14	75.54 ± 22.73	18	71.16 ± 26.61	4.380	0.6266
Cr4	14	74.80 ± 15.50	18	65.99 ± 21.76	8.807	0.2102
Cr5	14	75.27 ± 25.70	18	62.44 ± 20.17	12.829	0.1238
Cr6	14	64.50 ± 17.63	18	63.66 ± 22.56	0.835	0.9198
Cr7	14	56.67 ± 19.03	18	61.05 ± 24.24	−4.381	0.6166
Postoperative TB comparison (μmol/L)						
TB1	14	76.20 ± 63.89	18	71.81 ± 35.09	4.390	0.8058
TB2	14	74.72 ± 48.48	18	70.76 ± 43.01	3.960	0.8086
TB3	14	65.38 ± 52.76	18	63.77 ± 40.03	1.619	0.9219
TB4	14	52.16 ± 37.59	18	73.14 ± 70.8	−20.978	0.3419
TB5	14	57.71 ± 37.32	18	62.53 ± 53.42	−4.815	0.7763
TB6	14	61.39 ± 37.96	18	52.81 ± 33.83	8.579	0.5393
TB7	14	57.25 ± 41.97	18	46.810 ± 25.21	10.440	0.4126

(Continued on following page)

TABLE 2 | (*Continued*) Postoperative data comparison.

	Control	Value	Reconstruction	Value	t/x2	*p*-value
Postoperative INR comparison						
INR1	14	1.60 ± 0.39	18	1.53 ± 0.24	0.067	0.5587
INR 2	14	1.44 ± 0.24	18	1.40 ± 0.17	0.045	0.5509
INR 3	14	1.36 ± 0.24	18	1.29 ± 0.20	0.070	0.3877
INR 4	14	1.34 ± 0.43	18	1.30 ± 0.21	0.042	0.7248
INR 5	14	1.30 ± 0.34	18	1.27 ± 0.21	0.033	0.7394
INR 6	14	1.29 ± 0.32	18	1.25 ± 0.22	0.035	0.7176
INR 7	14	1.26 ± 0.29	18	1.24 ± 0.24	0.022	0.8169

**** , ** and * shows the level of significance at 1%, 5% and 10%, respectively.*

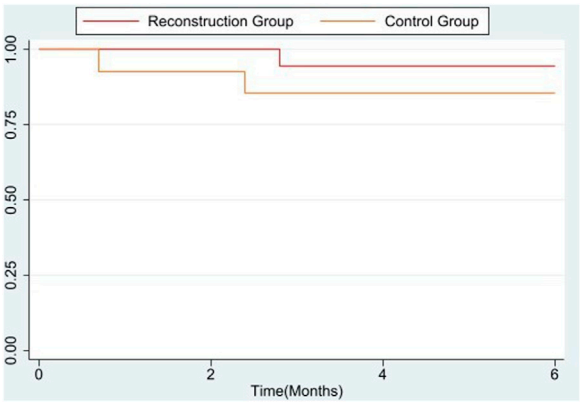


FIGURE 2 | Survival rate analysis of 6 months between control and reconstruction group.

liver parenchyma, the acquisition of donor liver, and the fine individual management after operation represents the forefront of the development of precision medicine (22). With the accumulation of clinical experience, especially the deepening of the research on the local anatomical structure of the liver, and the continuous summary and exchange of the experience of multi center split liver transplantation, the effect of split liver transplantation has been significantly improved (23).

The recipient selection of donation after brainstem death (DBD) orthotopic split liver transplantation is also key to the success of the transplantation, especially when the recipient is a double adult split liver transplantation. The matching degree between the graft size and the recipient needs to be carefully evaluated before operation to prevent the possibility of small for size syndrome or large for size syndrome due to the mismatch between the donor and the recipient. The GRWR standard of DBD orthotopic split liver transplantation should be appropriately increased compared with living donor liver transplantation, and it is recommended to be greater than 1.0%–1.2% (24). The GRWR of adult recipients of DBD *in situ* split liver transplantation in our center was controlled at more than 1.0%, and there was no obvious small liver syndrome after operation. We believe that the hyperoxia environment of the transplanted liver is beneficial to the regeneration of liver cells.

