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Single-Center Long-Term Analysis of Combined Liver-Lung Transplant Outcomes

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Background. Combined lung-liver transplantation (LLT) applies 2 technically challenging transplants in 1 patient with severe 2-organ failure. **Methods.** Institutional medical records and United Network for Organ Sharing database were queried for patients at our institution that underwent LLT from 2000 to 2016. **Results.** Twelve LLTs were performed from 2000 to 2016 including 9 male and 3 female recipients with a median age of 28.36 years. Indications for lung transplantation were cystic fibrosis (8), idiopathic pulmonary fibrosis (3), and pulmonary fibrosis secondary to hepatopulmonary syndrome (1). Indications for liver transplantation were cystic fibrosis (8), alcoholic cirrhosis (1), idiopathic cirrhosis (2), and alpha-1 antitrypsin deficiency (1). Median forced expiratory volume in 1 second at transplant was 27.8% (±20.38%), and mean Model for End-Stage Liver Disease was 10.5 (±4.68). Median hospital stay was 44.5 days. Seventy-five percent of recipients had 1+ new infection during their transplant hospitalization. Patients experienced 0.68 incidences of acute rejection per year with a 41.7% (95% confidence interval, 21.3%-81.4%) probability of freedom from rejection in the first-year. Patient survival was 100% at 30 days, 91.6% at 1 year, and 71.3% at 3 years. At the time of analysis, 7 of 12 patients were alive, of whom 3 survived over 8 years post-LLT. Causes of death were primary liver graft failure (1), bronchiolitis obliterans syndrome (2), and solid tumor malignancies (2). **Conclusions.** Our results indicate that LLT is associated with comparable survival to other LLT series and provides a granular assessment of infectious and rejection rates in this rare population.

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Combined liver-lung transplantation (LLT) is indicated in patients with both end-stage liver and lung disease who cannot survive single-organ transplantation alone. The most common indication for LLT is cystic fibrosis (CF), but patients with alpha-1-antitrypsin (AAT) deficiency or separate liver and lung etiologies may also benefit from LLT due to the high probability of postoperative mortality with a single-organ transplant. Liver-lung transplantation is a rare procedure because of its complexity and need for coordination of multiple teams. As a result, the procedure is only performed at transplant centers with large experience in thoracic and abdominal transplantation. Because of its rarity, there is limited information regarding patient characteristics and outcomes.

Because of the limited volume of patients, there has been significant variability in studies regarding patient selection for LLT, patient demographics, immunosuppression management, and outcomes. Much of the literature consists of single-patient case reports or case series with fewer than 5 patients, and many of the more comprehensive reports are now a decade old or more and do not capture new immunosuppressant and antimicrobial prophylaxis protocols that have since been introduced.[1-11] Therefore, we sought to present a contemporary analysis of LLT to help define indications, most effective technical approach, infectious complications,

and a detailed analysis of rejection morbidity and mortality. The purpose of this report is to assess the outcomes of LLT, including infection, mortality, acute rejection, and other complications of immunosuppression. Using institutional medical records and the United Network for Organ Sharing (UNOS) database, we present an analysis of a large single-center retrospective LLT cohort.

MATERIALS AND METHODS

Study Design

The institutional review board approved this retrospective analysis of institutional medical records with data confirmed using the UNOS database. Eligible patients were 18 years or older at the time of transplantation and have undergone combined consecutive liver and lung transplantation for end-stage liver and lung disease at our institution from January 1, 2000, to December 31, 2016. Any patient receiving any additional allografts at the time of consecutive LLT, including en-bloc heart and lung transplant, was excluded from analysis.

Study Endpoints

The primary endpoint was overall survival. Secondary endpoints included short-term perioperative and graft outcomes including graft failure, perioperative complications, rejection episodes, retransplantation, and 30-day postoperative mortality. Assessment of invasive infections was done by chart review. For patients with CF, isolation of known colonizing organisms posttransplant was adjudicated as infection based on review of Transplant Infectious Diseases assessment during the transplant hospitalization. Rejection was defined as any acute cellular or antibody-mediated rejection confirmed on biopsy. After retransplantation of an allograft, no further immunological or surgical complications are reported for the new allograft.

