OPEN

Progress in Combined Liver–lung Transplantation at a Single Center

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Background. Combined liver–lung transplantation is an uncommon, although vital, procedure for patients with simultaneous end-stage lung and liver disease. The utility of lung–liver transplant has been questioned because of initial poor survival outcomes, particularly when compared with liver-alone transplant recipients. **Methods.** A single-center, retrospective review of the medical records of 19 adult lung–liver transplant recipients was conducted, comparing early recipients (2009–2014) with a recent cohort (2015–2021). Patients were also compared with the center's single lung or liver transplant recipients. **Results.** Recent lung–liver recipients were older (P = 0.004), had a higher body mass index (P = 0.03), and were less likely to have ascites (P = 0.02), reflecting changes in the etiologies of lung and liver disease. Liver cold ischemia time was longer in the modern cohort (P = 0.004), and patients had a longer posttransplant length of hospitalization (P = 0.048). Overall survival was not statistically different between the 2 eras studied (P = 0.61), although 1-y survival was higher in the more recent group (90.9% versus 62.5%). Overall survival after lung–liver transplant was equivalent to lung-alone recipients and was significantly lower than liver-alone recipients (5-y survival: 52%, 51%, and 75%, respectively). Lung–liver recipient mortality was primarily driven by deaths within 6 mo of transplant due to infection and sepsis. Graft failure was not significantly different (liver: P = 0.06; lung: P = 0.74). **Conclusions.** The severity of illness in lung–liver recipients combined with the infrequency of the procedure supports its continued use. However, particular attention should be paid to patient selection, immunosuppression, and prophylaxis against infection to ensure proper utilization of scarce donor organs.

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Combined liver–lung transplantation (CLLT) is performed in patients with end-stage lung and liver failure who are not expected to benefit from liver-alone (LiT) or lung-alone (LuT) transplant. CLLT is one of the least common types of multiorgan transplantation, utilized in only 16 patients in 2021 and 22 patients in 2020 in the United States.[1] Historically, CLLT was most frequently performed in patients with systemic illnesses affecting the lungs and liver, especially cystic fibrosis (CF)[2,3] with associated cirrhosis.[4-6] Most initial cases in the United States were pediatric, with adult cases growing in prevalence over time.[2,7,8] Many CF patients with severe liver dysfunction who received LuT would experience hepatic decompensation postoperatively, leading to increased mortality.[2] Patients with α-1 antitrypsin deficiency may also have concurrent lung and liver failure necessitating CLLT.[3,9] Liver-specific indications for CLLT include patients with

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porto-pulmonary hypertension who do not respond to treatment.[10] Liver dysfunction is common in LuT candidates and recipients. For example, 41.4% of COPD patients experience steatosis, 36.9% develop nonalcoholic steatohepatitis, and 61.3% develop fibrosis.[11] Therefore, LuT candidates with severe liver dysfunction may have improved outcomes with CLLT.

Initial outcomes in CLLT recipients were suboptimal. Early studies reported 1-y survival rates ranging from 56% to 70%.[2,12] However, advances in immunosuppressive medications, patient selection, and postoperative monitoring have resulted in 1-y survival rates ranging from 82.5% to 89.5% in recent publications.[4,13,14] Survival after CLLT is now statistically comparable to LuT recipients[13] but is lower than LiT recipients.[14] These results have led to some debate about the utility of CLLT in the literature and call for improved protocols for recipient selection and patient care.[13-15] The small number of CLLTs performed each year makes these improvements slow and generally incremental despite the growing need for this lifesaving procedure.

The JC Walter Jr Transplant Center at Houston Methodist Hospital (HMH) has performed a relatively high volume of CLLT procedures in adults since 2009. Therefore, this article presents detailed perioperative information for these patients and describes center-specific practice guidelines informed by posttransplant outcomes for this unique population. We aim to provide insights beyond what is reported in United Network for Organ Sharing (UNOS) database.[13] The high transplant volume has also allowed our center to develop and implement patient selection and treatment protocols that have improved patient outcomes in recent years.[16]

Here, we perform a retrospective analysis of CLLT recipients at HMH to demonstrate how our center's protocols have improved CLLT outcomes over time. This study builds upon data previously published by Yi et al[3,7] from our center to suggest how providers might recognize potential CLLT recipients and improve posttransplant outcomes.

MATERIALS AND METHODS

The medical records of all patients over 18 y of age undergoing CLLT at HMH between February 1, 2009, and November 30, 2021, were reviewed retrospectively under IRB protocol #Pro00000587. The research was conducted in accordance with the Declaration of Helsinki and the Declaration of Istanbul. Patients receiving organs in addition to a lung and liver (eg, heart–lung–liver transplant) were excluded from this analysis. Decisions for dual listing of patients on the liver and lung waitlists were made at multidisciplinary review boards. Donor and patient operations for CLLT followed the surgical procedures described previously utilizing a lung-first approach.[3,7]

To better understand how patient selection and outcomes have changed over time, the cohort was divided into 2 eras: 2009 to 2014 and 2015 to 2021. In 2015, the lung transplantation team at HMH introduced the Houston Methodist Lung Transplant Risk Model[16] to inform the decision on whether to list a patient for transplant. The model is now used along with other metrics of patient health to inform whether a patient should be listed for LuT at HMH. Additionally, physician experience and patient management have evolved over time.

