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The state of combined thoracoabdominal triple-organ transplantation in the United States

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KEYWORDS:
heart-kidney-liver transplant;
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BACKGROUND: As triple-organ transplantation (TOT) has become more common, we evaluate patient characteristics, risk factors, and clinical outcomes of patients undergoing thoracoabdominal TOT.
METHODS: This retrospective study utilized data from heart-lung-liver (HLL), heart-lung-kidney (HLK), heart-kidney-liver (HKL), and heart-kidney-pancreas (HKP) recipients from the United Network for Organ Sharing registry between 1989 and 2023. Recipient and donor characteristics and risk factors for mortality were analyzed using Cox regression hazard models. Recipient survival up to 10 years was analyzed using the Kaplan-Meier method.
RESULTS: During the study period, 81 TOTs were performed (13 HLLs, 13 HLKs, 46 HKLs, and 9 HKPs). There were no statistically significant differences in long-term survival between TOTs ($p = 0.13$). However, HLL and HLK recipients had significantly worse ($p < 0.0001$) and improved ($p < 0.0001$) survival, respectively, when compared to heart-lung, isolated heart, and lung transplant recipients. HLK was associated with improved survival (hazard ratios [HR]: 0.22, $p = 0.033$). We found no differences in survival among HKL ($p = 0.24$) and HKP ($p = 0.19$) recipients compared to their dual- and single-organ counterparts. TOTs after 2007 (HR: 0.29, $p = 0.003$) were associated with improved survival, whereas increased recipient age (HR: 1.06, $p = 0.037$), estimated glomerular filtration rate (HR: 1.02, $p = 0.005$), and donor age (HR:1.05, $p = 0.031$) were associated with higher mortality.
CONCLUSIONS: The prevalence of TOTs has dramatically increased over the past decade. While overall survival between TOTs appears similar, adding a liver to a heart-lung transplant may be associated with a poorer prognosis compared to adding a kidney. A careful, multidisciplinary approach to

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patient selection and management remains paramount in optimizing outcomes for high-risk patients undergoing TOTs.

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Background

Thoracoabdominal triple-organ transplantation (TOT), while exceedingly rare, may represent the only curative treatment option for patients with end-stage heart failure complicated by multiorgan dysfunction involving the lungs, liver, and kidneys.[1] While the pathophysiology of multiorgan injury secondary to end-stage heart failure remains unknown, it is predominantly thought to be caused by worsening congestion, followed by hypoperfusion and cardiogenic shock.[2] Neurohormones, oxidative stress, and overt inflammation may further contribute to systemic congestion and peripheral hypoperfusion seen in acute heart failure.[3] Dual-organ transplantation involving the heart has been increasingly performed for patients with end-stage heart failure and other organ dysfunction with comparable outcomes to single-organ transplants.[4-8] Under the current allocation policies set by the United Network for Organ Sharing (UNOS), secondary organs may have higher priority for recipients of the primary organ on the waitlist.[9] This, while subject to ongoing reviews and updates, may allow for optimal outcomes for complex heart failure patients with concurrent irreversible extracardiac organ failure.

While dual-organ transplantation has been well documented in the literature, TOT involving the heart has seldom been analyzed, and no guidelines for candidate selection have been published. A recent analysis of the UNOS database reported that 10-year survival for heart-lung-kidney (HLK) and heart-liver-kidney transplants were noninferior to heart-lung (HL), heart-kidney (HK), or lung-kidney transplants.[10] Single-center experiences with heart-liver-kidney or heart-lung-liver (HLL) transplants were also noted to have adequate outcomes in select patients.[1,11] However, to our knowledge, there is a paucity of data comparing outcomes of HLL, HLK, heart-kidney-liver (HKL), and heart-kidney-pancreas (HKP) transplantation using a national database.

Given the complex, higher-risk profiles of patients requiring TOTs, ongoing assessment of current perioperative practices and outcomes is warranted to guide patient selection and management better. Here, we aim to provide a comprehensive evaluation of patient characteristics and an analysis of the long-term outcomes of patients undergoing 4 combinations of thoracoabdominal TOTs.

Materials and methods

Source of data

This study utilized the UNOS Standard Analysis and Research database, which facilitates the Organ Procurement and Transplantation Network (OPTN) under the United States Department of Health and Human Services contract. This prospectively maintained database contains patient information listed for solid-organ transplantation in the United States since 1987. This study followed the Strengthening The Reporting of Observational Studies in Epidemiology guidelines. As all data are deidentified, this retrospective cohort study was deemed exempt from the Virginia Commonwealth University Institutional Review Board.

Study population

The OPTN/UNOS Standard Analysis and Research file was queried to identify records of all patients, without age restriction, undergoing HLL, HLK, HKL, and HKP between January 1989 and June 2023. Subgroup analyses were conducted between TOT recipients and isolated heart, lung, HL, and HK transplants to isolate the effects of additional liver, kidney, or pancreas, depending on the organ combinations involving the heart.

Statistical analysis

Comprehensive donor and recipient demographics and baseline characteristics were collected, with categorical variables reported as percentages and continuous variables reported as medians and interquartile range. A Kaplan-Meier function was then created with a type of TOT and single- or double-organ combinations as the strata and survival as the outcome, and a log-rank test was used to test for significance between groups. Survival of the entire population and a 95% confidence interval were also reported. Finally, a multivariate Cox-proportional hazards model was created to test for the association of various risk factors with survival. Z-test was used to test for significance for each covariate, while the likelihood ratio test was used for the overall significance of the model; hazard ratios (HR) were reported as the exponent of the coefficient for each covariate. Additional backward stepwise Cox regression models were used to identify independent risk factors associated with survival after each combination of TOTs. All statistical analyses were conducted using R (version 4.3.1). All p-values were based on 2-sided statistical tests, with significance at $p < 0.05$.

