Sequential Versus Combined Heart–Liver Transplantation in the USA

Yoshikazu Yamaguchi^{1,2} · Candice Burrier^{1,2} · Catherine Roth¹ · Dmitry Tumin^{1,3} · Eliza W. Beal⁴ · Kenneth Washburn⁴ · Don Hayes Jr.⁵ · Joseph D. Tobias^{1,2}

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Abstract

Introduction Combined heart–liver transplantation (CHLT) has resulted in acceptable survival rates compared to orthotopic liver transplantation (OLT) alone and orthotopic heart transplantation alone. Using the US transplant registry, we compared outcomes following sequential and combined HLT.

Methods We conducted a retrospective cohort study. De-identified data were obtained from the United Network Organ Sharing Registry. The primary outcome was patient survival from the date of OLT. Secondary outcomes included liver allograft survival and heart allograft survival.

Results The study cohort included 301 CHLT recipients and six sequential heart–liver transplantation (SHLT) recipients. Patient survival after CHLT was 88% at 1 year, 84% at 3 years, and 82% at 5 years compared to 83%, 67%, and 50% in the SHLT group ($p=0.010$). Liver allograft survival at 1, 3, and 5 years was 88%, 83% and 82%, respectively, in the CHLT group compared to 83% and 67%, and 50%, respectively, in the SHLT group ($p=0.009$). After OLT, heart allograft survival at 1, 3, and 5 years was 86%, 79%, and 74% in the CHLT group, respectively, compared to 83%, 67%, and 50% in the SHLT group ($p=0.037$).

Conclusions Despite the limited size of the SHLT cohort, we found that CHLT was superior to SHLT in survival rate and graft survival. The better outcomes noted in CHLT may relate to immunoprotection provided by liver transplantation from the same donor.

Keywords Combined heart–liver transplantation · Heart–liver transplantation · Liver transplantation · Heart transplantation · Immunoprotection · The United Network Organ Sharing Registry

Introduction

Combined heart–liver transplantation (CHLT) is a complex surgical procedure indicated for patients with a single underlying disease process causing both heart and liver failure or patients with heart and liver pathology of different etiologies. Accumulating experience with CHLT in the USA has demonstrated acceptable survival compared to orthotopic liver transplantation (OLT) alone and orthotopic heart transplantation (OHT) alone [1, 2]. In most cases of CHLT, the heart is transplanted first as the heart is less tolerant of ischemia, and the heparin needed for cardiopulmonary bypass for the heart transplant can be reversed prior to the liver transplant [3]. However, in specific circumstances, the liver may be transplanted first to protect the heart from donor-specific antibodies (DSA) in patients with high DSA titers.

✉ Yoshikazu Yamaguchi
yoshikaz@rd6.so-net.ne.jp

¹ Department of Anesthesiology and Pain Medicine, Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205, USA

² Department of Anesthesiology and Pain Medicine, The Ohio State University Wexner Medical Center, Columbus, OH, USA

³ Department of Pediatrics, Brody School of Medicine at East Carolina University, Greenville, NC, USA

⁴ Division of Transplantation, Department of General Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, USA

⁵ Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University Wexner Medical Center, Columbus, OH, USA

Sequential heart liver transplantation (SHLT) has been performed when heart and liver allografts could not be obtained from the same donor, or the liver allograft was deemed unacceptable for transplant after its recovery [4, 5]. However, data comparing outcomes of heart and liver transplantation (HLT) performed as a sequential versus a combined procedure are limited. Using data from the United States transplant registry, we compared outcomes of patients undergoing sequential versus combined HLT to determine whether SHLT was associated with an increased risk of adverse outcomes relative to CHLT.

Methods

Following Institutional Review Board approval, de-identified data were obtained from the United Network Organ Sharing (UNOS) Registry. Data from transplants performed in 1987–2018 were included in our analysis, with patient follow-up censored in March 2019. Patients were evaluated for inclusion in the study if they received a first-time OHT either (a) in combination with OLT (combined group, CHLT), or (b) after having been listed for OLT, and having subsequently received OLT (sequential group, SHLT). Patients who received OLT after OHT, but were listed for OLT subsequent to receiving OHT, were excluded from the analysis, as it was unclear whether their OLT was planned to follow OHT (Fig. 1). The primary outcome in the analysis was patient survival from the date of OLT. Secondary outcomes included liver allograft survival and heart allograft survival. Due to variable durations between OHT and OLT in SHLT cases, heart allograft survival was analyzed from the date of the OLT. Actuarial 1-, 3-, and 5-year survival rates were reported for each outcome, and Kaplan–Meier curves with log-rank tests were used to compare patient and graft survival between recipients of combined and sequential