Statistics

Demographics, medical condition, vital status, and graft status were reported as frequencies and proportions for categorical variables and as the median and interquartile range for continuous variables. Comparisons were made retrospectively to patients undergoing solitary LuT and LiT at HMH during the same period. No lung or liver grafts were treated with machine perfusion in this cohort. Differences between groups (liver alone, lung alone, and CLLT) were determined by chi-square or Fisher exact tests for categorical variables and the Kruskal-Wallis test for continuous variables as appropriate. Patient and graft survival at 6 mo and 1, 5, and 10 y was depicted using Kaplan-Meier survival curves. Differences in the outcomes between groups (organ transplant type and LAS ≤/≥50) were determined by the log-rank test. All the analyses were performed on Stata version 17.0 (StataCorp LLC, College Station, TX). A P value of <0.05 was considered statistically significant.

RESULTS

Recipient Details

During the study period, 19 patients underwent CLLT. The median waitlist time for transplantation was 91 d (range: 9–865 d). None of the patients tested positive for severe acute respiratory syndrome coronavirus 2019 in the perioperative period. Recipient demographics are presented in Table 1. The median age was 54.1 (31.4–63.9) y. The median body mass index (BMI) was 22.1 (20.1–28.3). The most common comorbidities were diabetes, hypertension, and tobacco use (Table 1). Only 3 patients had no comorbidities; 7 patients had 1 comorbidity, 6 had 2 comorbidities, and 3 had 3 comorbidities. Seven had prior abdominal surgery, including cholecystectomies, umbilical hernia repairs, and appendectomies. Most (12, 63.2%) were waiting at home when they received their organ allocation offer, and 7 (36.8%) were inpatients, including 3 (15.8%) in intensive care.

In general, recipient demographics were similar between the earlier era (2009–2014) and the recent era (2015–2021, Table 1). However, there were 2 notable differences. First, patients receiving CLLT between 2015 and 2021 were significantly older (P = 0.004). These patients also had a significantly higher BMI (P = 0.033), although the median BMI of 24.9 still qualified as normal.

Indications for Transplantation

Lung disease etiologies were most often CF (5, 26.3%), predominantly in the initial era, and idiopathic pulmonary fibrosis (5, 26.3%; Table 2), predominantly in the more recent era. Primary lung disease etiology was similar between the 2 eras (P = 0.40, Table 2). The median LAS was 44.2 (36.0–74.7). Seven patients (36.8%) had an LAS over 50. Three (15.8%) patients received pretransplant mechanical ventilation. Patients required neither extracorporeal membrane oxygenation nor inotropes before transplant. There were no statistically significant differences in lung function tests between the 2 eras studied (Table 2). The Houston Methodist Lung Transplant Risk Model scores were similar between the 2 eras (P = 0.72, Table 2).

TABLE 1.

Demographics and clinical characteristics of patients receiving combined liver–lung transplant by era

	All patients	Era 2009–2014	Era 2015–2021	
Variable	**N = 19**	**n = 8**	**n = 11**	***P***
Age in years, median (IQR)	54.1 (31.4–63.9)	46.2 (27.4–52.5)	62.7 (58.7–66.1)	**0.004**
Sex, n (%)				
Male	10 (52.6)	3 (37.5)	7 (63.6)	0.37
Female	9 (47.4)	5 (62.5)	4 (36.4)	
Race/ethnicity, n (%)				
White	17 (89.5)	8 (100.0)	9 (81.8)	0.49
Hispanic	2 (10.5)	0 (0.0)	2 (18.2)	
Time on waitlist in days, median (IQR)	91 (41–356)	142 (90–385)	65.0 (23–235)	0.11
BMI, median (IQR)	22.1 (20.1–28.3)	20.4 (18.6–21.7)	24.9 (22.1–29.3)	**0.03**
Comorbidities, n (%)				
Diabetes (type 1 or 2)	7 (36.8)	4 (50.0)	3 (27.3)	0.38
Hypertension	7 (36.8)	2 (25.0)	5 (45.5)	0.63
Tobacco Use	7 (36.8)	2 (25.0)	5 (45.5)	0.63
Hypothyroidism	5 (26.3)	4 (50.0)	1 (9.1)	0.11
Chronic renal insufficiency	1 (5.3)	0 (0.0)	1 (9.1)	1.00
Coronary artery disease	1 (5.3)	0 (0.0)	1 (9.1)	1.00
Heavy alcohol use	1 (5.3)	0 (0.0)	1 (9.1)	1.00
Pretransplant medical condition, n (%)				0.27
In ICU	3 (15.8)	0 (0.0)	3 (27.3)	
In hospital, not in ICU	4 (21.1)	3 (25.0)	1 (9.1)	
Not hospitalized	12 (63.2)	5 (62.5)	7 (63.6)	
Pretransplant ventilatory support, n (%)	3 (15.8)	2 (25.0)	1 (9.1)	0.55
Pretransplant dialysis, n (%)	0 (0)	0 (0.0)	0 (0.0)	1.00

BMI, body mass index; ICU, intensive care unit; IQR, interquartile range.