Results

Comparison across all TOTs

We identified 81 patients who underwent 1 of 4 types of TOTs (46 HKLs, 9 HKPs, 13 HLKs, and 13 HLLs) during

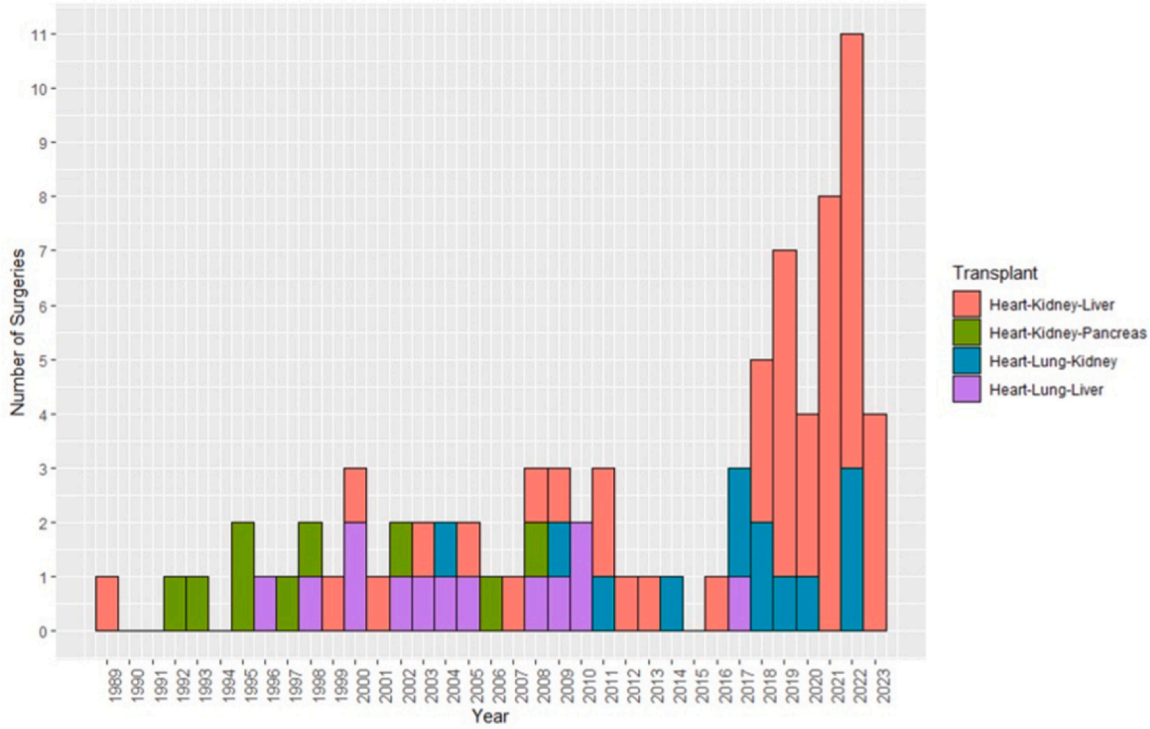

Figure 1 Trends in the number of different combinations of triple-organ transplants performed in the United States by year.

the study period (Figure 1). The volume of TOTs has seen a marked increase since 2018, when most cases comprised HKLs and few HLKs. Several differences in recipient characteristics were identified between patients receiving different combinations of TOTs (Table 1). Patients receiving HKL were older than all other TOTs ($p < 0.001$). Patients receiving HKLs were most likely to have used cigarettes ($p = 0.004$) and been on dialysis after listing ($p = 0.028$). HKL patients also had the highest body mass index (BMI) compared to recipients of other TOTs ($p < 0.001$). HKP patients were most likely to have undergone prior cardiac surgery, followed by HLL and HKL ($p = 0.007$). We observed no different differences in primary diagnoses for TOTs ($p = 0.71$). We found no differences in prior support on extracorporeal membrane oxygenation (ECMO) machines ($p = 0.051$), ventilators ($p = 0.10$), or ventricular assist devices (VADs) between types of TOTs ($p = 0.7$). We observed no differences in donor left ventricular ejection fraction ($p = 0.3$), ischemia time for the primary cardiac allograft ($p = 0.2$), and donor-recipient distance ($p = 0.092$). Importantly, we observed no significant differences in survival between different types of TOTs ($p = 0.13$) (Figure 2). However, acute rejection ($p = 0.008$) and treatment for rejection within 1 year of transplant rates ($p = 0.014$) were significantly different between TOTs (Table 2). There were significant differences in the hospitalization rates for infection during follow-up ($p = 0.032$), with the highest rates among HKP recipients. Rates of lowest functional status during follow-up were also significantly different between TOTs ($p = 0.016$), with HLL and HKP recipients being more likely to have below 30% preserved functional status postoperatively.

Conditional multivariate Cox regression analysis, including transplant centers with multiple TOTs as a covariate, demonstrated that TOTs performed after 2007 (HR: 0.29, $p = 0.003$) were associated with improved survival, whereas increased recipient age (HR: 1.06; $p = 0.037$), days on the waitlist (HR: 1.00; $p = 0.001$), and donor age (HR: 1.05; $p = 0.031$) were significantly associated with worse survival for all TOT recipients (Table 7). Notably, none of the analyzed categories of primary cardiac diagnoses significantly impacted survival.

Comparison of HLL to heart-lung

Compared to HL, isolated heart, and lung transplant, HLL recipients were younger ($p < 0.001$), had no history of cigarette use ($p = 0.005$), did not require dialysis at listing ($p < 0.035$), had lower BMI ($p < 0.001$), less likely to have undergone prior cardiac surgery ($p = 0.002$), and did not require ECMO machine at transplant ($p < 0.001$) (Table S1). HLL donors experienced shorter ischemic times ($p < 0.001$) and travel distance to the recipient ($p < 0.001$) compared to HL. While HLL recipients did not experience any acute rejection events ($p < 0.001$), they were more likely to have preserved less than 70% of their functional status during the follow-up period ($p < 0.002$) (Table 3). There were significant differences in long-term survival between HLL, HL, isolated heart, and lung transplant recipients ($p < 0.0001$) (Figure 3A). However, this is likely due to the similarly worse 5- and 10-year survivals between HLL, HL, and isolated lung transplant recipients compared to isolated heart. On multivariate Cox regression, the

Table 1 Baseline Recipient and Donor Characteristics by Type of Combined Triple-organ Transplant

