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Combined Lung and Liver Transplantation: Cleveland Clinic Experience

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Abstract

Background: Combined Lung and Liver Transplantation (CLLT) is a lifesaving procedure for patients with coexisting end-stage lung and liver disease. CLLT is infrequently performed due to organ availability, dual organ allocation, limited guideline for candidate selection, and surgical complexity. This retrospective analysis of nineteen CLLT recipients, the largest known single-center cohort of these patients, focuses on complications and short- and long-term survival.

Methods: The charts of nineteen recipients and their donors who underwent combined CLLT at a tertiary care center from 2006 to 2021 were retrospectively chart reviewed.

Results: Indications for lung transplant included cystic fibrosis (n=11), idiopathic pulmonary fibrosis (n=6), and alpha-1 antitrypsin deficiency (n=2). Liver transplant indications included cystic fibrosis (n=11), alpha-1 antitrypsin deficiency (n=2), alcohol-related cirrhosis (n=2), non-alcoholic steatohepatitis (NASH) (n=2), cryptogenic cirrhosis (n=2), and hepatopulmonary syndrome (n=1). Median recipient age at transplant was 30 years (IQR 25.0-55.5), and eight recipients (42.1%) were female. Mean Lung Allocation Score (LAS) at transplant was 56.4 (SD, 17.3) and mean Model for End-Stage Liver Disease (MELD)-Na score was 17.7 (SD, 8.3). Ten patients experienced acute lung rejection post-transplant, and one of whom was diagnosed with chronic allograft lung dysfunction (CLAD) six years after transplant. The most common post-operative complication was sepsis, with *Pseudomonas aeruginosa* as the most common infection (n=8). However, at time of current analysis, no incidences of graft loss or re-transplantation were reported. Overall survival probabilities were 84% at 1 year after transplant, 69% at 3 years, and 55% at 5 and 10 years.

Conclusions: This largest retrospective analysis of CLLT recipients to date demonstrates favorable survival outcomes with no incidences of re-transplantation, suggesting that CLLT is a viable option in selective recipients.

Abbreviations: AAT: Alpha-1 antitrypsin deficiency; AMR: Immune Mediated rejection; BMI: Body Mass Index; BOS: Bronchiolitis Obliterans Syndrome; CLAD: Chronic allograft lung function; CLLT: Combined Lung and Liver Transplantation; CPS: Child-Pugh Score; DSA: Donation Service Area; ECMO: Extracorporeal Membrane Oxygenation: FEV1: Forced Expiratory Volume in 1 second; FiO2: Fraction of inspired Oxygen; HCV: Hepatitis C Virus; HVPG: Hepatic Portal Venous Pressure Gradient; ICU: Intensive Care Unit; IQR: Interquartile Range; ISHLT: International Society for Heart and Lung Transplantation; LAS: Lung Allocation Score; MELD: Model for End-Stage Liver Disease; NASH: Non-alcholic steatohepatitis; OPTN: Organ Procurement Transplantation Network; RAS: Restrictive Allograft Syndrome; RRT: Renal Replacement Therapy; SD: Standard Deviation; TIPS: Transjugular Intrahepatic Portosystemic Shunt; TRALI: Transfusion-Related Acute Lung Injury

Introduction

Combined Lung and Liver Transplantation (CLLT) is a life-saving procedure for patients with end-stage lung and liver disease. The most common indication for CLLT is cystic fibrosis followed by alpha-1 antitrypsin (AAT) deficiency and portopulmonary hypertension [1]. However, the procedure is infrequently performed due to organ availability, and the ethical issues associated with multi-organ allocation for one candidate, challenging surgical techniques, and limited information regarding appropriate recipient selection.