Statistical Analysis

Baseline characteristics and unadjusted outcomes were computed using descriptive statistics. Survival was plotted using the Kaplan-Meier method.[12] A *P* value less than 0.05 was deemed statistically significant. Statistical analysis was performed using R version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Selection

Lung-liver transplantation is used as a lifesaving therapy in candidates who are contraindicated for isolated lung or liver transplantation is contraindicated due to the severity of the disease process in the nontransplanted organ. In this way, LLT extends transplantation to candidates who otherwise would not be eligible for this therapy.

Candidates selected for and then undergoing LLT all had end-stage lung disease complicated by liver dysfunction to the degree that the multidisciplinary listing committee determined that isolated lung transplantation would pose an unacceptably high risk of hepatic decompensation. Hepatic decompensation risk was defined by the presence of clinical manifestations of liver disease in the setting of elevated bilirubin and/or decreased liver synthetic function. Patients determined to be at risk for liver decompensation underwent liver biopsy. Splenomegaly (n = 6) and portal hypertension with varices (n = 4) were the most common manifestations of liver dysfunction in the cohort.

Although some candidates for LLT had 2 separate etiologies, others had a single underlying diagnosis that manifested in both the lung and liver. This included candidates with underlying diagnoses, such as AAT deficiency, which can manifest the lung as emphysema due to degradation of elastin and in the liver as cirrhosis due to accumulation of unsecreted AAT. Even more prevalently, patients with CF may develop CF-associated liver disease concurrently with lung disease, which is currently the third largest killer of CF patients behind lung disease and transplantation complications.[13]

Patient Demographics

Twelve consecutive LLT operations were performed at our institution from January 1, 2000, to December 31, 2016 (Table 1). This group of liver-lung recipients represents our complete experience with LLT during the study period. There were 9 male and 3 female recipients with median age of 28.36 years and body mass index (BMI) of 20.72. Indications for lung transplantation were CF (8), idiopathic pulmonary fibrosis (3), and pulmonary fibrosis with hepatopulmonary syndrome (1). Indications for liver transplantation were CF (8), alcoholic cirrhosis (1), idiopathic cirrhosis (2), and AAT deficiency (1). At time of transplant, the recipients' mean forced expiratory volume in 1 second at the time of transplant was 27.8%, and Model for End-Stage Liver Disease (MELD) score was 10.5. Mean Lung Allocation Score (LAS) was 58.32 (SD, 21.26; n = 10).

Ten (83.3%) of the patients had biopsy-confirmed cirrhosis. Seven (58.3%) patients had portal hypertension, and 5 (41.7%) patients had varices with 2 patients having 1 or more varicella bleeds. Splenomegaly was present in 8 (66.7%) of

TABLE 1.

Baseline recipient and donor characteristics

Patient characteristics (n = 12)	
Median recipient age at transplant	28.36 years (IQR = 20.33, Range 19.66-56.66)
Median recipient BMI at transplant	20.72 (IQR = 3.33, Range 17.54-25.85)
Recipient sex (male vs female)	75% vs. 25%
Median recipient FEV1% at transplant	19.0% (IQR = 13.75, Range 13.0%-76%)
Mean LAS (n = 10)	58.32 (±21.26, Range 37.38-91.66)
Mean recipient MELD at transplant	10.5 (±4.68, Range 7-24)
Mean INR at transplant	1.19 (±0.20)
Mean total bilirubin at transplant	0.78 (±0.42)
Mean albumin at transplant	3.02 (±0.51)
Mean serum creatinine at transplant	0.74 (±0.42)
Median waitlist time, d	106 (IQR = 182.5, Range 15-975)
Donor characteristics	
Median age, y	29.0 (IQR = 23, Range 21-64)
Median BMI	23.62 (IQR = 4.56, Range 18.32-30.27)
Liver transplant indications	
CF	8 (66.67%)
Idiopathic cirrhosis	2 (16.67%)
Alcoholic cirrhosis	1 (8.33%)
AAT deficiency	1 (8.33%)
Lung transplant indications	
CF	8 (66.67%)
Idiopathic pulmonary fibrosis	3 (25%)
Hepatopulmonary syndrome	1 (8.33%)

IQR, interquartile range; FEV1, forced expiratory volume in 1 second; NR, not reported.

TABLE 2.