TABLE 2.

Lung disease severity and etiology in combined liver–lung transplant recipients

	All patients	Era 2009–2014	Era 2015–2021	
Variable	**(N = 19)**	**(n = 8)**	**(n = 11)**	***P***
Lung allocation score, median (IQR)	44.2 (36.0–74.7)	40.2 (37.4–50.6)	47.7 (39.3–76.7)	0.53
Lung function tests, median (IQR)				
FEV1 % predicted[a]	26.5 (20.5–36.0)	25.0 (19.5–31.5)	25.0 (20.0–36.0)	0.37
FVC in L[a]	43.0 (31.3–49.5)	36.5 (29.8–48.0)	43.0 (31.0–48.0)	0.28
pCO_2 in mm HG	44 (41–61)	50.5 (43.3–78.5)	44.5 (41.0–61.0)	0.20
6-min walk in feet, median (IQR)	600 (78–888)	575 (175–856)	588 (119–855)	0.92
Lung disease diagnosis, n (%)				0.40
Cystic fibrosis	5 (26.3)	4 (50.0)	1 (9.1)	
Idiopathic pulmonary fibrosis	5 (21.1)	2 (25.0)	3 (27.3)	
Alpha-1 antitrypsin deficiency	2 (10.5)	1 (12.5)	1 (9.1)	
Bronchiectasis	2 (10.5)	0 (0.0)	2 (18.2)	
Usual interstitial pneumonia	2 (10.5)	0 (0.0)	2 (18.2)	
Interstitial lung disease	1 (5.3)	0 (0.0)	1 (9.1)	
Obliterative bronchiolitis	1 (5.3)	1 (12.5)	0 (0.0)	
Pulmonary hypertension	1 (5.3)	0 (0.0)	1 (9.1)	
Lung transplant risk model score,[16] n (%)				0.72
Low risk	4 (21.1)	2 (25.0)	2 (18.2)	
Medium risk	8 (42.1)	4 (50.0)	4 (36.4)	
High risk	7 (36.8)	2 (25.0)	5 (45.5)	

[a]Data available for 18 of 19 patients.
FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range; pCO_2, partial pressure of carbon dioxide.

Patients' primary liver diseases were most frequently CF (4, 21.1%) in the initial era and hepatitis C cirrhosis (5, 26.3%) in the more recent era. Liver disease etiologies were similar in the 2 eras studied (P = 0.10, Table 3). The median model of end-stage liver disease (MELD) score was 10 (7–11), and median albumin was 2.8 (2.6–3.4). All but 2 patients had a MELD score below 15 (89.5%, Table 3). Only 1 patient had a MELD score above 30 (5.3%) due to autoimmune hepatitis and cirrhosis in combination with pulmonary hypertension. Additional variables describing the patients' pretransplant

TABLE 3.

Liver disease severity and etiology in combined liver–lung transplant recipients

Variable	All patients (N = 19)	Era 2009–2014 (n = 8)	Era 2015–2021 (n = 11)	*P*
MELD score, median (IQR)	10 (7–11)	10 (9–11)	11 (7–13)	0.99
Serum albumin in g/dL, median (IQR)	2.8 (2.6–3.4)	3.3 (2.8–3.6)	2.8 (2.5–3.3)	0.18
Primary liver disease diagnosis, n (%)				0.10
Hepatitis C cirrhosis	5 (26.3)	2 (25)	3 (27.3)	
Cystic fibrosis	4 (21.1)	4 (50)	0 (0.0)	
Nonalcoholic steatohepatitis	3 (15.8)	0 (0.0)	3 (27.3)	
Alpha-1 antitrypsin deficiency	2 (10.5)	1 (12.5)	1 (9.1)	
Autoimmune hepatitis	2 (10.5)	1 (12.5)	1 (9.1)	
Cryptogenic cirrhosis	2 (10.5)	0 (0.0)	2 (18.2)	
Alcohol-associated liver disease	1 (5.3)	0 (0.0)	1 (9.1)	
Liver disease complications, n (%)				
Ascites	10 (52.6)	7 (87.5)	3 (27.3)	**0.02**
Encephalopathy	6 (31.6)	4 (50.0)	2 (18.2)	0.32
Varices	11 (57.9)	7 (87.5)	4 (36.4)	0.06
TIPS	1 (5.3)	0 (0)	1 (5.3)	1.00
Spontaneous portosystemic shunts[a]	4 (21.2)	2 (10.6)	2 (10.6)	1.00

[a]Spontaneous portosystemic shunts included 3 splenic veins to left renal vein shunts and 1 superior mesenteric vein to right renal vein shunts.
IQR, interquartile range; MELD, model of end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt.