Based on Organ Procurement Transplantation Network (OPTN) data for January 1, 1988 to November 30, 2021, it comprises only 0.009% of 16,426 multi-organ transplantation in the United States [2]. The first CLLT was performed at the University of Illinois in 1994 and since then a total of 160 CLLT cases have been performed in the United States, per OPTN database [3]. Our center has performed 2,207 cases of single, double en-bloc, and bilateral sequential lung transplantations since 1990, and the 19 cases of CLLT, the largest number in the published literature. Due to theoverall limited experience in CLLT, the selection and management of this patient population is not yet standardized.

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Table 1. Baseline Recipient Characteristics

Total number of patients	19
Recipient age at transplant	30.00[25.0,55.5]
Recipient BMI at transplant	20.43[18.5,24.5]
Gender = Female	8(42.1%)
Liver transplantation indications	N (%)
Cystic fibrosis	11(57.9)
AAT deficiency	2(10.5)
Alcoholic cirrhosis	2(10.5)
NASH	2(10.5)
HCV	0(0.0)
HBV	0(0.0)
Cryptogenic cirrhosis	2(10.5)
Hepatopulmonary syndrome	1(5.3)
Lung Transplant Indications	
Cystic fibrosis	11(57.9)
AAT deficiency	2(10.5)
Idiopathic pulmonary fibrosis	6(31.6)
Hepato pulmonary syndrome	0(0.0)
COPD	1(5.3)
Others	0(0.0)
Waitlist time (days)	160.0[63.0,382.0]
Pre-transplant Past Medical History	N (%)
Hypertension	1 (5.3)
Type1 diabetes	8(42.1)
Type2 diabetes	3(15.8)
CKD	0(0.0)
Cardiovascular disease	2(10.5)
Hypercoagulable state	1 (5.3)
FEV1% at transplant	28.0[17.0,42.4]
FVC% at transplant	41.0 [32.0-53.4]
Six-minute walk test (m)	291.7 (144.3)
Oxygen requirement (FiO_2) prior to transplant (%) Resting Exertion	 34.8 (17.0) 48.7 (27.8)
LAS*at transplant	56.4(17.3)
MELD-Na at transplant	17.7(8.3)
Child-Pugh score at transplant	7.05 (1.22)
INR at transplant	1.38(0.37)
Total bilirubin at transplant	1.46(1.12)
Albumin at transplant	3.14(0.62)
Serum creatinine at transplant	0.69(0.43)
Recipient prior to admission status	N (%)
Home	11(57.9)
Regular nursing floor	6(31.6)
ICU	2(10.5)

Note: Values in [x,y] represent median[Q1,Q3], while values in (x) represent mean(standard deviation).
BMI: Body Mass Index, AAT: alpha 1 antitrypsin, NASH: Nonalcoholic Steatohepatitis, HCV: Hepatitis C Virus, HBV: Hepatitis B Virus, COPD: chronic obstructive lung disease, CKD: chronic kidney disease, FEV1: Forced Expiratory Volume in the First Second, FVC: Forced Vital Capacity, FiO_2: the Fraction of inspired Oxygen, LAS: Lung Allocation Score, MELD: Model For End-Stage Liver Disease, INR: International Normalized Ratio, ICU: Intensive Care Unit
*This study have had access to LAS only instead of CAS (lung composite allocation score), which is a new term as of 2023.

We sought to describe our center's experience with CLLT by defining indications, patient demographics, perioperative and post-transplant course and complications, including acute and chronic rejection, and early and latesurvival outcomes.

Methods

A retrospective medical chart review was performed using the electronic medical record at Cleveland Clinic for all patients older than 18 years who received CLLT due to end-stage lung and liver disease, from January 2007 to June 2022. Patients who received additional organ transplantation at the time of CLLT were excluded from analysis. Patients who underwent staged lung and liver transplantation were also excluded.

Information was collected on patients' baseline demographic characteristics, pre-transplantation medical history, donor characteristics, intraoperative characteristics, post-operative management course and complications, including any infections, instances of rejection according to the International Society for Heart and Lung Transplantation (ISHLT) guideline [4,5] or the need for re-transplantation. (IRB#22-654)

Statistical analysis

Baseline characteristics and unadjusted outcomes were computed using descriptive statistics. Survival outcomes were represented using Kaplan-Meier curves. P-value of less than 0.05 were deemed statistically significant.