Therefore, the receptor should be emphasized to ensure long-term oxygen inhalation after operation. CT examination involves radiation and may affect the regeneration of liver cells. Therefore, we suggest that abdominal CT examination should be avoided as much as possible in the early stage after operation. Split liver transplantation is complex, the operation time is relatively increased, there are risks such as cross-sectional bile leakage and infection after operation, and the general requirements for the recipient are high because relevant studies show that a high MELD score before operation is an independent risk factor for serious complications after liver transplantation, so care should be taken to select recipients with a MELD score >14 for split liver transplantation (17, 18, 25). The donor liver splitting operation in our center adopts *in situ* splitting *in vivo* compared with the traditional *in vitro* splitting after acquisition, it can significantly reduce the cold ischemia time, dissect the hilar tissue more finely, deal with the liver section more accurately, and reduce the incidence of postoperative complications. It is suggested that the middle hepatic vein should be accurately located by intraoperative ultrasound before splitting, and perfusion can be carried out after splitting when the middle hepatic vein is exposed (26).

Although the vascular reconstruction and repair molding of the left and right liver halves respectively increase the operation time, it ensures that the left and right liver grafts have a complete middle hepatic vein system, the operation method is more reasonable, the necrosis of the graft liver tissue caused by outflow tract obstruction is avoided, and the functional liver volume of the graft is effectively increased. After the blood supply of the donor liver is restored during the operation, the sections of each anastomosis and liver parenchyma are comprehensively checked, and the bleeding points and broken ends with bile leakage are also treated in time. The reconstruction of the artery is flexibly evaluated according to the distribution of the donor hepatic artery and the recipient's own arterial conditions. If the length of the vessel is not sufficient, the donor iliac vessel can be used for bridging if necessary. In general, T-tube drainage is routinely placed in our center. The advantages of T-tube drainage are as follows: first, the recovery of donor liver function and the occurrence of rejection can be evaluated by observing the amount and color of drained bile in the early stage after operation; The second is that it can fulfil the role of biliary decompression before the recovery of gastrointestinal function, so as to reduce the occurrence of biliary complications such as bile leakage.

In conclusion, split liver transplantation can effectively alleviate the problem of liver shortages. Split liver transplantation can give the same clinical results as whole liver transplantation if the right donors and recipients are chosen and if the surgery is planned and carried out well. With the continuous maturity and progress of split liver transplantation technology, split liver transplantation is expected to become a routine operation in clinical liver transplantation and to become widely used. To sum up, our center's exploration of portal vein reconstruction in segment IV of the liver in split liver transplantation is a reasonable attempt based on anatomy, which is conducive to the recovery of patient's early postoperative liver function in clinical practice. However, because this surgical method is in the early exploratory stage, the number of samples included in this study is limited and, due to the differences in the technical level of the operators, the results have certain limitations that need to be further verified by continuing to expand the sample size in a multi-center practice.

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 ethics committee of organ transplant center and affiliated Hospital of Qingdao University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

IM and FR participated in research design, data collection and writing of paper. FW, XX, and ZL helped in data collection. CJ participated in the research design the writing of the paper.