TABLE 4.

Demographics and clinical characteristics of donors for combined lung–liver transplant recipients

Variable	All patients (N = 19)	2009–2014 (n = 8)	2015–2021 (n = 11)	*P*
Age, n (IQR)	23.0 (20.0–35.0)	25.0 (21.0–35.5)	22.0 (19.0–32.0)	0.71
Sex, n (%)				
Male	15 (78.9)	7 (87.5)	8 (72.7)	0.60
Female	4 (21.1)	1 (12.5)	3 (27.3)	
Race, n (%)				0.82
White	11 (57.9)	4 (50.0)	7 (63.6)	
Hispanic	5 (26.3)	3 (37.5)	2 (18.2)	
Black	3 (15.8)	1 (12.5)	2 (18.2)	
BMI, median (IQR)	22.5 (19.9–25.2)	21.6 (20.1–25.3)	22.9 (20.5–24.8)	0.82
Diabetes	0 (0)	0 (0)	0 (0)	
Cause of death, n (%)				1
Head trauma	10 (52.6)	4 (50.0)	6 (54.5)	
Cerebrovascular/Stroke	8 (42.1)	4 (50.0)	4 (36.4)	
Anoxia	1 (5.3)	0 (0.0)	1 (9.1)	

BMI, body mass index; IQR, interquartile range.

condition are presented in Table 3. Most recipients (12, 63.2%) had at least 1 common liver disease complication (encephalopathy, ascites, and/or varices), with 5 recipients having all 3.

CLLT recipients in the 2015–2021 cohort were less likely to have ascites than patients in the 2009–2014 cohort (P = 0.020, Table 3). Recent CLLT recipients also trended toward a reduced likelihood of having varices at transplant, but the differences were not statistically significant (P = 0.059, Table 3). Otherwise, these 2 groups of patients experienced similarly severe liver disease (Table 3).

Donor Details

Donor demographics and ischemia times are presented in Table 4. All were brain-dead donors. The donors were predominantly White and male. Median age and BMI were 23.0 (20.0–35.0) and 22.5 (19.9–25.2), respectively. None were positive for hepatitis B virus or hepatitis C virus; most were positive for cytomegalovirus (84.2%). Clinical infections were present in 13 (68.4%). The donor demographics were not significantly different between the 2009–2014 and 2015–2021 cohorts (Table 4).

Operative Details

Data summarizing operative procedures are presented in Table 5. All patients underwent sequential lung and then liver transplantation under the same anesthesia. Median lung ischemia time was 3.6 (2.6–4.1) h. Most patients (17/19, 89.4%) received double lung transplants; 1 patient (5.3%) received a right lung, and a second patient (5.3%) received a left lung. A greater proportion of CLLT recipients received a double-lung transplant (n = 17; 89.5%) than LuT recipients (n = 669/1055; 63.4%) during the same period at our center (P = 0.02).

TABLE 5.

Operative details, postoperative outcomes, and causes of death for combined lung–liver transplant recipients

Variable	All patients (N = 19)	Era 2009–2014 (n = 8)	Era 2015–2021 (n = 11)	*P*
Operative variables, median (IQR)				
Lung ischemia time in hours	3.6 (2.6–4.1)	3.3 (2.5–3.6)	3.8 (3.2–5.1)	0.12
Liver cold ischemia time in hours	7.3 (6.0–8.6)	6.0 (5.8–6.4)	8.5 (7.5–10.4)	**0.004**
Liver warm ischemia time in minutes	27.0 (20.5–31.5)	27.5 (19.8–20.3)	27.3 (20.3–29.9)	0.73
PRBC units administered	5.0 (2.0–8.0)	7.5 (4.0–8.3)	6.0 (2.5–8.0)	0.12
FFP units administered[a]	2.5 (0.0–5.8)	5.0 (2.0–9.0)	3.0 (0.0–6.0)	**0.049**
Platelet units administered[a]	0.5 (0.0–6.0)	6.0 (3.0–12.0)	0.0 (0.0–0.0)	0.07
Immunosuppression, induction, n (%)				**0.031**
Methylprednisolone	2 (10.6)	2 (25)	0 (0)	
Methylprednisolone, daclizumab	2 (10.6)	2 (25)	0 (0)	
Methylprednisolone, basiliximab	15 (78.9)	4 (50)	11 (100)	
Immunosuppression, maintenance, n (%)				1.00
Tacrolimus, mycophenolate, prednisone	18 (94.7)	8 (100)	10 (90.9)	
Tacrolimus, sirolimus, prednisone	1 (5.3)	0 (0)	1 (9.1)	
Postoperative outcomes				
ICU length of stay in days,[b] median (IQR)	9.0 (5.3–23.3)	6.0 (4.0–22.0)	12.0 (8.5–33.5)	0.22
Hospital length of stay in days, median (IQR)	29.0 (14.5–59.5)	12.5 (10.3–40.0)	43.0 (27.5–63.5)	**0.048**
Posttransplant dialysis, n (%)	4 (21.1)	2 (25)	2 (18.2)	1.00
Sepsis within 30 d of transplant, n (%)[c]	4 (21.1)	4 (50)	0 (0)	**0.02**
Acute rejection, n (%)				1.00
Lung	1 (5.3)	1 (12.5)	0 (0.0)	1.00
Liver	0 (0.0)	0 (0.0)	0 (0.0)	
Graft failure				
Lung graft failure	0 (0.0)	0 (0.0)	0 (0.0)	1.00
Liver graft failure	1 (5.3)	1 (12.5)	0 (0.0)	
Causes of death	**(n = 9)**	**(n = 5)**	**(n = 4)**	1.00
Liver graft failure[d]	1 (11.1)	1 (20.0)	0 (0.0)	
Infection/sepsis	5 (55.6)	2 (40.0)	3 (75.0)	
Cerebrovascular hemorrhage	1 (11.1)	1 (20.0)	0 (0.0)	
Cardiovascular	1 (11.1)	0 (0.0)	1 (25.0)	
Pulmonary graft failure (BOS)	1 (11.1)	1 (20.0)	0 (0.0)	