Characteristics	Overall, N = 81[a]	Heart-kidney-liver, N = 46[a]	Heart-kidney-pancreas, N = 9[a]	Heart-lung-kidney, N = 13[a]	Heart-lung-liver, N = 13[a]	*p*-value[b]
Female (%)	25 (31)	6 (13)	5 (56)	7 (54)	7 (54)	< 0.001
Age (years)	46.00 (36.00, 55.00)	52.50 (43.50, 57.75)	40.00 (37.00, 46.00)	40.00 (31.00, 55.00)	34.00 (18.00, 41.00)	< 0.001
Time on waitlist (days)	69.00 (31.00, 157.00)	66.00 (29.00, 143.26)	98.00 (40.00, 171.96)	44.04 (16.00, 123.00)	112.96 (49.00, 255.04)	0.5
LAS	42.14 (34.04, 59.98)	-	-	47.68 (33.99, 79.34)	37.85 (37.25, 51.00)	0.5
Creatinine (mg/dl)	1.80 (1.34, 2.70)	1.90 (1.42, 2.67)	4.50 (3.05, 7.25)	2.35 (1.65, 3.02)	0.90 (0.50, 0.97)	< 0.001
eGFR (ml/min/1.73 m^2)	41.87 (25.97, 70.88)	41.66 (28.89, 55.30)	14.26 (8.21, 20.46)	31.68 (24.34, 42.09)	100.58 (86.03, 148.88)	< 0.001
Diabetes (%)	26 (32)	17 (37)	5 (56)	2 (15)	2 (15)	0.12
Cigarette use (%)	21 (26)	18 (39)	0 (0)	3 (23)	0 (0)	0.004
FEV1 (%)	44.00 (28.00, 53.00)	-	-	44.00 (33.00, 52.00)	43.50 (25.00, 56.75)	0.9
Dialysis after listing (%)	26 (32)	17 (37)	2 (22)	7 (54)	0 (0)	0.028
BMI (kg/m^2)	23.10 (21.15, 26.48)	24.90 (22.90, 28.90)	21.90 (21.20, 22.20)	21.40 (20.60, 23.40)	20.20 (17.70, 22.00)	< 0.001
Ventilator at transplant (%)	5 (6.2)	2 (4.3)	0 (0)	3 (23)	0 (0)	0.10
ECMO at transplant	7 (8.6%)	3 (6.5%)	0 (0%)	4 (31%)	0 (0%)	0.051
Bilirubin (mg/dl)	0.90 (0.50, 1.60)	1.04 (0.65, 1.76)	0.40 (0.30, 0.58)	0.70 (0.40, 1.20)	0.90 (0.45, 2.10)	0.025
Albumin (g/dl)	3.70 (3.10, 4.03)	3.80 (3.70, 4.30)	2.90 (2.50, 3.30)	3.10 (2.35, 3.35)	3.40 (3.03, 3.93)	0.14
Prior cardiac surgery (%)	37 (46)	19 (41)	7 (78)	2 (15)	9 (69)	0.007
VAD on waitlist (%)	2 (2.5)	1 (2.2)	0 (0)	0 (0)	1 (7.7)	0.7
Diagnosis (%)						0.71
Cystic fibrosis	4 (5.0)	0 (0)	0 (0)	2 (15)	2 (15)	
Fibrosis/pulmonary hypertension/ sarcoidosis	12 (15)	0 (0)	0 (0)	6 (46)	6 (46)	
Myopathy	43 (54)	31 (69)	7 (78)	4 (31)	1 (7.7)	
Other	21 (26)	14 (31)	2 (22)	1 (7.7)	4 (31)	
Donor age (years)	28.00 (21.00, 37.00)	31.00 (25.00, 39.75)	17.00 (16.00, 21.00)	28.00 (27.00, 32.00)	24.00 (17.00, 41.00)	0.016
Donor BMI (kg/m^2)	24.68 (22.07, 27.99)	25.51 (22.55, 29.84)	22.85 (21.40, 24.67)	24.68 (23.14, 25.78)	21.48 (19.27, 26.89)	0.043
Donor left ventricular ejection fraction (%)	63.00 (60.00, 65.00)	62.50 (60.00, 65.75)	56.50 (54.25, 58.75)	65.00 (62.00, 65.00)	60.00 (57.50, 65.00)	0.3
Donor diabetes (%)	3 (3.7)	1 (2.2)	2 (22)	0 (0)	0 (0)	0.10
Ischemic time (hours)	3.40 (2.80, 4.10)	3.40 (2.70, 4.10)	2.80 (2.50, 3.00)	3.70 (3.50, 4.30)	2.95 (2.63, 5.18)	0.2
Donor distance to transplant center (nautical miles)	105.50 (12.75, 207.50)	125.00 (16.00, 251.00)	20.00 (8.00, 73.00)	122.00 (51.00, 343.00)	66.00 (0.00, 119.00)	0.092

Abbreviations: BMI, body mass index; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 sec; IQR, interquartile range; LAS, lung allocation score; VAD, ventricular assist devices.

Notes: - denotes not applicable.

[a]*n* (%); Median (IQR).

[b]Pearson's chi-square test; Kruskal-Wallis rank sum test; Fisher's exact test.

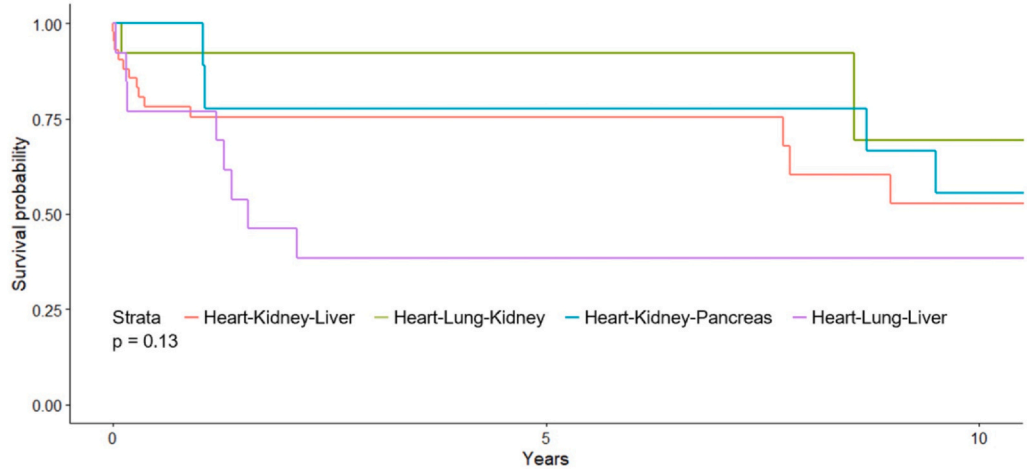

Figure 2 Kaplan-Meier survival curve demonstrating differences in short-, medium-, and long-term survival by types of triple-organ transplants.

addition of liver to HL transplant did not confer additional risk of mortality (HR: 1.15, $p = 0.686$) (Table 7).

Comparison of HLK to heart-lung

Compared to HL, isolated heart, and lung transplant, HLK recipients were younger ($p < 0.001$), spent fewer days on the waitlist ($p < 0.001$), were more likely to be on dialysis at listing ($p < 0.001$), had lower BMI ($p < 0.001$), and more likely to be on the ventilator ($p < 0.001$) or ECMO ($p < 0.001$) at transplant (Table S2). HLK donors experienced shorter ischemic times ($p < 0.001$) and travel distances to the recipients ($p < 0.001$) compared to HL donors. There were significant differences in long-term survival between HLK, HL, isolated heart, and lung transplant recipients ($p < 0.0001$) (Figure 3B), demonstrating a superior survival for HLK recipients. Accordingly, HLK recipients were least likely to have been hospitalized for rejection postoperatively ($p = 0.03$) despite the similar rates of acute rejection ($p = 0.08$) to HL, isolated heart, and lung transplant recipients (Table 4). On multivariate Cox regression, adding a kidney to the HL transplant reduced the mortality risk (HR: 0.22, $p = 0.033$) (Table 7).