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CONFLICT OF INTEREST

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

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LETTER TO THE EDITOR
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Assessment of Acute Rejection in a Lung Transplant Recipient Using a Sentinel Skin Flap

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Keywords: transplantation, vascularized composite allotransplantation, lung, sentinel flap, sentinel

Dear Editors,

Lung transplantation remains one of the only therapeutic options for patients suffering from end-stage lung disease (1). The long-term outcome of lung transplantation is limited because of acute rejection and chronic lung allograft dysfunction (CLAD) (1). The management of lung transplant recipients hinges on selecting the appropriate dose of immunosuppression which remains challenging and is currently guided by drug levels, clinical parameters, pulmonary function and surveillance transbronchial lung biopsies (TBBX). AR is graded according to the International Society for Heart and Lung Transplantation (ISHLT) grading system (2) which can be inaccurate, non-diagnostic, and carries risks including pulmonary hemorrhage, pneumothorax and death. Less invasive means for diagnosing AR are needed for management of lung transplant recipients.

The monitoring of acute skin rejection within vascularized composite allotransplants (VCA) involves a biopsy of the skin and subcutaneous tissue and interpreted using the Banff 2007 working classification (3). AR in VCA requires multiple biopsies and can lead to aesthetic deformities. Hence, "sentinel flaps" have become a useful tool. Sentinel flaps are composed of skin, subcutaneous tissue and the vessels which supply them. They are procured from the same donor and transplanted into a recipient in an easily accessible site. They serve as secondary monitoring sites for rejection. These flaps can easily be biopsied with minimal risks and no pain. We describe the first clinical use of a sentinel flap in a lung transplant recipient.

Research ethics board approval was obtained. A local donor was required to minimize flap ischemia time. Donor criteria was restricted to match recipient skin colour. The sentinel flap was procured by a team of plastic surgeons, composed of 4 cm × 8 cm of skin, subcutaneous tissue, radial artery and veins from the forearm of the donor from which the lungs were retrieved. The flap was flushed with heparinized saline solution and preserved under static cold storage at 4°C. The lungs were preserved in low potassium dextran solution for transportation.

Sentinel flap transplantation was performed in the same setting as lung transplantation by a team of plastic surgeons. The radial artery and veins within the flap were anastomosed in an end-to-end fashion to the recipient vessels in the left forearm under microscope magnification. The time required to perform this procedure was 1.5 h after induction. The preservation time limitation of the sentinel flap kept the total lung preservation time well within the usual clinical time.

The first patient to have undergone a sentinel flap procedure with bilateral lung transplantation is currently 3 years post-surgery. At the time of transplantation, the patient was 62 years old with chronic obstructive pulmonary disease with several severe exacerbations. The patient was right hand dominant with an intact palmar arch in the left hand and no history of trauma or surgeries to left upper extremity. The patient consented to undergo both procedures.

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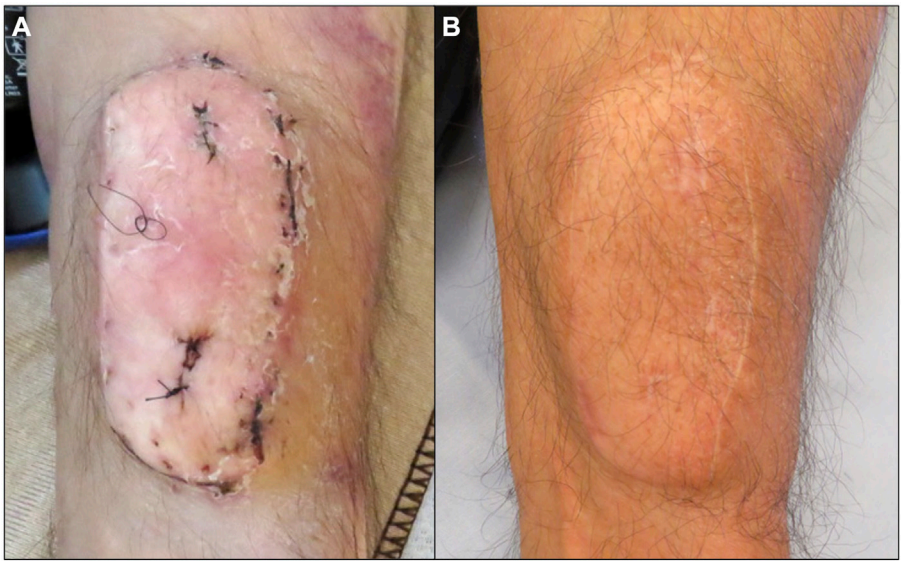

FIGURE 1 | Macroscopic image of the sentinel flap at 2 weeks **(A)** and 3 years **(B)** after surgery. Erythema and dermatitis were observed at 3 weeks **(A)** which led to skin biopsies demonstrated by nylon sutures.