[a]Data available for 18 of 19 patients.
[b]Data available for 14 of 19 patients.
[c]All infections consisted of gram-negative bacterial respiratory sepsis, with concordant positive blood cultures in 4 of 5 cases. These infections all progressed to sepsis and death. Gram-negative bacteria were always *Klebsiella* and/or *Pseudomonas* species.
[d]Graft failure due to recurrent hepatitis C virus.
Bold *P* values denote statistical significance ($P > 0.05$).
BOS, bronchiolitis obliterans syndrome; FFP, fresh frozen plasma; ICU, intensive care unit; IQR, interquartile range; PRBC, packed red blood cells.

All patients received whole liver allografts. Liver cold ischemia time (CIT), at 7.3 h (6.0–8.6), was predictably longer than the lung ischemia time. Liver CIT was also significantly longer in the 2015–2021 era ($P = 0.004$, Table 5). Median liver warm ischemia time was 27.0 min (20.5–31.5, Table 5). Five patients had portosystemic shunts, including 1 transjugular intrahepatic portosystemic shunt catheter and 4 spontaneous venous collaterals. No venous collaterals were addressed intraoperatively because our center's experience is that these spontaneously close with the resolution of portal hypertension.

Coagulopathy was monitored intraoperatively by rotational thromboelastography. Measurements were routinely taken at incision, before reperfusion, and after arterial anastomosis for each organ. Intraoperative blood product administration included 5 (2–8) units of packed red blood cells, 2.5 (0–5.8) units of fresh frozen plasma, and 0.5 (0–6) units of platelets. Recent CLLT recipients (2015–2021) received significantly fewer units of fresh frozen plasma during the transplant operation ($P = 0.048$, Table 5). Only 2 patients required cryoprecipitate, receiving 3 and 10 units, respectively.

Postoperative Management and Complications

Median postoperative intensive care unit (ICU) length of stay was 9 d (5.3–23.3), and median hospitalization length of stay was 29 d (14.5–59.5, Table 5). Patients in the recent cohort had a longer hospital length of stay than early CLLT recipients ($P = 0.048$, Table 5). Fluid and inotrope management was optimized for target values of mean arterial pressure > 65 mm Hg. Before 2018, nutrition care occurred at the clinical team's discretion. In 2018, our lung transplant team initiated a nutrition inpatient posttransplant clinical practice guideline. This protocol includes a goal to start feeding within 24 h of surgery (oral or feeding tube). Parenteral supplementation is utilized when the patient does not meet enteral or oral nutrition goals.

In the 2008–2014 cohort, 2 patients received methylprednisolone alone for induction. In addition to methylprednisolone, 2 patients in the early cohort also had daclizumab, and

4 received basiliximab ($P = 0.031$, Table 4). In the 2015–2022 cohort, the induction regimen was standardized to methylprednisolone and basiliximab. Maintenance immunosuppression was almost universally tacrolimus, mycophenolate, and prednisone. The initial tacrolimus target at 6 mo posttransplant was 10 to 12 ng/mL from 2008 to 2012, 10 to 15 ng/mL from 2013 to 2021, and 8 to 10 ng/mL in 2022.

From 2008 to 2017, antibiotic prophylaxis included imipenem/cilastatin, cefepime, piperacillin/tazobactam, aztreonam, metronidazole, vancomycin, linezolid or clindamycin, and micafungin until chest tubes and central lines were removed. Patients with pretransplant multidrug-resistant infections were given intravenous colistimethate. Starting in 2018, patients received cefepime and vancomycin for up to 7 d posttransplant, with continued administration if cultures were positive. Patients with a history of multidrug-resistant infections received meropenem intravenously. Nystatin was given for the duration of hospitalization. Voriconazole was administered for 3 mo after the transplant. Patients who were intolerant of voriconazole received itraconazole.