Comparison of HKL to heart-kidney

Compared to HK and isolated heart transplant recipients, HKL recipients were younger ($p < 0.001$) but more likely

Table 2 Long-term Postoperative and Functional Outcomes Between the Types of Triple-organ Transplants

Characteristics	Overall, N = 81[a]	Heart-kidney-liver, N = 46[a]	Heart-kidney-pancreas, N = 9[a]	Heart-lung-kidney, N = 13[a]	Heart-lung-liver, N = 13[a]	*p*-value[b]
Acute rejection (%)	8 (13)	3 (7.7)	2 (22.2)	3 (23)	0 (0)	0.008
Treated for rejection within 1 year of transplant (%)	14 (28)	4 (14)	4 (80)	3 (30)	3 (43)	0.014
Lowest functional status during follow-up (%)						0.016
10	2 (5.1)	1 (5.0)	0 (0)	0 (0)	1 (14)	
20	1 (2.6)	0 (0)	1 (25)	0 (0)	0 (0)	
30	3 (7.7)	0 (0)	1 (25)	1 (13)	1 (14)	
40	2 (5.1)	0 (0)	0 (0)	1 (13)	1 (14)	
50	3 (7.7)	1 (5.0)	0 (0)	0 (0)	2 (29)	
60	7 (18)	5 (25)	0 (0)	0 (0)	2 (29)	
70	8 (21)	6 (30)	0 (0)	2 (25)	0 (0)	
80	13 (33)	7 (35)	2 (50)	4 (50)	0 (0)	
90	2 (5.1)	1 (5.0)	0 (0)	0 (0)	1 (14)	
Hospitalized for infection during follow-up (%)	25 (40)	8 (25)	7 (78)	5 (45)	5 (45)	0.032
Hospitalized for rejection during follow-up (%)	10 (16)	3 (9.4)	2 (22)	1 (9.1)	4 (36)	0.15

Abbreviation: IQR, interquartile range.
[a]*n* (%); median (IQR).
[b]Pearson's chi-square test; Kruskal-Wallis rank sum test; Fisher's exact test.

Table 3 Long-term Postoperative and Functional Outcomes Between Heart-lung-liver, Heart-lung, Isolated Heart, and Lung Transplants

Outcomes	Heart only, N = 84,051[a]	Lung only, N = 48,362[a]	Heart-lung, N = 1,424[a]	Heart-lung-liver, N = 13[a]	*p*-value[b]
Acute rejection (%)	8,675 (17)	2,956 (8.0)	80 (13)	0 (0)	< 0.001
Treated for rejection within 1 year of transplant (%)	13,915 (27)	9,786 (29)	200 (34)	3 (43)	0.064
Lowest functional status during follow-up (%)					< 0.002
10	2,240 (4.8)	3,440 (11)	62 (11)	1 (14)	
20	1,252 (2.7)	2,079 (6.7)	35 (6.0)	0 (0)	
30	473 (1.0)	575 (1.8)	20 (3.5)	0 (0)	
40	1,294 (2.8)	1,427 (4.6)	24 (4.1)	1 (14)	
50	1,685 (3.6)	2,070 (6.6)	34 (5.9)	1 (14)	
60	2,510 (5.4)	2,763 (8.9)	36 (6.2)	2 (29)	
70	6,790 (15)	5,126 (16)	70 (12)	2 (29)	
80	13,337 (29)	7,601 (24)	139 (24)	0 (0)	
90	16,964 (36)	6,133 (20)	159 (27)	0 (0)	
Hospitalized for infection during follow-up (%)	26,977 (36)	22,436 (52)	587 (54)	5 (45)	0.68
Hospitalized for rejection during follow-up (%)	13,683 (18)	11,321 (26%)	305 (28)	4 (36)	0.32

Abbreviation: IQR, interquartile range.
[a]*n* (%); Median (IQR).
[b]Pearson's chi-square test; Kruskal-Wallis rank sum test; Fisher's exact test.

to have a history of cigarette use ($p < 0.001$). They required ventilator ($p < 0.001$) or ECMO ($p < 0.001$) at transplant (Table S3). HKL donors were significantly older ($p < 0.001$) and experienced longer ischemic times ($p < 0.001$). However, long-term survival remained comparable between HKL, HK, and isolated heart transplant recipients ($p = 0.24$) (Figure 4A). Notably, rates of acute rejection ($p < 0.001$) and hospitalization for infection ($p = 0.004$) or rejection ($p < 0.001$) postoperatively were lowest among HKL recipients (Table 5). However, we found no differences in postoperative functional status between HKL, HK, and isolated heart transplant recipients ($p = 0.5$). On multivariate Cox regression, the addition of liver to HK transplant had no impact on the risk of mortality (HR: 1.36, $p = 0.293$) (Table 7).

Comparison of HKP to heart-kidney

Compared to HK and isolated heart transplant recipients, HKP recipients were younger ($p < 0.001$), without a history of cigarette use ($p < 0.001$), and had lower BMI ($p < 0.001$) (Table S4). However, HKP recipients were most likely to have diabetes ($p < 0.001$). No HKP patients required VAD on the waitlist ($p < 0.001$), ECMO ($p < 0.001$), or ventilator ($p < 0.001$) at transplant. HKP donors experienced the lowest ischemic times ($p < 0.001$).

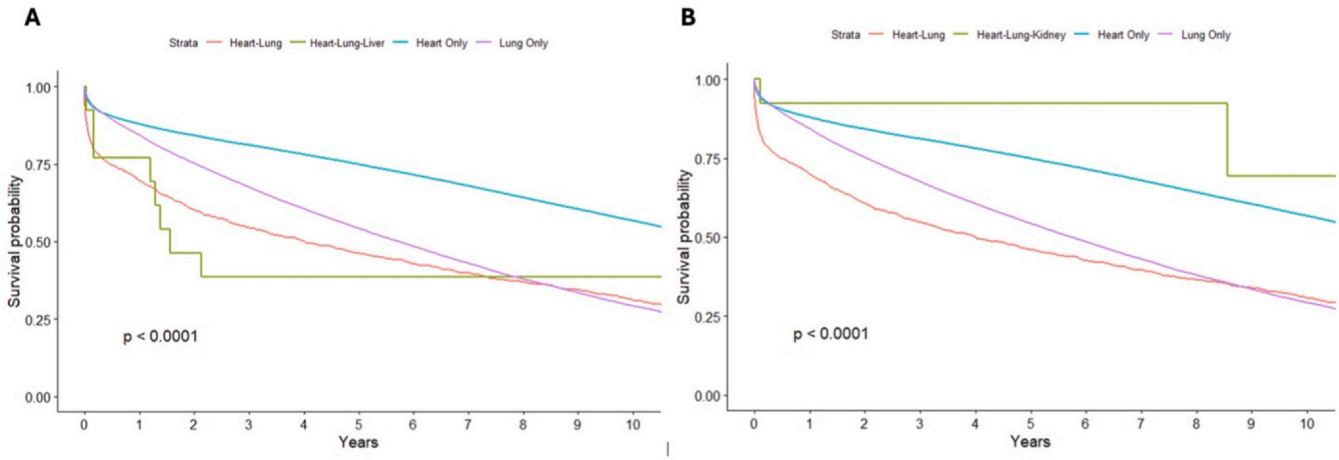

Figure 3 Kaplan-Meier survival curves of triple-organ transplants involving the heart and the lung. (A) Recipient survival between heart-lung-liver, heart-lung, isolated heart, and lung transplants. (B) Recipient survival between heart-lung-kidney, heart-lung, isolated heart, and lung transplants.