Infections during initial hospitalization for transplantation

Infections during transplant hospitalization	58.33% (7/12)[a]
Bloodstream infection	3 (25%)
Candida parapsilosis	
Candida albicans	
VRE	
Clostridium difficile colitis	3 (25%)
VRE peritonitis	2 (16.67%)
Surgical site infection	2 (16.67%)
VRE (abdominal wound)	
Mycobacterium abscessus (clamshell)	
Empyema	2 (16.67%)
Candida albicans	
Mycoplasma species	
Hospital-acquired pulmonary infections	3 (25%)
Mycobacterium abscessus	
Pseudomonas aeruginosa	
Chryseobacterium	

VRE, vancomycin-resistant enterococcus.

patients. The median waitlist time was 106 days for transplantation. All patients received bilateral orthotopic lung transplant (BOLT) and liver transplant on the same day. The mean donor age was 29.0, and the mean BMI was 23.62. Further demographic characteristics are described in Table 1.

Infectious Disease and Immunosuppression

Before transplantation, our hospital's transplant infectious disease service followed up patients per protocol. All lung transplant recipients with CF received at least 3 weeks of antibiotics directed toward pretransplant colonizing organisms. Seven patients had 1 or more new infections during their transplant hospitalization (Table 2). Of those with a significant infection, 57.1% (4/7) had CF. No infections by pretransplant colonizing organisms were seen in CF patients after transplantation. No patients died of infectious complications during their transplant hospitalization.

Over 2 decades encompassed by this study, the immunosuppression regimens were remarkably similar for all patients (Table 3). All patients underwent induction therapy with basiliximab and methylprednisolone. Maintenance immunosuppression consisted of steroid, a calcineurin inhibitor, and either mycophenolate or azathioprine. Nine patients received tacrolimus, whereas 3 received cyclosporine. Six patients received mycophenolate and 1 patient azathioprine. One patient received weekly IVIg treatment due to primary liver dysfunction Before his or her death (Table 3).

Operative Details

Two patients underwent Roux-en-Y choledochojejunostomy, whereas 10 underwent choledochodochostomy. Mean total operative time was 16.17 (SD, 1.97) hours. Mean total ischemia times were 9.12 (SD, 3.13) hours for the liver allografts, 5.40 (SD, 1.81) hours for left lungs, and 5.25 (SD, 1.97) hours for right lungs. Average warm ischemia times were 36.33 (SD, 7.60) minutes for liver, 31.67 (SD, 6.71) minutes for right lung, and 34.67 (SD, 12.34) minutes for left lung allografts (Table 4). One patient underwent liver transplant 4.03 hours before BOLT due to technical considerations and the potential for alloantibody protection.[14]

Outcomes

The patients' median hospital stay was 44.5 days (range, 13-147) posttransplant. Two patients needed reoperation during their transplant hospitalization, 1 for a biliary leak and 1 to control postoperative bleeding in the chest. Two patients had acute kidney injury after their operation, and 1 patient experienced several complications including a biliary stricture, bile leak, idiopathic thrombocytopenic purpura, and hemoperitoneum secondary to a laceration of segment 6 requiring hepatic artery embolization. One patient died of primary liver graft dysfunction during the index hospitalization. No patients experienced primary lung graft dysfunction.

Acute and Chronic Rejection Analyses

Seventy-five percent of patients experienced at least minimal (A1) acute cellular rejection of their lung allografts during the course of the study, based on International Society of Heart and Lung Transplantation criteria.[15] There was high probability of at least 1 rejection episode within the first year posttransplant. Probability of recipient freedom from all rejection was 41.7% (95% confidence interval [CI], 21.3%-81.4%) at 0.5 years after transplantation. However, most rejection in the first year occurred within the first 6 months posttransplantation (Figure 1). The median number of acute rejections was 2 (interquartile range, 0.75-4). Over the course of the study, the average recipient had 0.68 incidences of acute rejections per year. In total, there were 32 lung allograft rejection episodes. Of which, 96.9% (31/32) involved acute cellular rejection and 3.1% (1/32) were primarily driven by antibody-mediated rejection. No patient experienced acute cellular or antibody-mediated liver rejection (Table 3). Overall, 3 patients developed and 2 patients died from chronic lung rejection or bronchiolitis obliterans syndrome (BOS). Freedom from BOS was 100% at 1 year, 88.9% (95% CI, 70.6%-100%) at 3 years, and 49.4% (95% CI 19-9%-100%) at 5 years. There was no chronic liver rejection.

Graft Survival Analysis

At time of analysis, overall 91.6% of liver allografts and 66.6% of initial lung allografts were functioning at the end point (Table 4). Two patients required lung retransplantation. No patients required liver retransplantation. Lung allograft survival probability was 100% at 1 year, 76.2% (95% CI, 52.1%-100%) at 3 years, and 57.1% (95% CI, 19.9%-100%) at 5 years. Liver allograft survival probability was 91.7% (95% CI, 77.3%-100%) at 1, 3, and 5 years (Figure 2).