Results

Patient Selection and Characteristics

Nineteen patients underwent CLLT at our center (Table 1); 8 patients were female. The median age was 30 years [interquartile range (IQR) 25.0-55.5] and median body mass index (BMI) 20.43 [IQR 18.45-24.48].

Common indications for both liver and lung transplantations included cystic fibrosis (n=11) and AAT deficiency (n=2). Separate etiologies for lung transplantation included idiopathic pulmonary fibrosis (n=6), and chronic obstructive pulmonary disease (n=1) and for liver transplantation included alcoholic cirrhosis (n=2), nonalcoholic steatohepatitis (NASH) (n=2), cryptogenic cirrhosis (n=2), and hepatopulmonary syndrome (n=1).

At time of transplant, median forced expiratory volume in 1 second (FEV1) was 28% (IQR 17.0-42.4). Prior to transplantation, mean fraction of inspired oxygen (FiO_2) was 34.8% [standard deviation (SD), 17.0] at rest and 48.7% (SD, 27.8) on exertion. Mean LAS was 56.4 (SD, 17.3). Mean MELD-Na score and Child-Pugh score (CPS) were 17.7 (SD, 8.3) and 7.05 (SD, 1.22) respectively.

All patients had cirrhosis on CT imaging, which was confirmed by liver biopsy in 12 cases. Eighteen patients had portal hypertension, defined by splenomegaly, esophageal/gastric/rectal varices, as cites, hepatic encephalopathy, porto-systemic shunt, or hepatic portal venous pressure gradient (HVPG) >10mmHg. Ten patients had measured HVPG prior to transplantation with a median of 9.5 mmHg (IQR 5-11.75). Three patients had ascites on ultrasound, and two requiring recurrent paracentesis.Two patients received a transjugular intrahepatic portosystemic shunt (TIPS) procedure prior to surgery due to recurrent ascites and varices. Median of the mean pulmonary artery pressure was 20 mmHg (IQR 17.5-29.4).

Eleven patients (57.9%) were admitted from home at the time of the transplant. Six awaited transplant in the hospital. Two candidates were managed in the intensive care unit (ICU); one patient required mechanical ventilation as a bridge to transplant, and the other patient required continuous renal replacement therapy for acute renal failure from hepatorenal syndrome. Median waitlist time was 160 days (IQR 63.0-382.0).

Baseline Donor Characteristics

Median donor age was 29 years (IQR 25.5-35.0). All donors were brain dead (Table 2). Median PaO_2/FiO_2 ratio (PF ratio) prior to

Table 2. Baseline Donor Characteristics

Donorage (years)	29.0[25.5,35.0]
Brain dead donor (BDD) or donoraftercardiac death(DCD)	BDD 19 (100%) DCD 0 (0%)
PaO_2/FiO_2 ratio prior to procurement	435.0[361.5,479.5]

PaO_2/FiO_2ratio: the arterial partial pressure of oxygen (PaO2) divided by the inspired oxygen concentration (FiO2)