The most common posttransplant complication was kidney injury, which occurred in 10 (52.6%) patients. Four (21%) required posttransplant dialysis. Steroid-induced hyperglycemia (5, 26.3%) and respiratory insufficiency (5, 26.3%) were also frequently experienced by this cohort. Four (21.1%) patients developed respiratory sepsis within the first 30 d after transplant, all in the 2008–2014 cohort.

Patients also experienced biliary complications (3, 15.8%), debility (3, 15.8%), deep vein thrombosis (2, 10.5%), mechanical ventilation dependence (2, 10.5%), and pleural effusion (2, 10.5%).

Rejection Episodes

Acute rejection was monitored with bronchoscopy for lung and serum biochemistry for liver both during admission for CLLT and postdischarge. One (5.3%) patient experienced the acute cellular rejection of the lung on index admission (Table 5), which was successfully treated with pulse steroids and resolved on subsequent biopsies. There were no instances of acute liver rejection. Frequencies of acute rejection at 1-y posttransplant were available for 18 of the 19 CLLT recipients. One patient (5.3%) experienced chronic lung and liver rejection and died of septic shock 1.5 y after the transplant. Another patient died of bronchiolitis obliterans syndrome 7.4 y after the transplant.

CLLT recipients were treated for lung rejection at similar rates to LuT recipients at our institution ($P = 0.70$, Table 6). These patients also experienced acute rejection episodes at similar rates ($P = 1.00$, Table 6).

Graft and Patient Outcomes

Median postoperative follow-up was 627 (180–2430) d. No patients required lung or liver retransplantation. Liver GS (including death with a functioning graft) rates were 77.8%, 59.1%, 51.7%, and 38.8% at 1, 3, 5, and 10 y after transplant, respectively, with 1 patient experiencing graft failure due to hepatitis C recurrence. This patient died 107 d after the liver graft failed. Lung graft loss was always due to patient death; therefore, lung graft survival rates are equal to CLLT OS rates.

OS rates were 78.6%, 59.1%, 51.6%, and 38.7% at 1, 3, 5, and 10 y after transplant, respectively. Survival rates of the 2 eras studied were not statistically different ($P = 0.61$, Figure 1). Survival rates for patients with LAS at transplant ≥50 were higher than LAS < 50, but the differences were not statistically significant ($P = 0.21$; **Figure S1, SDC**, http://links.lww.com/TXD/A526).

Nine CLLT patients died a median of 480 (74–627) d after transplant (Table 5). Causes of death included infection (5, 55.6%), liver graft failure due to recurrent hepatitis C (1, 11.1%), respiratory failure due to bronchiolitis obliterans syndrome (1, 11.1%), cerebral hemorrhage (1, 11.1%), and cardiac arrest (1, 11.1%). All 5 terminal infections consisted of gram-negative respiratory sepsis, with positive pulmonary and blood cultures for *Klebsiella* and/or *Pseudomonas* species. Only 1 of these patients had CF; 3 had idiopathic pulmonary fibrosis, and 1 had porto-pulmonary hypertension. Four of these patients died within 6 mo after transplant. A significantly higher proportion of CLLT recipients died from infection relative to LiT and LuT recipients overall ($P < 0.001$; **Table S1, SDC**, http://links.lww.com/TXD/A526). The rates at which 3 groups (CLLT, LuT, and LiT) experienced early sepsis (within 6 mo of transplant) approached but did not meet significance ($P = 0.06$).

Comparisons to LuT and LiT Transplant Recipients

OS rates were significantly different between CLLT, LuT, and LiT recipients ($P < 0.001$, Figure 2). LiT recipients had better survival than LuT ($P < 0.001$) or CLLT recipients ($P = 0.01$). CLLT and LuT OS rates were not statistically different ($P = 0.84$). Mortality for CLLT recipients was largely driven by death within the first 6 mo after transplant (**Figure S2, SDC**, http://links.lww.com/TXD/A526). Only 78.9% (n = 15) of CLLT recipients were alive 6 mo posttransplant compared with 95.2% (1067) of LiT recipients and 90.1% (951) of LuT recipients ($P < 0.001$).

Liver and lung GSs post-CLLT were analyzed separately because they were not equal because of 1 instance of liver graft failure before death. Direct comparisons showed that CLLT lung GS was statistically equivalent to LuT graft survival ($P = 0.74$; **Figure S3, SDC**, http://links.lww.com/TXD/A526). There also was not a significant difference between LiT GS and CLLT liver GS, but the comparison approached statistical significance ($P = 0.06$; **Figure S4, SDC**, http://links.lww.com/TXD/A526).