Patient Survival Analysis

Overall, patient survival probability was 100% at 30 days, 91.7% at 90 days, 91.7% at 1 year, and 71.3% at 3 years (Figure 3). One patient developed posttransplant lymphoproliferative disorder. One patient was notably nonadherent to immunosuppression and subsequently developed BOS as stated above (Table 3). At the time of this analysis, 7 of 12 patients were alive, and 3 of these had survived over 8 years post-LLT. Two patients died from de novo solid tumor malignancies, a possible complication of chronic immunosuppression.[16,17] Of the deceased patients, the causes of death were primary liver graft failure (1), BOS (2),

TABLE 3.

Rejection and infectious complication by immunosuppression

ID	Induction	Maintenance	Posttransplant rejection/treatment course	Graft loss	Retransplantation	Status
1	Basiliximab (20 mg) Methylprednisolone (1000 mg)	Cyclosporine Prednisone (20 mg) Mycophenolate (500 mg BID)	15 mo: Liver mild ACR, treated with steroids 18 mo: Liver mild ductal atrophy, possible early chronic rejection 20 mo: Lung acute and chronic bronchitis/bronchiolitis by biopsy	Lung—2 y, 2 mo, 25 d	No	Died of BOS—2 y, 2 mo, 25 d
2	Basiliximab (20 mg) Methylprednisolone (1000 mg)	Cyclosporine Prednisone (20 mg) Mycophenolate (250 mg BID)	6 mo: lung mild ACR ISHLT grade 2, treated with steroids 8 y: lung mild ACR, A2Bx, treated with steroids 9 y, 3 mo: lung moderate ACR, A3Bx, treated with steroid protocol 9 y, 4 mo: minimal ACR, A1B0, treated with rATG	No	No	Alive—13 y, 6 mo, 12 d
3	Basiliximab (20 mg) Methylprednisolone (1000 mg)	Tacrolimus Prednisone (5 mg)	12 d: mild ACR A2B0, treated with steroids 1 mo: mild ACR, A2B, treated with rATG 4 mo: mild ACR, A2B0, treated with steroids 7 mo: minimal ACR A1B1 8 mo: minimal ACR, A1B1, treated with steroids 3 y: minimal ACR w/ mild lymphocytic bronchiolitis, A1B2, treated with rATG 3 y, 1 mo: minimal ACR 3 y, 5 mo: Constrictive bronchiolitis obliterans w/ minimal lymphocytic bronchiolitis, B1, Ca, treated with Alemtuzumab	Lung—4 y, 4 mo, 14 d	Yes—lung with kidney	Alive—10 y, 3 mo, 10 d
4	Basiliximab (20 mg) Methylprednisolone (1000 mg)	Cyclosporine Prednisone (5 mg) Mycophenolate (1000 mg BID)	3 mo: lung minimal ACR, A1B0, treated with steroids	No	No	Alive—8 y, 11 mo, 10 d
5	Basiliximab (20 mg) Methylprednisolone (1000 mg)	Tacrolimus Prednisone (5 mg)	1 y, 11 mo: lung minimal ACR, A1B0 2 y: no lung ACR, acute and chronic mild bronchiolitis 2 y, 2 mo: new DSA w/ rapidly progressive BOS, treated with rATG, plasmapheresis, rituximab, bortezomib, and alemtuzumab	Lung—2 y, 6 mo, 17 d	Yes	Died of metastatic large cell carcinoma of lung—5 y, 5 mo, 27 d