Table 3. Operative Characteristics and Complications and Outcomes

Transplant order: lung first	19 (100%)
Total operative time lung to liver closure (minutes)	827.0[728.5,919.0]
Total ischemic time (lungs)	352.0 [296.0, 409.0]
Total ischemic time (liver)	604.0 [549.6, 638.5]
Transfusions	
Intraoperative total amount fluid received (mL) excluding transfusion product or albumin	6250.0[5487.5,7250.0]
RBC transfused(unit)	6.0[4.0,10.5]
Platelet at time of transplant	74.0[52.5,118.0]
FFP transfused(unit)	3.0[1.0,5.0]
Cryoprecipitate transfused(unit)	3.5[0.0,9.8]
Albumin transfused(mL)	2750.0[1937.5,3250.0]
Nissen fundoplication or anti-reflux procedure	0(0.0 %)
Open chest post-operatively	3(15.8 %)
Open abdomen post-operatively	6(31.6 %)
Complications	
Surgical site (chest/abdomen) issues	0 (0.0 %)
Need for renal replacement therapy post-transplantation	5 (27.8 %)
Renal function recovered	0 (0.0 %)
Peri-operative outcomes	
Return to OR	10(52.6)
Returnto ICU (only during the indexad mission)	6(33.3)
Number of readmission to ICU	2.0[1.3,2.0]
Length of stay after surgery (days)	29.0[14.0,61.0]
Total length of stay in ICU (days)	9.0[6.5,21.5]

RBC: Red Blood Cells, FFP : Fresh Frozen Plasma, OR: Operating Room, ICU: Intensive Care Unit

procurement was 435 [IQR 361.5-479.5].United Network for Organ Sharing (UNOS) regions were identified as local(by Donation Service Area (DSA) until November 2017 and by 250-nautical mile radius afterwards) (n=8), regional (n=7), and national (n=4). One hepatitis C virus (HCV) positive donor was identified (genotype 1a), and the CLLT patient was treated with glecaprevir and pibrentasvir.

Intra-operative Characteristics and Post-operative Complications and Outcomes

All CLLT were performed with bilateral sequential lung transplantation, followed by liver transplantation (Table 3). Median total operative time from chest incision for lung transplant till abdominal closure for liver transplant was 827 minutes (IQR 729-919). Median total ischemic periods were 352 minutes for lung (IQR 296-409) and 604 minutes for liver (IQR550-639). Median total intraoperative fluid requirement excluding transfusion products or albumin, was 6250 ml. Complete transfusion data is described in Table 3. The chest was left open in three patients and the abdomen was left open in 6 patients. All patients had closure in the early post-operative period.

Three patients required Extracorporeal Membrane Oxygenation (ECMO): one via veno-arterial cannulation and two via veno-venous cannulation. Five patients required renal Replacement Therapy (RRT) postoperatively, without renal function recovery. A total of 10 patients (52.6%) returned to the operating room: 9 patients required delayed chest and/or abdomen closure, 2 patients required re-exploration and washout of the chest due to bleeding, and 4 patients required exploratory laparotomy for portal vein thrombectomy (1), revision of vascular anastomosis (1), hematoma evacuation (1), and lysis of intestinal adhesions between small intestines and abdominal wall (1).

Six patients were readmitted to the Intensive Care Unit (ICU) during the index admission. Median length of hospital stay after surgery was 29 days (IQR 14.0-61.0). Median length of ICU stay was 9 days (IQR 6.5-21.5).

Infections during Initial Hospitalization for Transplantation

Ten patients had one or more infections during initial hospitalization for transplantation. Intravenous antibiotics,consultations with Infectious Disease specialists and modification of ongoing treatment were required. Specific post-operative infectious complications are listed in Table 4.

Post-transplant Immunosuppression and Rejection

A total of 10 patients (52.6%) experienced acute rejection based on ISHLT classification of lung allograft rejection [4] (Table 5). Two of them had Antibody Mediated Rejection (AMR) [5] as well which were treated with plasmapheresis and intravenous immunoglobulin. Most of these patients (90%, n=9) developed acute rejections within the first year of transplantation.

Probability of recipient freedom from all rejection was 55.26% (95% Confidence Interval [CI], 36.20%-84.36%) at 0.5 years after transplantation (Figure 1). One patient (5.3%) developed Chronic Lung Allograft Dysfunction (CLAD) [6] with mixed Bronchiolitis Obliterans Syndrome (BOS) and Restrictive Allograft Syndrome (RAS) phenotype 6 years after transplantation. One patient (5.3%) had biopsy-proven mild liver rejection postoperative day 4 and received a steroid therapy.