We also compared pretransplant medical condition between CLLT, LuT, and LiT recipients, which was significantly different between groups ($P < 0.001$). A greater proportion of CLLT patients were hospitalized (not in the ICU) pretransplant compared with LuT and LiT recipients (21.1% versus 11.3% and 13.6%, respectively). However, LiT recipients were in the ICU before transplant (44.6%) in greater frequencies than LuT (11.2%) or CLLT recipients (26.3%).

DISCUSSION

Although relatively few patients receive a CLLT each year, the allocation of multiple organs to 1 patient necessitates a careful look at recipient outcomes. The OS rates of HMH CLLT patients are similar to survival rates reported by other authors (**Table S2, SDC**, http://links.lww.com/TXD/A526). Our CLLT patients transplanted since 2015 have seen improved OS. By many measures, these patients were sicker or at higher risk than patients transplanted in 2014 or earlier (older, higher BMI, longer CIT, longer postoperative hospital

TABLE 6.

Lung graft rejection in combined lung–liver transplant recipients compared with lung-alone recipients

	Number with available data	Lung alone (n = 1055)	CLLT (n = 19)	*P*
Treated for lung rejection on index admission, n (%)	794			0.70
No		661 (84.5%)	11 (91.7%)	
Yes		121 (15.5%)	1 (8.3%)	
Lung acute rejection episode within 1 y, n (%)	1074			1.00
No		974 (92.3%)	18 (94.7%)	
Yes		81 (7.7%)	1 (5.3%)	

CLLT, combined lung–liver transplant.

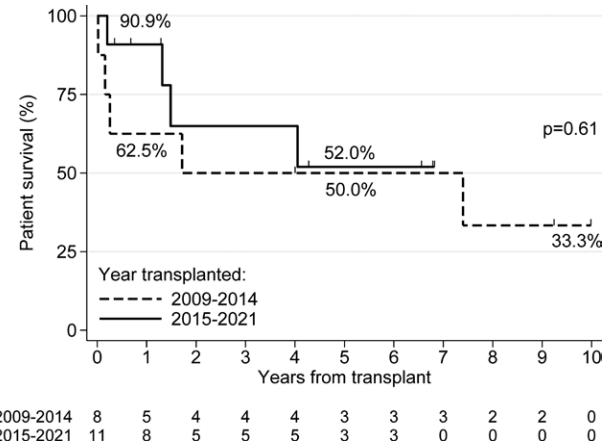

FIGURE 1. Patient survival (at 1, 5, and 10 y) in patients with combined lung–liver transplant stratified by transplant era (2009–2014 vs 2015–2021). For 1-y overall survival, 2009–2014 era vs 2015–2021 era: $P = 0.13$.

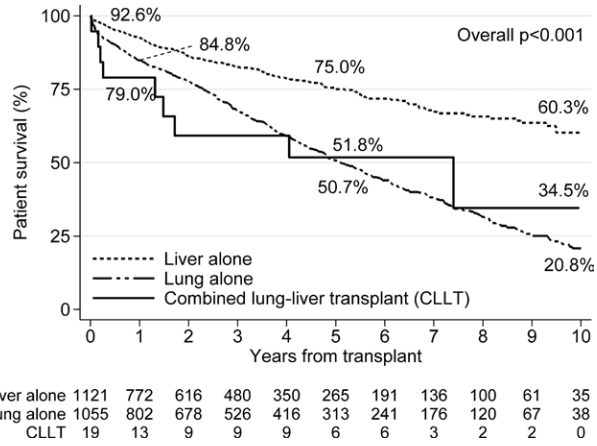

FIGURE 2. Overall patient survival (at 1, 5, and 10 y). Lung-alone vs combined liver–lung transplant: $P = 0.84$. Liver-alone vs combined lung–liver transplant: $P = 0.01$. Lung-alone vs liver-alone transplant: $P < 0.001$.

stay). Yet, these patients experienced an excellent 1-y OS rate of 90.9%. Patient survival in the recent cohort was greater than in the early cohort, although this did not reach statistical significance in this small sample size and limited follow-up time. We nonetheless suggest that accrued experience in patient care can increase survival in CLLT recipients.

We attribute improvements in post-CLLT outcomes to increased center-specific experience[3,7,16] with patient selection, immunosuppression, and antimicrobial stewardship. In addition, changes in postoperative surveillance helped defer complications to later dates posttransplant. This was especially seen in infectious complications: patients were more likely to recover from infection when they were further from their transplant date. Target immunosuppression levels were also lower in more recent years, which likely enhanced patients' ability to fight infections.

Compared with a US national cohort of CLLT recipients, our patients had similar MELD scores (HMH median: 10, UNOS mean: 11.2).[14] Diabetes and pretransplant dialysis prevalence were also similar. HMH patients had a higher incidence of ascites (HMH: 52.6%, UNOS: 19.6%) and were hospitalized before transplant in higher numbers (HMH: 36.8%, UNOS: 33.0%). These data suggest that HMH CLLT recipients may have been slightly sicker than the national average, which could explain any differences in survival rates.