6	Basiliximab (20 mg) Methylprednisolone (1000 mg)	Tacrolimus Prednisone (5 mg) Mycophenolate (1000 mg BID)	1 mo: lung minimal ACR, A1Bx 2 mo: lung mild ACR with minimal lymphocytic bronchiolitis, A2B1, treated with rATG 11 mo: lung minimal ACR, A1Bx, treated with steroids 14 mo: lung mild ACR, A1B2, treated with rATG 22 mo: lung minimal ACR, A1B0 25 mo: lung minimal ACR, A1B0 30 mo: lung no ACR, constrictive BOS 33 mo: no lung ACR but concern for rejection with CD4 staining on bx., treated with plasmapheresis, rituximab, bortezomib	No	No	BOS - 4 years, 7 months, 22 days
7	Basiliximab (20 mg) Methylprednisolone (1000 mg)	Tacrolimus Methylprednisolone (20 mg) Mycophenolate (1000 mg BID) IVIg q7d	None	Liver—1 mo, 27 d	No	Died of primary liver graft dysfunction—1 mo, 27 d
8	Basiliximab (20 mg) Methylprednisolone (1000 mg)	Tacrolimus Prednisone (5 mg)	1 y, 9 mo: lung minimal ACR, A1B0, treated with steroids	No	No	Died of disseminated nocardiosis with CNS involvement and metastatic squamous cell CA—2 y, 4 mo, 21 d
9	Basiliximab (20 mg) Methylprednisolone (1000 mg)	Tacrolimus Prednisone (5 mg)	None	No	No	Alive—3 y, 7 mo, 6 d
10	Basiliximab (20 mg) Methylprednisolone (1000 mg)	Tacrolimus Prednisone (5 mg)	5 mo: lung minimal ACR, A1Bx, treated with steroids 7 mo: lung minimal ACR, A1Bx, treated with steroids 10 mo: lung mild ACR, A2B0	No	No	Alive—3 y, 6 mo, 30 d
11	Basiliximab (20 mg) Methylprednisolone (1000 mg)	Tacrolimus Prednisone (5 mg) Azathioprine (50 mg)	2 mo: lung minimal ACR, A1B0, treated with steroids	No	No	Alive—2 y, 1 mo, 20 d
12	Basiliximab (20 mg) Methylprednisolone (1000 mg)	Tacrolimus Prednisone (5 mg)	None	No	No	Alive—1 y, 7 mo, 11 d

[a] Several patients had more than one infection during posttransplant hospitalization.

CNS, central nervous system; ISHLT, The International Society for Heart & Lung Transplantation; rATG, rabbit antithymocyte globulin.

TABLE 4.

Operative characteristics and complications of combined LLTs

Years	Transplant order	Operative time, min	Liver ischemic time, min		Total lung ischemic time, min		Gallbladder procedures	Nissen fundoplication	Postoperative complications
			Total	Warm	Total	Warm			
2003	Lungs first	891	600	25	295	NR	Choledochocholedochostomy	No	
2003	Lungs first	1064	720	40	442	NR	Roux-en-Y choledochojejunostomy	No	
2006	Lungs first	982	569	47	412	51	Choledochodochostomy	Yes	
2008	Lungs first	876	558	NR	366	34	Choledochocholedochostomy	No	AKI
2008	Lungs first	974	437	32	227	26	Roux-en-Y choledochojejunostomy	No	
2010	Lungs first	854	414	30	308	38	Choledochodochostomy	No	
2012	Lungs first	1474	1020	NR	468	NR	Choledochocholedochostomy	No	AKI, Primary liver graft dysfunction
2013	Lungs first	904	387	NR	291	50	Choledochocholedochostomy	No	
2013	Lungs first	850	480	30	267	NR	Choledochocholedochostomy	Yes	
2013	Lungs first	1058	600	40	345	NR	Choledochocholedochostomy	No	
2014	Lungs first	896	486	46	282	NR	Choledochocholedochostomy	No	AKI, Biliary leak, Right and main hepatic artery thrombectomy
2015	Liver first	820	293	37	598	25	Choledochocholedochostomy	No	Biliary stricture, Hemoperitoneum requiring hepatic artery embolization, ITP

NR, not reported.

large cell lung carcinoma after lung retransplantation (1), and metastatic head and neck squamous cell carcinoma (1). One patient died of BOS after stopping immunosuppressive therapy against physician advice.

DISCUSSION

Lung-liver transplantation is a means to extend the lifesaving therapy of transplantation to those candidates with advanced liver and lung disease for whom single organ transplantation is associated with an unacceptably high risk of mortality or graft loss. Multiorgan transplantation has garnered acceptance in the last decade, but many factors have yet to be effectively measured and studied. This study represents the most recent single-center series to examine outcomes after LLT. We found that patients in our series had favorable 1- and 3-year survival rates in comparison to previous LLT series. Additionally, we examined the occurrence and probability of infection and rejection in this rare population.