Three patients (15.8%) received induction therapy with rabbit anti-thymocyte globulin. Eighteen patients (94.7%) received maintenance

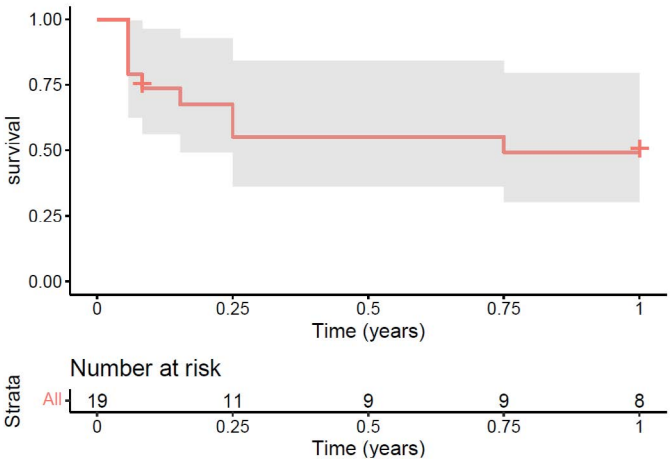

Figure 1. Freedom from All Rejection during the First Post-Transplant Year

Table 4. Infectious Complications during Initial Hospitalizations for Transplantation

Clostridium difficile	3 (16.7 %)
Pseudomonas aeruginosa	8 (44.4 %)
Fungal (eg. Candida)	5 (27.8 %)
Cytomegalovirus viremia	3 (16.7 %)
Post-Transplant Lymphoproliferative Disorder (PTLD)	2 (11.1%)
Peritonitis	1 (5.6%)

Table 5. Post-transplant immunosuppression and rejection

ID	PGD at T0, T72	Induction, type	Maintenance	Posttransplant rejection† and treatment	CLAD	Graft loss	Re-transplantation	Status (as of 1.2023)	Number of days of follow-up
1	1, 0	N	Tacrolimus, Mycophenolate mofetil	3 weeks A1B0: prednisone taper	N	N	N	Alive	1626
2	0, 2	N	Tacrolimus Mycophenolate mofetil	None	N	N	N	Alive	4990
3	3, 3	N	Tacrolimus	None	N	N	N	Dead	10
4	3, 3	Y, rATG	Tacrolimus Mycophenolate mofetil	None	N	N	N	Dead	221
5	1, 1	N	Cyclosporin Mycophenolate mofetil	1 month: empiric pulse steroid concern for ACR; 1 month: De novo class II DQ2 s/p 5-day course of PLEX and IVIG	N	N	N	Dead	848
6	1, 0	N	Tacrolimus Mycophenolate mofetil	3 months A2B0: pulse and taper steroid	N	N	N	Alive	1369
7	1, 1	N	Tacrolimus Mycophenolate mofetil	None	N	N	N	Alive	2678
8	0, 0	N	Tacrolimus Mycophenolate mofetil	None	N	N	N	Alive	5060
9	2, 1	N	Tacrolimus Mycophenolate mofetil	None	N	N	N	Dead	909
10	3, 1	N	Tacrolimus Mycophenolate mofetil	9 months A1B0: steroids; 13 months A2B0: steroid pulse and taper	Y (BOS and RAS)	N	N	Alive	2443
11	N/A	N	Tacrolimus Mycophenolate mofetil	3 weeks A2B0: steroid; 6 weeks A2B0: not treated	N	N	N	Alive	5840
12	1, N/A	N	None	N	N	N	N	Dead	605
13	1, 1	N	Tacrolimus Mycophenolate mofetil	3 weeks A2B0: pred taper; 6 weeks A2B0: steroid pulse and taper	N	N	N	Alive	1398
14	0, 1	Y, rATG	Tacrolimus Mycophenolate mofetil	13 months A1B0: prednisone taper	N	N	N	Alive	1204
15	3, 2	Y, rATG	Tacrolimus	8weeks A1B0, 3months A2B0, 4 months A1B0, 5months A1B0, 6 months A2B0, 7 months A1B0: all treated with steroids	N	N	N	Alive	445
16	0, 1	N	Tacrolimus Mycophenolate mofetil	3 months A2B0: steroid; 9 months A1B0: steroid; 11 months: treated with PLEX, IVIG and rituximab	N	N	N	Alive	844
17	2, 1	N	Tacrolimus Mycophenolate mofetil	3 weeks A2B1R: steroid	N	N	N	Alive	880
18	0, 2	N	Tacrolimus Mycophenolate mofetil	None	N	N	N	Alive	708
19	0, 0	N	Tacrolimus	None	N	N	N	Alive	1294