HLT. To assess priority for OLT among patients age 12 and older transplanted since February 2002, the final the laboratory model for end-stage liver disease score was compared according to type of OHLT (combined vs. sequential) using a Wilcoxon rank-sum test. To assess priority for OHT since 1998, listing with UNOS Status 1A was compared according to the type of HLT (combined vs. sequential) using Fisher's exact test. Data analysis was performed using Stata 15\IC (College Station, TX: StataCorp, LP). $p < 0.05$ was considered statistically significant.

Results

The initial cohort included a total of 381 first-time OHT recipients who were also listed for OLT prior to receiving OHT. Twenty-seven patients were excluded as they received OLT prior to OHT. Forty-seven patients received OLT prior to OHT and were not simultaneously listed for both heart and liver at the time they received OLT. In total, 301 CHLT recipients (195/106 male/female, mean age 47 ± 15 years) and six SHLT recipients (all male, mean age at LT 54 ± 6 years) remained for our analysis. The SHLT recipients were listed for both OHT and OLT at the time of the OHT (Fig. 1). Among patients receiving SHLT, median time to OLT was 331 days (interquartile range: 149, 634). Recipient characteristics are summarized in Table 1, and donor characteristics are summarized in Tables 2 and 3. Median MELD laboratory scores did not significantly differ between 275 CHLT recipients (15; interquartile range [IQR]: 10, 19) and four SHLT recipients (11; IQR: 10, 18; $p = 0.613$) transplanted since the MELD score was incorporated into donor liver allocation. The proportion of patients listed as Status 1A on the heart waitlist did not differ between the CHLT (160/289, 55%) and SHLT (1/4, 25%) cohorts ($p = 0.330$).

Fig. 1 Diagram of included patients

Table 1 Characteristics of combined and sequential heart–liver transplant recipients ($N=307$)

Variable ^a	Cases missing data	CHLT ($N=301$) Median (IQR) or N (%)	SHLT ($N=6$) Median (IQR) or N (%)	p value ^b
Age (year)	0	49 (37, 59)	55 (50, 57)	0.431
Male gender	0	215 (71%)	6 (100%)	0.191
Race/ethnicity	0			0.461
Non-Hispanic white		195 (65%)	6 (100%)	
Non-Hispanic black		61 (20%)	0	
Other		45 (15%)	0	
Height (cm)	0	173 (167, 180)	180 (168, 185)	0.241
Weight (kg)	0	74 (63, 88)	74 (70, 83)	0.963
BMI (kg/m^2)	0	24 (22, 28)	23 (22, 24)	0.427
Primary indication for OHT	0			0.027
Dilated cardiomyopathy		87 (29%)	0	
Restrictive cardiomyopathy		93 (31%)	5 (83%)	
Congenital heart defect		73 (24%)	0	
Other		48 (16%)	1 (17%)	
Primary indication for OLT	0			0.429
Cirrhosis		159 (53%)	2 (33%)	
Other ^c		142 (47%)	4 (66%)	
UNOS status 1A	14	160 (55%)	1 (25%)	0.330
Final MELD score at OLT	28	15 (10, 19)	11 (10, 18)	0.613
MELD exception at OLT	0	51 (17%)	3 (50%)	0.070
Concurrent kidney transplant	0	16 (5%)	0	> 0.999
Mechanical ventilator	0	4 (1%)	0	> 0.999
Ventricular assist device	30	19 (6%)	1 (17%)	0.335
Inotropes	0	155 (52%)	2 (33%)	0.439
Intra-aortic balloon pump	0	33 (11%)	0	> 0.999
Medical condition	0			0.035
In ICU		135 (45%)	0	
In hospital		54 (18%)	1 (17%)	
Outpatient		112 (37%)	5 (83%)	
Cardiac output (L/min)	46	4.4 (3.5, 5.5)	5.7 (4.3, 6.2)	0.157
Days on wait list	0	109 (46, 275)	115 (44, 370)	0.976