Table 4 Long-term Postoperative and Functional Outcomes Between Heart-lung-kidney, Heart-lung, Isolated Heart, and Lung Transplants

Outcomes	Heart only, N = 84,051[a]	Lung only, N = 48,362[a]	Heart-lung, N = 1,424[a]	Heart-lung-kidney, N = 13[a]	*p*-value[b]
Acute rejection (%)	8,675 (17)	80 (13)	2,956 (8.0)	3 (23)	0.08
Treated for rejection within 1 year of transplant (%)	13,915 (27)	200 (34)	9,786 (29)	3 (30)	0.5
Lowest functional status during follow-up (%)					0.8
10%	2,240 (4.8)	62 (11)	3,440 (11)	0 (0)	
20%	1,252 (2.7)	35 (6.0)	2,079 (6.7)	0 (0)	
30%	473 (1.0)	20 (3.5)	575 (1.8)	0 (0)	
40%	1,294 (2.8)	24 (4.1)	1,427 (4.6)	1 (13)	
50%	1,685 (3.6)	34 (5.9)	2,070 (6.6)	1 (13)	
60%	2,510 (5.4)	36 (6.2)	2,763 (8.9)	0 (0)	
70%	6,790 (15)	70 (12)	5,126 (16)	0 (0)	
80%	13,337 (29)	139 (24)	7,601 (24)	2 (25)	
90%	16,964 (36)	159 (27)	6,133 (20)	4 (50)	
Hospitalized for infection during follow-up (%)	26,977 (36)	587 (54)	22,436 (52)	5 (45)	0.26
Hospitalized for rejection during follow-up (%)	13,683 (18)	305 (28)	11,321 (26)	1 (9.1)	0.03

Abbreviation: IQR, interquartile range.
[a]n (%); Median (IQR).
[b]Pearson's Chi-squared test; Kruskal-Wallis rank sum test; Fisher's exact test.

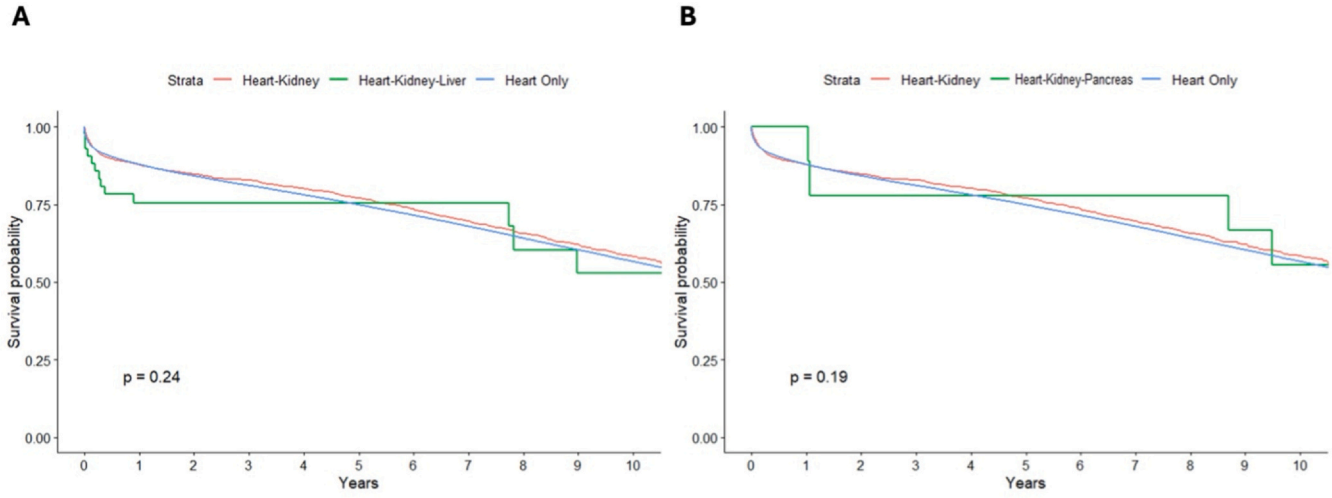

Figure 4 Kaplan-Meier survival curves of triple-organ transplants involving the heart and the kidney. (A) Recipient survival between heart-kidney-liver, heart-kidney, and isolated heart transplants. (B) Recipient survival between heart-kidney-pancreas, heart-kidney, and isolated heart transplants.

However, rates of acute rejection ($p < 0.001$) and treatment for rejection events within 1 year postoperatively ($p < 0.001$) remained the highest among HKP recipients (Table 6). Similarly, HKP recipients were most likely to have been hospitalized for infection ($p < 0.001$) or rejection events ($p < 0.001$). Despite the higher rates of adverse outcomes, long-term survival remained similar between HKP, HK, and isolated heart transplant recipients ($p = 0.19$) (Figure 4B). Accordingly, on multivariate Cox regression, the addition of pancreas to HK transplant had no impact on the mortality risk (HR: 0.75, $p = 0.575$) (Table 7).