PGD: Primary lung Graft Dysfunction, T0: within 6 hours of reperfusion, T72: within 72 hours of reperfusion, rATG: rabbit Anti-Thymocyte Globulin, ACR: Acute Cellular Rejection, PLEX: plasma exchange, IVIG: Intravenous Immune Globumin; BOS: Bronchiolitis Obliterans Syndrome, RAS: Restrictive Allograft Syndrome

†Allograft rejection grading is based on International Society for Heart and Lung Transplantation (ISHLT) grading scheme for pulmonary allograft rejection [4].

therapy with tacrolimus. One patient was switched to cyclosporine due to altered mental status, presumed to be an adverse effect of tacrolimus. No acute or chronic graft loss was attributable as a cause of death, and no re-transplantation was performed for neither lung nor liver.

Patient Survival Analysis

Mean survival after transplant probabilities were 84% at 1-year after transplant, 69% at 3 years, and 55% at both 5 and 10 years (Figure 2). At the time of analysis, 14 of 19 patients (73.7%) were alive; 3 of these patients survived for more than 10 years after transplant. Five patients died. Three were CF patients who died during index admission: 2 patients due to septic shock and multiorgan failure, and one patient due to right thalamic intracranial hemorrhage and intraventricular hemorrhage. In the other 2 patients, the causes of death were sepsis and cardiogenic shock, respectively.

Discussion

This analysis is one of the largest retrospective studies of CLLT recipients in the United States. Previous single-center studies have reported 1-year survival rates from 56 to 92% and 3-year survival rates from 62 to 79% [1,7-16]. Most of these studies presented data from three-years of follow up. Overall, our center's CLLT patient population received ten years' follow up and demonstrated higher long-term survival compared to previously published case series. Similar to

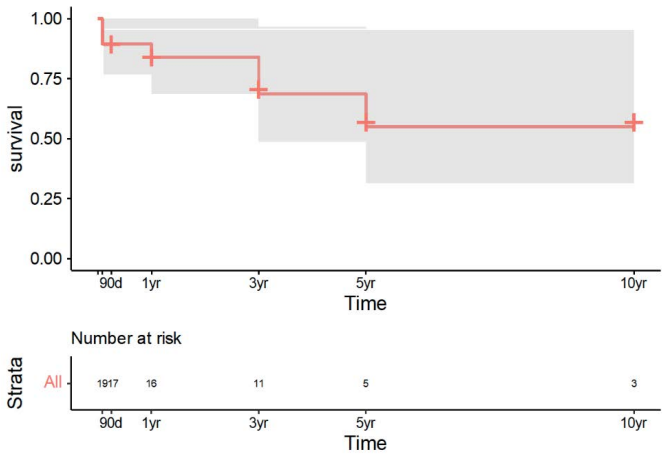

Figure 2. Lung and Liver Transplant Survival Probability in Patients after combined liver and lung transplantation

lung-alone transplant outcomes performed between 2008 and 2015, according to OPTN database, our CLLT survival outcomes were 87.2% at 1-year, 68.7% at 3-years, and 53.5% at 5-years [17].