Previous case series have shown 1-year survival at 56% to 80% and 3-year survival at 62% to 70% (Table 5). Our study demonstrated 91.7% survival probability at 1 year and 71.3% survival at 3 years (Figure 1). Overall, these outcomes compare similarly with isolated lung transplantation.[18] For bilateral lung transplants performed between 2008 and 2015, UNOS reports overall 1-year and 3-year survivals as follows: 87.7% (95% CI, 86.8-88.6), 71.6% (95% CI, 70.4-72.9), and 58.4% (95% CI, 57.0-59.9).[19] Wolf et al[18] examined the UNOS database from 1987 to 2010 and found 42 LLT recipients. Similar to our study, the majority of patients listed for LLT were younger, had CF as their primary indication, and had primary lung-based allocation with a LAS of 35.9 and MELD of 10.9. They found that among the 42 recipients, a notably lower 1-year survival (75.5%) than what was seen in our study. Although this study was an excellent look at larger trends in LLT, our study attempts to answer questions concerning survival, infection, and rejection in these patients with greater granularity.

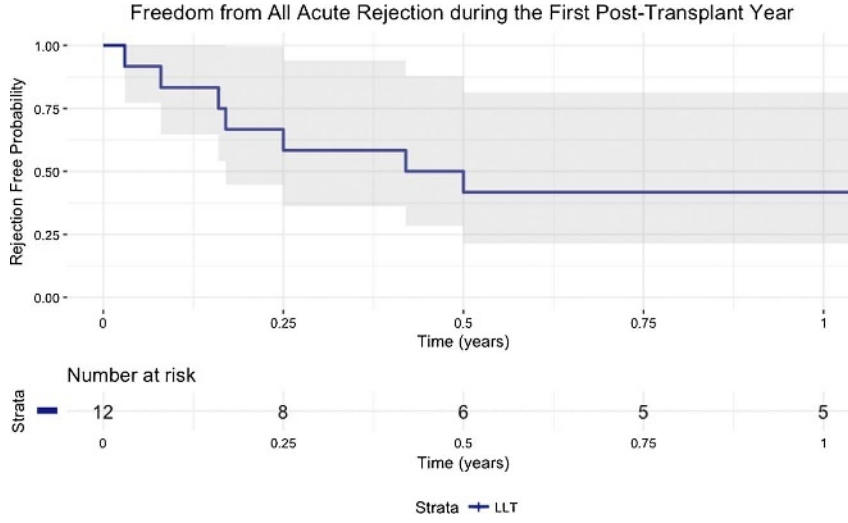

FIGURE 1. Freedom from all acute lung rejection episodes during the first year posttransplant among LLT recipients.

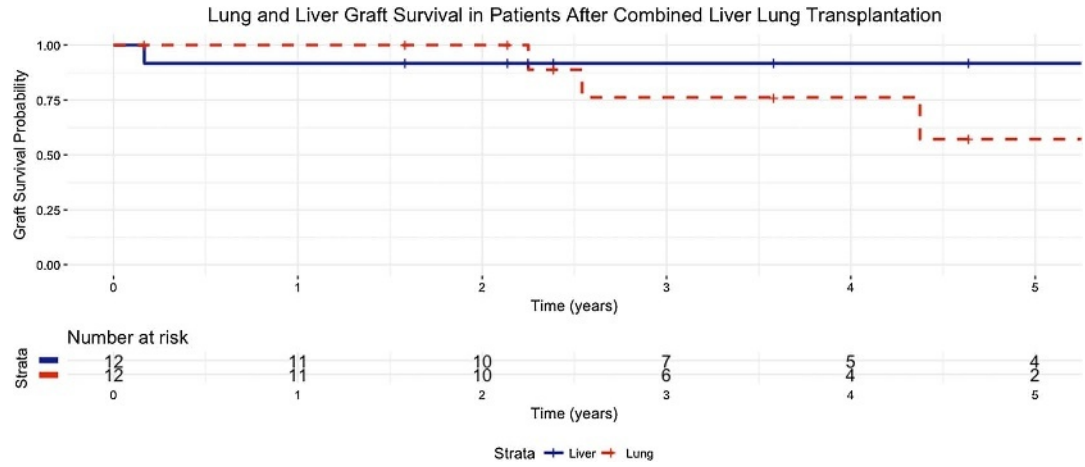

FIGURE 2. Graft survival probability in patients after combined LLT.