Discussion

While rare, combined thoracoabdominal TOTs involving the cardiac allograft continue to be performed more frequently, with observed sharp increases since 2018. Notably, the year 2022 recorded the highest number of TOTs performed. This may be attributed to the backlog of elective surgeries and delayed complex transplants accumulated during the COVID-19 pandemic.[12] As thoracoabdominal dual-organ transplants become more common with improving outcomes, clinicians may encounter the quandary

Table 5 Long-term Postoperative and Functional Outcomes Between Heart-kidney-liver, Heart-kidney, and Isolated Heart Transplants

Outcomes	Heart only, N = 84,051[a]	Heart-kidney, N = 3,150[a]	Heart-kidney-liver, N = 46[a]	*p*-value[b]
Acute rejection (%)	8,675 (17)	231 (8.4)	3 (7.7)	< 0.001
Treated for rejection within 1 year of transplant (%)	13,915 (27)	201 (9.3)	4 (14)	< 0.001
Lowest functional status during follow-up (%)				0.5
10	2,240 (4.8)	93 (4.8)	1 (5.0)	
20	1,252 (2.7)	79 (4.0)	0 (0)	
30	473 (1.0)	29 (1.5)	0 (0)	
40	1,294 (2.8)	70 (3.6)	0 (0)	
50	1,685 (3.6)	69 (3.5)	0 (0)	
60	2,510 (5.4)	120 (6.2)	1 (5.0)	
70	6,790 (15)	291 (15)	5 (25)	
80	13,337 (29)	583 (30)	6 (30)	
90	16,964 (36)	617 (32)	7 (35)	
Hospitalized for infection during follow-up (%)	26,977 (36)	1,056 (38)	8 (25)	0.004
Hospitalized for rejection during follow-up (%)	13,683 (18)	348 (13)	3 (9.4)	< 0.001

Abbreviation: IQR, interquartile range.
[a]*n* (%); median (IQR).
[b]Pearson's chi-square test; Kruskal-Wallis rank sum test; Fisher's exact test.

Table 6 Long-term Postoperative and Functional Outcomes Between Heart-kidney-pancreas, Heart-kidney, and Isolated Heart Transplants

Outcomes	Heart only, N = 84,051[a]	Heart-kidney, N = 3,150[a]	Heart-kidney-pancreas, N = 9[a]	*p*-value[b]
Acute rejection (%)	8,684 (17)	230 (8.3)	2 (22.2)	< 0.001
Treated for rejection within 1 year of transplant (%)	13,914 (28)	200 (9.2)	4 (44.4)	< 0.001
Lowest functional status during follow-up (%)				0.2
10	2,240 (4.8)	93 (4.8)	0 (0)	
20	1,252 (2.7)	79 (4.0)	0 (0)	
30	473 (1.0)	29 (1.5)	1 (11.1)	
40	1,294 (2.8)	70 (3.6)	1 (11.1)	
50	1,685 (3.6)	69 (3.5)	0 (0)	
60	2,510 (5.4)	120 (6.2)	0 (0)	
70	6,790 (15)	291 (15)	0 (0)	
80	13,337 (29)	583 (30)	0 (0)	
90	16,964 (36)	617 (32)	2 (22.2)	
Hospitalized for infection during follow-up (%)	26,977 (36)	1,056 (38)	7 (78)	< 0.001
Hospitalized for rejection during follow-up (%)	13,683 (18)	348 (13)	2 (22.2)	< 0.001

Abbreviation: IQR, interquartile range.
[a]*n* (%); median (IQR).
[b]Pearson's chi-square test; Kruskal-Wallis rank sum test; Fisher's exact test.

of whether to propose a simultaneous TOT to a potential recipient with concurrent third or more end-organ failure.[13,14] Without prospective clinical trials or historical guidelines on TOTs, this study represents the most extensive retrospective study on the long-term outcomes of all 4 combinations of TOTs in the United States. When compared directly to one another, HLL, HLK, HKL, and HKP demonstrate comparable short- and long-term survival. However, HLL recipients may experience worse outcomes compared to other types of TOTs, particularly when compared to HL and isolated heart or lung transplant recipients. In contrast, adding kidneys to HL recipients may be associated with superior long-term survival. Among HK transplant recipients, neither the addition of the liver nor the pancreas had any impact on survival.

Our findings are broadly consistent with previous studies that have found relatively poor prognosis among HLL transplant recipients. While the majority of HLL recipients in our study were diagnosed with a combination of fibrosis, pulmonary hypertension, or sarcoidosis, previous studies have found that patients with cystic fibrosis also have a relatively poor prognosis with a 5-year survival rate of 42.9%.[11] This is in alignment with an older case series that reported a 5-year mortality rate of 37.5% in patients with

Table 7 Multivariate Analysis for Predictors of Overall Survival for Patients Undergoing Triple-organ Transplants With Transplant Centers With Multiple Procedures Added as a Mixed Effect

Predictors	Hazard ratio	CI	*p*-value
Year of transplant (after 2007)	0.29	0.15-0.31	0.003
Sex (male)	0.95	0.33-2.75	0.919
Recipient age	1.06	1.00-1.12	0.037
Time on waitlist	1.00	1.00-1.01	0.001
Diabetes	1.34	0.47-3.80	0.588
MELD-XI	0.99	0.34-2.17	0.820
eGFR	1.02	1.01-1.03	0.005
ECMO	5.03	0.88-28.87	0.070
BMI	1.04	0.94-1.15	0.452
Donor age	1.05	1.00-1.09	0.031
Diagnosis (cystic fibrosis as reference)			
Fibrosis/pulmonary hypertension/sarcoidosis	4.35	0.31-60.56	0.274
Myopathy	7.84	0.50-123.02	0.143
Others	9.87	0.59-166.10	0.112
Heart-lung-liver (heart-lung as reference)	1.15	0.59-2.21	0.686
Heart-lung-kidney (heart-lung as reference)	0.22	0.06-0.89	0.033
Heart-kidney-liver (heart-kidney as reference)	1.36	0.77-2.40	0.293
Heart-kidney-pancreas (heart-kidney as reference)	0.75	0.28-2.02	0.575

Abbreviations: BMI, body mass index; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; MELD, model for end-stage liver disease.

cystic fibrosis undergoing HLL compared to 64% and 69% in lung-liver and isolated liver transplants, respectively.[15] In patients with primary end-stage liver disease complicated by advanced lung and heart failure, HLL has demonstrated a low 5-year survival rate of 42%.[16] These results further confirm that lung involvement in HL or HLL may be associated with worse survival than other TOTs, even after adjusting for transplant center volume or expertise in our analyses. It is important to note that these findings were mainly attributed to increased perioperative mortality, with similar survival rates among dual and TOTs outside of that period.[15] Though pre-existing conditions and severity of pretransplant disease were proposed as plausible explanations, our study did not find them to be associated with decreased survival rates.

For all TOTs, we found that increased days on the waitlist were associated with a higher risk of mortality. Indeed, prior literature has demonstrated that TOT patients experienced significantly longer waitlist times, resulting in higher mortality rates on the waiting list.[15] While Bell et al found that protracted waitlist time may be associated with worse outcomes in HLL,[11] we found that HLL recipients had spent fewer days on the waitlist than HL recipients. However, this may be influenced by some degree of "survivorship bias," particularly as most of the waitlist outcomes have only been studied in patients who survive the transplant.[11] Despite seemingly poor survival, HLL recipients did not experience any acute rejection events in our analysis. This may be mediated by the significantly decreased ischemic times and shorter donor-recipient distances among HLL recipients, as prolonged bilateral lung allograft ischemia has been associated with worse outcomes.[17] Considering the patient's quality of life beyond survival metrics, our analyses demonstrate that most HLL recipients have regained 60% to 70% of their functional status in our study. However, this still falls short of the 80% to 90% preserved functional status among most HL and isolated heart or lung transplant recipients. It is essential to consider whether the upfront surgical risk may account for the lost functional status earlier in the recovery. However, HLL recipients had higher 30-day survival at 92.3% compared to 84.6% in HL recipients, which decreased to 76.92% and 69.57% in 1 year among HLL and HL recipients. Nevertheless, it is critical to consider whether HLL candidates can tolerate the operation and the protracted recovery.