Candidate selection for combined lung and liver transplantation

Definitive criteria for CLLT patient selection have not yet been determined. Current guidelines recommend against CLLT in patients with albumin < 2g/dL, prothrombin time international normalized ratio (INR) >1.8, severe ascites or encephalopathy. One patient who underwent CLLT despite high INR (2.6) and low albumin (1.7) and had an uncomplicated post-operative course and remains alive, 3 years and 10 months after transplant. Yi et al selected CLLT candidates who qualified for lung transplant after multidisciplinary board review, had both biopsy-proven cirrhosis and a ≥ 10 mmHg portal gradient [11]. In all previously published case series, patients were selected after multidisciplinary discussion. Five patients had good liver function (MELD-Na <17 and CPS ≤ 6) but underwent CLLT due to the presence of cirrhosis. Two patients with high MELD-Na score and low CPS had lower mortality (0/2 patients expired) compared to 9 patients with low MELD-Na and high CPS (1/9 patients expired). These results may indicate CPS is a better predictor of survival outcomes, but the number of patients is too small to be conclusive. At our institution, CLLT candidates were selected after lung and liver multidisciplinary committee review. The decision to CLLT was made after careful evaluation of isolated lung and isolated liver transplantation.

Surgical considerations in combined liver and lung transplantation

While data have been published on liver-first CLLT, all patients in this case series underwent lung-first transplantation. In general, both lungs and liver can be safely transplanted with the acceptable donor ischemic time. Immediate postoperative management of CLLT can be challenging as liver transplantation and lung transplantation have opposing goals regarding volume resuscitation [18-20]. For volume resuscitation, liver transplant requires aggressive colloid resuscitation due to perioperative low systemic vascular resistance and the high likelihood of reperfusion syndrome with reactive oxygen species release from an ischemic liver. However, excess volume administration put transplanted lungs at higher risk of hypervolemia and transfusion-related acute lung injury (TRALI).

Although there are no absolute guidelines that specify which organ should be transplanted first, most centers report a lung-first approach, since lungs are thought to be more sensitive to ischemia than the liver. Some studies report success with a liver-first approach and hypothesized potential benefit from absorption of donor-specific HLA antibodies, correction of coagulopathy prior to lung transplantation, decreased reperfusion injury to transplanted lungs, and decreased in biliary stricture from shorter liver ischemic time [21,22]. Freischlag, et al. reported a patient who received a liver-first CLLT and had numerous initial complications, including biliary stricture, immune thrombocytopenic purpura, and hemoperitoneum [14]. However, further studies are needed to define whether the liver-first approach has advantages over the lung-first approach.

Outcomes of combined lung and liver transplant recipients

Our institution transplants organs from donors who have tested positive for the Hepatitis C virus (HCV), only with recipient patients' consents. One donor was HCV-positive and the recipient was successfully treated with glecaprevir/pibrentasvir after transplantation. Patients with AAT deficiency received chronic augmentation therapy with an alpha-1 proteinase inhibitor until the day of transplantation, as well as postoperatively to preserve function of the newly transplanted organs.

Sepsis was the most common cause of mortality in this study. Patients with cystic fibrosis, who comprise the majority of our CLLT patients, are especially vulnerable to infections postoperatively. Patients with cystic fibrosis undergoing transplantation have demonstrated worse outcomes when colonized with microorganisms such as *Pseudomonas aeruginosa* or *Burkholderiacepacia* [23,24]. The infectious disease specialists determine appropriate antibiotics peri- and post-operatively. Our center's mortality for CLLT cystic fibrosis patients (3/11, 27.2%) was similar compared to overall mortality for all CLLT patients (5/19, 26.3%). Of the 3 cystic fibrosis patients who died, 2 patients had sepsis as cause of death. Aris et al. reports that cystic fibrosis patients colonized with pan drug-resistant microorganisms had similar outcomes as patients colonized with sensitive bacteria [25]. Five of our patients (26.3%) had fungal infection during index hospitalization. Majority of our CLLT population was cystic fibrosis patients with pre-existing fungal colonization. Therefore, we provide at least 3-month fungal prophylaxis post-transplantation. We also recommend such infections should not be contraindications for multiorgan transplantation.