Our CLLT recipients experienced very low rates of rejection, similar to other reports.[8,10,17-19] Rejection rates are also lower for combined heart–lung–liver transplant recipients relative to LuT recipients.[12] In addition, others have reported that CLLT recipients have significantly lower biopsy-confirmed rejection rates relative to LuT recipients.[4,18] The low rejection rates *may* be due to immunoprotection provided by the liver. Some authors have suggested that the liver's immune privilege may protect against rejection and other immune-mediated complications after simultaneous multiorgan transplantation from the same donor,[20,21] including in CLLT.[18] Although the CLLT patients in this study had statistically similar rejection rates to LuT recipients (Table 6), our observations may have been influenced by the low rejection event rate in CLLT recipients.

Organ Allocation Scores in CLLT Recipients

CLLT patients had low MELD scores compared with LiT recipients. Organ allocation for CLLT patients is generally driven by the lungs.[7,13,14,22] The MELD scores for HMH patients are similar to the MELD scores of US national CLLT recipients.[14] These allocation scores may not accurately reflect illness severity in multiorgan transplant candidates.[7,13] Previous studies from our center reported inferior survival for patients with an LAS >50.[3,7] Our current analysis showed statistically equivalent survival for patients with LAS ≥50 and LAS <50. These outcomes suggest that patients who are otherwise good candidates for CLLT should not be excluded from transplant based on high LAS alone.

Infections in CLLT Recipients

Infections and sepsis were major drivers of mortality in this patient cohort, with infections present in 100% (n = 4) of the

patients who died within 6 mo of transplant. Two of the 4 deaths were directly attributable to sepsis. This is in line with a study by Grannas et al,[10] who reported that 50% of their patient deaths (3 of 6) were due to infectious causes. Barshes et al[8] reported that 1 of 3 deaths in their cohort (33.3%) was due to sepsis. Other single-center studies have reported no sepsis deaths.[22] Some have suggested that CLLT recipients may have had too much immunosuppression, leading to higher infection rates.[10] The high overall mortality from sepsis suggests that CLLT recipients may benefit from more aggressive infection prophylaxis and carefully monitored immunosuppression.

CF and CLLT

CF is a common indication for CLLT, and it has historically been the most common diagnosis for these multiorgan transplant recipients.[8] However, in our population, patients with CF were in the minority (26.3% of CLLT recipients). In fact, only 1 CLLT recipient at HMH has had a CF diagnosis since 2015 (1/11 = 9.1%). Most recipients in the recent era have had pulmonary fibrosis combined with cirrhosis. These results are in contrast to an analysis of pooled UNOS data, which found that indications for CLLT were not different before and after 2005.[19] The recent drop in CLLTs for CF patients at HMH may be due to improved CF treatments, or expanded access to CLLT for patients with different disease etiologies, or changes in referral patterns.

Ethics of CLLT

Posttransplant outcomes have led to a growing debate in the literature about the utility of CLLT. The study by Purvis et al[14] of UNOS registry data showed CLLT recipients have significantly worse OS than propensity-matched LiT recipients (P = 0.005). Nationally, CLLT recipients have statistically similar OS to propensity-matched LuT recipients.[13] Our observations agree with these reports. CLLT is rare. The 16 performed nationally in 2021 were dwarfed by the 9236 LiTs performed that year. Therefore, the overall effect on the allocation of liver allografts is quite low, and there are no alternative treatments for recipients experiencing end-stage disease in multiple organs.

Future Directions

Normothermic machine perfusion reduces liver CIT, ischemia-reperfusion injury, and biliary complications.[23] Because CLLT donors in this study were young and healthy (Table 4) and all operations were performed under 1 anesthetic, concerns for longer CIT and liver-specific injuries were mitigated (Table 5). However, if a center's experience suggests prolonged CIT, then normothermic machine perfusion is advisable.

All patients undergoing CLLT in this cohort underwent a lung-first transplant because lung dysfunction was greater than liver dysfunction. A liver-first approach has also been described to reduce primary graft dysfunction and intraoperative blood product usage.[4,6,17] This may be advantageous in highly sensitized patients, although we did not observe a difference in lung-specific rejection (Table 6).

Limitations

This study is limited by its single-center, retrospective nature. The small sample size (n = 19) limits the statistical power to detect differences between CLLT, LuT, and LiT recipients. Also, the 2015–2021 cohort had inherently shorter follow-up durations, including 3 patients transplanted in late 2021 and in 2022, right censored just beyond the 1-y mark in our survival analysis (Figure 1).

Summary

CLLT is a lifesaving procedure for patients with concomitant end-stage liver and lung failure, with improving outcomes over time with accrued experience. OS rates for CLLT recipients are lower than for LiT recipients but are similar to LuT recipients, even beyond 5 y after transplant. Recipients rarely experience graft failure and rejection episodes. For the small number of LuT candidates each year who have severe liver disease and risk hepatic decompensation post-LuT, CLLT should continue to be considered.

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