BMI body mass index, CHLT combined heart–liver transplant, ICU intensive care unit, IQR interquartile range, MELD model for end-stage liver disease, OHT orthotopic heart transplant, OLT orthotopic liver transplant, SHLT sequential heart–liver transplant, UNOS United Network for Organ Sharing

^aAssessed at the time of OHT, except where indicated

^bWilcoxon rank-sum test for continuous data and Fisher's exact test for categorical data

^cThis included cholestasis, ulcerative colitis, atresia, Budd–Chiari syndrome, hemochromatosis, hyperlipidemia, and hepatoma

Patient survival after CHLT was 88% at 1 year, 84% at 3 years, and 82% at 5 years, compared to 83%, 67%, and 50% in the SHLT group (Fig. 2; log-rank test $p=0.010$). Liver allograft survival at 1, 3, and 5 years was 88%, 83%, and 82%, respectively, in the CHLT group compared to 83%, 67%, and 50%, respectively, in the SHLT group (Fig. 3; log-rank test $p=0.009$). After OLT, heart allograft survival at 1, 3, and 5 years was 86%, 79%, and 74% in the CHLT group, respectively, compared to 83%, 67%, and 50% in the SHLT group (Fig. 4; log-rank test $p=0.0037$).

Discussion

Although CHLT remains rare compared to individual organ transplantation, expertise in this procedure and other double-organ transplant procedures has rapidly increased in the USA [6, 7]. The current study demonstrates an increasing use of CHLT with 72% (218/301) of CHLT procedures being performed since 2010. As previously reported by European experts, SHLT is considered a less optimal procedure, commonly performed when a donor liver cannot be transplanted

Table 2 Characteristics of heart donors in combined and sequential heart–liver transplant procedures ($N = 307$)

Variable ^a	Cases missing data	CHLT ($N = 301$) Median (IQR) or N (%)	SHLT ($N = 6$) Median (IQR) or N (%)	p value ^b
Age (year)	0	27 (21, 37)	22 (21, 44)	0.863
Male gender	0	222 (74%)	6 (100%)	0.344
Race/ethnicity	0			0.437
Non-Hispanic white		177 (59%)	6 (100%)	
Non-Hispanic black		61 (20%)	0	
Other		63 (21%)	0	
Height (cm)	3	173 (168, 180)	178 (172, 185)	0.117
Weight (kg)	0	74 (67, 84)	77 (68, 84)	0.652
BMI (kg/m^2)	3	25 (23, 28)	25 (21, 25)	0.516
Cause of death	0			0.196
Anoxia		77 (26%)	1 (17%)	
Cerebrovascular/stroke		52 (17%)	0	
Head trauma		165 (55%)	4 (67%)	
CNS tumor		1 (< 1%)	0	
Other		6 (2%)	1 (17%)	
Type of liver graft ^c	0			> 0.999
Whole		300 (> 99%)	6 (100%)	
Split		1 (< 1%)	0	
Number of HLA mismatches	18	5 (4, 6)	5 (4, 5)	0.401
Heart allograft cold ischemia time (h)	7	2.9 (2.2, 3.8)	3.1 (2.0, 3.5)	0.879
Liver allograft cold ischemia time (h)	9	7.0 (5.1, 8.0)	7.3 (6, 8.3)	0.438

BMI body mass index, *CHLT* combined heart–liver transplant, *HLA* human leukocyte antigen, *IQR* interquartile range, *SHLT* sequential heart–liver transplant

^aAdditional data for liver donors in SHLT are presented separately (Table 3)

^bWilcoxon rank-sum test for continuous data and Fisher's exact test for categorical data

^cData shown for SHLT represent liver donors

at the same time as a donor heart [3, 4]. Our results seem to substantiate these findings. In the USA, the UNOS Registry includes six cases where a patient received an OLT following an OHT, while listed for OLT at the time they received OHT. Despite the small size of this SHLT cohort, patient and allograft survival in this SHLT cohort were consistently lower than the CHLT cohort. Potential disadvantages of SHLT include a delay in identifying a donor and receiving an OLT, with a median time between OHT and OLT exceeding 6 months in the SHLT cohort, as well as a lack of immunoprotection observed from previous studies from the transplantation of multiple organs from the same donor [6–8]. In particular, hepatic transplantation induces immunoprotection to subsequent grafts by reduction in DSAs [8, 9]. When compared with OHT, CHLT decreases the risk of T cell-mediated rejection, antibody-mediated rejection, and cardiac allograft vasculopathy [9, 10]. Similar findings have been demonstrated in other combined solid organ transplantations as combined liver–kidney transplantation has also been shown to impart similar immunoprotection, compared with solitary kidney transplantation [9, 11, 12].