Unlike HLL recipients, lung involvement in HLK was not associated with worse outcomes. This is despite the similar lung function (forced expiratory volume in 1 sec 43.5% vs 44%) and lung allocation score (38.36 vs 39.6) between HLL and HLK recipients. Similar to the findings by Adjei et al,[10] we demonstrate that HLK recipients experienced improved survival compared to HL, isolated heart, or lung transplant recipients. Interestingly, adding the liver to the HL transplant may have added immunoprotective benefits as acute rejection rates remained higher in HLK vs HLL (23% vs 0%). In contrast, adding a kidney to the HL transplant may increase the rates of acute rejection (8% in HL vs 23% in HLK). This is particularly impressive given the higher rates of hospitalization for rejection among HLL recipients compared to those of HLK transplants (36% vs 9.1%). While the underlying mechanism is unclear, previous studies have reported that, at least in combined heart-liver transplants, the liver allograft may provide a relative immunoprotective effect for the heart.[4,18]

It is also unclear as to why HKL appears to be the dominant type of TOTs in recent years, especially since HKL might represent higher risks given their more frequent smoking and dialysis history, higher BMIs, and older ages.

However, our findings indicate that donors for HKL recipients were equally likely to be older and have higher BMIs than those of other TOTs. It is plausible that more patients require HKLs due to the inherent close relationship between cardiogenic hepatic dysfunction and cardiorenal syndrome, which may share synergistic prognostic implications.[19] In chronic heart failure, venous congestion may impair estimated glomerular filtration rate (eGFR) by reducing the glomerular net filtration pressure, leading to cardio-hepato-renal syndromes. Indeed, previous studies have demonstrated that hepatic and renal dysfunctions were closely correlated with the severity of heart failure.[20] eGFR was an independent predictor of transplant-free survival in their cohort.[20] In our study, HKL recipients had significantly impaired eGFR of 41.66. However, we did not find eGFR to be significantly associated with survival.

Furthermore, HKL's rising case volume relative to all other types of TOTs may also be due to the growing recognition of the neuroprotective effects of liver transplants, demonstrated particularly among combined heart-liver recipients.[4,18,21] Indeed, compared to HK, acute rejection rates were lower among HKL recipients (8.4% vs 7.7%), and HKL recipients were less likely to be hospitalized for infection or rejection events than HK recipients. However, these may also be due to the higher propensity for HKL recipients to be treated for rejection within the first year postoperatively compared to HK recipients (14% vs 9.3%). Together, these findings indicate that despite the complexity of patients requiring HKLs, these procedures are increasingly performed with acceptable outcomes.

We have also reported on the outcomes of HKP, which has been even more seldomly documented in the literature compared to other TOTs in our analyses.[22,23] Unsurprisingly, HKP candidates were more likely to have diabetes than HK or isolated heart transplant candidates. Thus, in patients with type 1 diabetes and simultaneous end-stage kidney and heart failure, HKP may offer comparable survival benefits to HK. However, several concerns merit careful consideration, including higher rates of acute rejection, hospitalization for infection, or rejection among HKP recipients compared to HK or isolated heart transplant recipients. To mitigate these risks, a staged approach of HKP, starting with HK and followed by a pancreas transplant, has been demonstrated to have adequate results.[22] Despite these complications, HKP recipients do not appear to have experienced detrimental effects of early graft complications, as 30-day survival remains higher among HKP recipients compared to HK recipients (100% vs 95.74%).

One of the main factors affecting survival outcomes in the overall cohort was the year of transplant. TOTs after 2007 were associated with an average mortality risk reduction of nearly 70% compared to TOTs before 2007. This may be due to the technical advancements that have pushed the boundaries of multiorgan transplants in recent years. The emergence of new technologies, such as the SherpaPak Cardiac Transportation System or XVIVO Heart/Liver Assist Transport, may allow for cold ischemic times for TOTs to be extended beyond the 4-hour purported limit with comparable outcomes.[24-26] Operative techniques, such as en-bloc heart-liver procurement and transplant, have also recently demonstrated acceptable survival with decreased operative, allograft ischemic times, and offering protection from excessive reperfusion injury.[27,28]

Limitations

First, the retrospective nature of our study introduces a level of selection bias. While patients with missing or incomplete data entry were excluded from our analysis, patient selection for TOTs may ultimately vary based on institutional policies and individual clinicians' decision-making. These factors introduce potential confounders that we were unable to consider. Similarly, while we could account for variances in experience level with TOTs between transplant centers (using multiprocedure transplant centers as a covariate in the multivariate analysis), we could not investigate the impact of specific transplant techniques or center-specific experiences on outcomes of TOTs. Since these data were extracted from a national registry, we cannot account for inherent patient selection biases between physicians and institutions. Second, particularly given the rare nature of TOTs, the lack of statistical significance in certain variables may be due to the insufficient power to identify a potential association. However, our data can still be used to draw clinically valuable conclusions as we cover more than 3 decades of national data, covering the full extent that the UNOS database can currently offer. Finally, the present study could not accurately discern why patients underwent multiorgan transplants simultaneously or sequentially. The UNOS/OPTN database does not have direct qualifiers to determine the multiorgan transplant sequence.

Conclusion

Using a national database, we provide an update on the state of the combined thoracoabdominal TOTs in the United States. While patient survival after HKL and HKP are comparable to their dual- or single-organ transplant counterparts, HLL patients have experienced worse survival, and HLK patients experience superior survival than HL. Notably, TOTs occurring after 2007 from younger donors with higher eGFR showed increased survival rates, while pre-existing conditions and pretransplant diagnoses were not associated with decreased survival rates. With a careful, multidisciplinary approach to evaluation and management, highly complex patients with multiorgan dysfunction secondary to end-stage heart failure may benefit from simultaneous TOTs.