The procedures occurred sequentially. The patient was started on standard immunosuppression with cyclosporine, azathioprine and methylprednisolone on day 0. The patient transitioned well from extubation on post-operative day (POD) 1 to recovery followed by rehabilitation and ambulation and was discharged at 3 weeks post-operatively. Pulmonary function tests showed steady improvement over time.

The sentinel flap remained viable. Two weeks post-surgery, it displayed new signs of swelling, patchy erythema and dermatitis which led to biopsies (**Figure 1A**) showing Banff Grade 1 rejection. A non-routine bronchoscopy was performed and the TBBX showed mild acute rejection Grade A2BX. The patient received a corticosteroid bolus for acute cellular rejection and the flap recovered. New signs of erythema and dermatitis were visible at 6 weeks corresponding to Banff Grade 2 rejection and the TBBX showed no acute rejection but scattered non-specific chronic inflammation and pneumonia. The patient was found to have developed *de novo* donor specific antibodies (DSA) which led to cessation of azathioprine and starting mycophenolate sodium. At the 2.5 months post-surgery, the skin biopsies showed Grade 3 rejection yet TBBX showed bronchus-associated lymphoid tissue but no rejection. There was no change in immunosuppression at this point. All following skin biopsies and TBBX showed no signs of rejection (**Figure 1B**).

An established scoring system (DASH and MHQ) was modified to assess acceptability.

In the initial post-operative period, the patient expressed some moderate difficulties with activities of daily living, related mainly to the lung transplant without issues related to the upper extremity. At two and 3 years post-operatively, the patient had almost no difficulties with activities of daily living, was very satisfied with appearance of the flap and had no issues related to social activities.

Vascularized sentinel forearm flaps offer a unique opportunity to monitor graft rejection and tailor immunosuppressive regimens (4). This study describes the first reported sentinel flap in the context of lung transplantation. Prior to this study, the safety of sentinel flaps performed in conjunction with the lung transplantation was unknown (4–10). There is currently no evidence to suggest an increased risk of solid organ allograft rejection when combined with VCA from the same donor.

The advantages of a sentinel flap can apply to all "hidden organs." In our case, the changes in the sentinel flap at 2 weeks post-operatively led to an early non-routine bronchoscopy. The presence of rejection on skin and lung samples led to an increase in immunosuppression. Although, skin rejection was observed more frequently than lung rejection, we chose not to treat as the purpose was to establish concordance between lung and skin rejection and to focus on safety and feasibility of sentinel flaps. Our results demonstrate that this is a safe and feasible procedure that can be done in conjunction with lung transplantation. Sentinel flap surgery can be performed immediately prior to or concurrent to a lung transplant procedure depending on the lung team preference.

Sentinel flaps have the potential to provide significant clinical utility in transplantation if concordance is found between skin rejection and lung rejection. Specifically, future work will examine whether higher grades of skin flap rejection occur with higher grades of lung rejection and whether an absence of skin flap rejection truly reflects an absence of rejection and stable graft function in the lung. Hopefully this will lead to

accurate monitoring of lung graft rejection and a safer patient experience.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Board-Toronto General Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SH designed the research study, performed the surgery, data analysis and writing of the paper and supervised the overall work. SJ, A-WC, MC, and SK participated in designing the project. AO'N assisted in the surgery. PP participated in the analysis of pathology specimens.

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CONFLICT OF INTEREST

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

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