The superior outcomes of CHLT is particularly relevant as this group contained what may be considered higher risk patients for OHT, although UNOS status 1A was not different between two groups. Previous studies of OHT have shown that pre-transplant severity of illness is associated with 1-year post-transplant mortality [13]. Forty-five percent of patients in CHLT cohort of our analysis were critically ill and admitted to the intensive care unit, while the majority of the patients in the SHLT cohort were outpatients. Moreover, the CHLT cohort included patients who also received concurrent kidney transplantation, those requiring mechanical ventilation, and patients requiring heart transplantation related to congenital heart defects, which are known to increase the risk of post-transplant mortality at 1 year. Other factors known to increase the risk of mortality, including advanced donor age, prolonged donor heart ischemia, and female donor to male recipient heart transplantation, did not differ between the two groups [13, 14].

Although there were no differences in the final MELD score between CHLT and SHLT recipients, the final laboratory MELD scores at OLT in the latter group (median of

Table 3 Characteristics of liver donors in sequential heart–liver transplant procedures ($N=6$)

Variable ^a	Cases missing data	Median (IQR) or N (%)
Age (year)	0	29 (22, 42)
Male gender	0	3 (50%)
Race/ethnicity	0	
Non-Hispanic white		6 (100%)
Height (cm)	0	175 (165, 183)
Weight (kg)	0	63 (61, 98)
BMI (kg/m^2)	0	23 (22, 29)
Cause of death	0	
Anoxia		1 (17%)
Cerebrovascular/stroke		2 (33%)
Head trauma		3 (50%)
Number of HLA mismatches	1	4 (3, 4)

BMI body mass index, HLA human leukocyte antigen, IQR interquartile range, SHLT sequential heart–liver transplant

^aData for liver donors in SHLT are presented separately (Table 3)

^bWilcoxon rank-sum test for continuous data and Fisher's exact test for categorical data

Number at risk						
CHLT	301	215	179	154	132	114
SHLT	6	5	4	4	4	3

Fig. 2 Patient survival

11, IQR: 10, 18) indicated low priority for OLT. No difference was found in the other risk factors for OLT in our analysis which included ischemic time, highest sodium level, gamma-aminotransferase values, and female sex [12, 15]. Although cardiovascular disease as the cause of death in donors is associated with poor recipient survival, this was not prevalent in the SHLT cohort with our analysis. This would support the claim that the worse outcomes associated with SHLT are not due to patient undergoing SHLT being

Number at risk						
CHLT	301	215	179	154	131	112
SHLT	6	5	4	4	4	3

Fig. 3 Liver allograft survival

Number at risk						
CHLT	298	220	181	161	137	117
SHLT	6	5	4	4	4	3

Fig. 4 Heart allograft survival

sicker or higher risk. These worse outcomes that occur are likely due to the lack of immunoprotection offered by multiple grafts from a single donor. This study indicates that, when possible, the heart and liver should be transplanted at the same time, with consideration of passing on single organs and waiting for the availability of both organs from a single donor.

The present study has limitations inherent to its retrospective analysis and the limited sample size of the SHLT cohort. Although the analysis included a relatively large CHLT cohort, only six patients could be included in the SHLT cohort. The study included a significant time period from 1987 to 2019, and therefore evolving changes in clinical

practice over the recent years may not be truly reflected in these data. The patients in the two groups were not precisely matched based on clinical data and severity of illness. However, the CHLT group contained higher risk patients based on commonly used clinical factors. Limitations are also derived from the current UNOS data. The authors were not able to evaluate the reason for delay in liver transplant nor the details of the perioperative course. Another limitation is the lack of inclusion of immunosuppression therapies in our analysis due to their unavailability. Despite these limitations, these data suggest that CHLT is superior to SHLT in survival rate and graft survival and may help guide clinicians in making important decisions in a very small and unique patient population. Future research in these patients should investigate the role of immunoprotection in combined organ transplantation from the same donor.

Compliance with Ethical Standards

Conflicts of interest The authors declare no conflict of interests.

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