Author contributions

E.D. and Z.A.H. conceived and designed the study. E.D. and Y.C.K. contributed to the production and editing of this article. M.A. contributed to the data and statistical analysis. E.D., Y.C.K., M.A., I.F.T., K.B.S., D.A.B., W.A.J., J.C., V.K., and Z.A.H. reviewed and edited this article. All authors agreed and approved of the contents of this article.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

1. Ebong IA, Sayer G, Kim G. Simultaneous heart, liver and kidney transplantation: a viable option for heart failure patients with multi-organ failure. J Heart Lung Transplant 2019;38:997-9. https://doi.org/10.1016/j.healun.2019.06.017.
2. Ponikowski P, Voors AA, Anker SD. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891-975. https://doi.org/10.1002/ejhf.592.
3. Rudiger A. Understanding cardiogenic shock. Eur J Heart Fail 2015;17:466-7. https://doi.org/10.1002/ejhf.302. [published correction appears in Eur J Heart Fail. 2015;17:639].
4. Rucker AJ, Anderson KL, Mulvihill MS, Yerokun BA, Barbas AS, Hartwig MG. Simultaneous versus sequential heart-liver transplantation: ideal strategies for organ allocation. Transplant Direct 2019;5:e415. https://doi.org/10.1097/TXD.0000000000000854.
5. Mulvihill MS, Yerokun BA, Patel P, Rogers JG, Milano CA, Patel CB. Simultaneous heart-kidney transplantation is superior to sequential heart-kidney transplantation in renal failure heart transplant candidates. J Heart Lung Transplant 2017. https://doi.org/10.1016/j.healun.2017.01.403.
6. Connor AA, Huang HJ, Mobley CM. Progress in combined liver-lung transplantation at a single center. Transplant Direct 2023;9. https://doi.org/10.1097/TXD.0000000000001482.
7. Hanish SI, Samaniego M, Mezrich JD. Outcomes of simultaneous liver/kidney transplants are equivalent to kidney transplant alone: a preliminary report. Transplantation 2010;90:52-60. https://doi.org/10.1097/tp.0b013e3181e17014.
8. Reich HJ, Chan JL, Czer LS. Combined lung-kidney transplantation: an analysis of the UNOS/OPTN database. Am Surg 2015;81:1047-52.
9. Engen R, Shepherd D, Bradford MC, Foutz J, Bartosh SM, Smith JM. Impact of multiorgan and kidney-pancreas allocation policies on pediatric kidney-alone transplant candidates in the United States. Pediatr Transplant 2022;26. https://doi.org/10.1111/petr.14394.
10. Adjei MA, Wisel SA, Steggerda JA. Incidence and outcomes of simultaneous thoracoabdominal triple organ transplantation in the United States. Transplant Proc 2024;56:161-8. https://doi.org/10.1016/j.transproceed.2023.11.029.
11. Bell PT, Carew A, Fiene A. Combined heart-lung-liver transplantation for patients with cystic fibrosis: the Australian experience. Transplant Proc 2021;53:2382-9. https://doi.org/10.1016/j.transproceed.2021.07.028.
12. Mehta A, Awuah WA, Ng JC, et al. Elective surgeries during and after the COVID-19 pandemic: case burden and physician shortage concerns. 2022;81.
13. Miklin DJ, Mendoza M, DePasquale EC. Two is better than one: when to consider multiorgan transplant. Curr Opin Organ Transplant 2022;27:86-91. https://doi.org/10.1097/MOT.0000000000000951.
14. Kwon YIC, Dunbar E, Wright K, et al. Differences in outcomes of combined heart-liver transplantation by primary cardiac diagnosis. JHLT Open 2024;6:100147. https://doi.org/10.1016/j.jhlto.2024.100147.
15. Nash KL, Collier JD, French J. Cystic fibrosis liver disease: to transplant or not to transplant? Am J Transplant 2008;8:162-9. https://doi.org/10.1111/j.1600-6143.2007.02028.x.
16. Praseedom RK, McNeil KD, Watson CJ, et al. Combined transplantation of the heart, lung, and liver. Lancet 2001;358:812-3. https://doi.org/10.1016/S0140-6736(01)06003-2.
17. Casillan AJ, Zhou AL, Ruck JM, et al. The effect of allograft ischemic time on outcomes following bilateral, single, and reoperative lung transplantation. J Thorac Cardiovasc Surg 2024;167:556-565.e8. https://doi.org/10.1016/j.jtcvs.2023.05.027.
18. Wong TW, Gandhi MJ, Daly RC, et al. Liver allograft provides immunoprotection for the cardiac allograft in combined heart-liver transplantation. Am J Transplant 2016;16:3522-31. https://doi.org/10.1111/ajt.13870.
19. Harjola VP, Mullens W, Banaszewski M. Organ dysfunction, injury and failure in acute heart failure: from pathophysiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail 2017;19:821-36. https://doi.org/10.1002/ejhf.872.
20. Poelzl G, Eberl C, Achrainer H, et al. Prevalence and prognostic significance of elevated γ-glutamyltransferase in chronic heart failure. Circ Heart Failure 2009;2:294-302. https://doi.org/10.1161/CIRCHEARTFAILURE.108.826735.
21. Beal EW, Mumtaz K, D Jr H, Whitson BA, Black SM. Combined heart-liver transplantation: indications, outcomes and current experience. Transplant Rev (Orlando) 2016;30:261-8.
22. Nguyen MTJP, Giannetti N, Cantarovich M, Cecere R, Chaudhury P, Paraskevas S. Pancreas transplantation after combined heart-kidney transplantation. Transplantation 2011;91:e13-4. https://doi.org/10.1097/TP.0b013e3181ff143d.
23. Mettauer B, Bellmont S, Epailly E, et al. First European combined heart, kidney, and pancreas transplantation 11 years after. Transplant Proc 2001;33:3496-8. https://doi.org/10.1016/S0041-1345(01)02413-7.
24. Radakovic D, Karimli S, Penov K, et al. First clinical experience with the novel cold storage SherpaPak™ system for donor heart transportation. J Thorac Dis 2020;12:7227-35.
25. Schlegel A, Mueller M, Muller X, et al. A multicenter randomized-controlled trial of hypothermic oxygenated perfusion (HOPE) for human liver grafts before transplantation. J Hepatol 2023;78:783-93.
26. McGiffin DC, Kure CE, Macdonald PS, et al. Hypothermic oxygenated perfusion (HOPE) safely and effectively extends acceptable donor heart preservation times. Results of the Australian and New Zealand trial. J Heart Lung Transplant 2024;43:485-95.
27. Brozzi NA, Loebe M, Souki FG. En-bloc simultaneous heart-liver transplantation in adult patients. Ann Surg 2021;274. https://doi.org/10.1097/SLA.0000000000003721.
28. Mullis DM, Garrison A, Heng E, et al. Heart-liver transplantation using the en bloc technique: a single-center experience over two decades. J Thorac Cardiovasc Surg 2024. https://doi.org/10.1016/j.jtcvs.2024.08.031.