Five of our CLLT patients (26.3%) had an irreversible kidney injury requiring RRT. Although acute kidney injury post-lung transplantation needing renal replacement therapy is a known complication, the rate of irreversible kidney injury on our CLLT population is higher than lung transplantation alone patients (5-13%) [26]. This can be explained by the prolonged nature of multiorgan transplantation surgery associated with higher bleeding risk and frequent hypotension episodes. Also, cystic fibrosis has been demonstrated to be independent factor for AKI after lung transplantation due to nephrotoxic drug exposure such as antibiotics, diabetes, and abnormal calcium metabolism [27]. Of note, one patient was on continuous renal replacement therapy while waiting for CLLT. At that time, kidney co-transplantation was not considered for this patient due to patient's critical illness and organ availability.

Cystic fibrosis patients comprised the majority of our CLLT cohort (57.9%). However, the severity of CF has been declining with CF transmembrane conductance regulator (CFTR) modulator therapy. Changes in overall indications and patient outcomes for CLLT are anticipated. Regardless, the need for CLLT will continue to exist given

the increased recognition of short telomere syndrome with high prevalence of idiopathic pulmonary fibrosis and end-stage liver disease [28].

In this study, 47.4% patients developed acute rejection within the first year, an outcome similar to lung transplantation alone (~50%) [29]. Surveillance transbronchial lung biopsies were performed during the first year to monitor for rejection. Donor-specific antigens were routinely assessed for 10 days postoperatively and with each surveillance bronchoscopy. No patients in this study developed graft loss or needed re-transplantation with median follow-up of 3.3 years and with the longest follow-up over 10 years.

Ethics of performing combined lung and liver transplantation

An important ethical issue in multiorgan transplantation is the equity of allocating multiple scarce and life-saving organs to one person, when they could potentially save more individual lives. OPTN emphasizes on optimal balance between equity (fairness in organ procurement and allocation system) and utility (maximization of net benefit to the community) and concluded that multi-organ transplantation is life-saving therapy for patients who do not have an alternative. However, it must be limited in situations when the expected survival of the multi-organ transplant candidate is poor or the need for second organ is unclear [30]. Comparing heart-lung recipients and bypassed liver transplant waitlist candidates, Goldberg, et al. found that waitlist candidates who had delayed transplantations did not have excess mortality compared to matched multiorgan transplant control groups, which may reduce concerns about inequity [31]. More data are needed to compare outcomes in CLLT patients and bypassed isolated lung or liver transplant patients. Careful selection of candidates under an established system, such as multidisciplinary committee review and standardized selection criteria, will minimize potential ethical issues regarding multi-organ transplantation.

Conclusion

We report one of the largest published retrospective analysis of patients with CLLT published to date over 17 years since 2007 with longer follow-up. Survival outcomes with CLLT compared favorably to survival with isolated lung transplantations. Our data provide the longest follow-up data up to 10 years. Although further study is needed regarding the lung-first vs. liver-first approach, our data confirmed that the lung-first approach was viable option for appropriately selected patients.

Authorship

Jee Young You, MD participated in writing of paper, performance of the research, data collection and analysis. Katie Shen, MD participated in writing of paper, performance of the research, and data collection. Atul C. Mehta, MD participated in research design, writing of the paper, and data analysis. William Carey, MD, Jamak Modaresi Esfeh, MD, Koji Hashimoto, MD, Kenneth McCurry, MD, and James Yun, MD participated in research design, revision of the manuscript, and performance of research. Yifan Wang, MPH and Xiaofeng Wang, PhD contributed to analytic tools and data analysis. Marie Budev, DO participated in research design, writing of the paper, revision of the paper, guiding the course of research progress, performance of the research, and data analysis.

Disclosure

The authors declare no conflict of interest.

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