Our study provides one of the first granular examinations of posttransplant de novo colonization and infection in LLT recipients. Although most patients had an infection during their hospitalization, no patient died due to infection or sepsis during their index transplant hospitalization. Lung-liver transplantation patients are more likely to be at an increased risk for infection due to prolonged hospitalization, pretransplant colonization with multidrug-resistant organisms in patients with CF and need for broad-spectrum antibiotics for perioperative prophylaxis. Yi et al[11] report that 50% of the deaths in their series were due to complications from sepsis, with all deaths in the first 90 days due to sepsis. This is an interesting difference between previous reports and this patient series. Although 7 of the patients had 1 or more new infections during their transplant hospitalization, no patients died of infectious complications during their transplant hospitalization. At odds with previous reports, our patients with CF were not at significantly higher odds of posttransplant infection.[11] Additionally, patients with CF are at especially high risk of infection with *Pseudomonas aeruginosa* or *Burkholderia cepacia*.[20,21] Although 1 patient in our series had a pulmonary infection with *P. aeruginosa*, no patients developed infection or morbidity from pretransplant colonizing organisms in the index hospitalization. Most of the infections in this study were caused by nosocomial pathogens, such as vancomycin-resistant enterococcus, Candida species, and *Clostridium difficile*. *Mycobacterium abscessus*, Mycoplasma, and Chryseobacterium are environmentally acquired organisms that can cause invasive infection in immunocompromised hosts. Of note, the 2 patients who had infection due to *M. abscessus* underwent transplantation during an *M. abscessus* outbreak due to environmental contamination of the water supply.[22] One patient did die 2 years after their initial transplantation from disseminated nocardiosis years, but this was also complicated by concurrent and significant central nervous system complications from squamous cell cancer.

We also examined acute rejection in more detail than previous LLT series. We estimated that only 41.7% of LLT recipients will not have any rejection within the first 6 months, and recipients will have 0.68 incidences of any acute rejection per year after LLT. This is not unexpected. In 2010, acute rejection was estimated to affect up to 55% of lung transplant recipients within the first year after transplant, and in 2016 was responsible for 3.6% of deaths among adult lung transplant recipients in the first 30 days, and 1.8% in the period from 1 to 12 months posttransplant.[23,24] The incidences of acute rejection were solely driven by lung acute cellular rejection with 1 instance of acute antibody-mediated lung rejection and no acute cellular- or antibody-mediated rejections

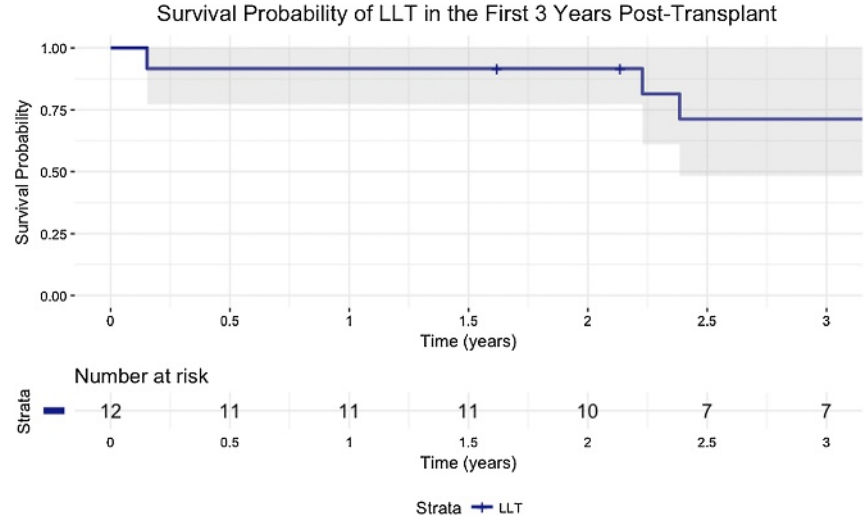

FIGURE 3. Three-year Kaplan-Meier survival analysis of combined LLT recipients.

TABLE 5.

Combined LLT case series with greater than 5 patients

Author	No. patients	30-d Survival	1-y Survival	3-y Survival
Couetil et al, 1995[6]	5	NR	70%	70%
Praseedom et al, 2001[8]	9	NR	56%	NR
Barshes et al, 2005[9]	11	79%	79%	63%
Grannas et al, 2008[10]	12	85%	69%	62%
Arnon et al, 2011[7]	15	80%	80%	NR
Yi et al, 2014[11]	7	87.5%	71.4%	NR
Wolf et al, 2013[18]	42	NR	75.5%	NR
Ceulemans et al, 2016[14]	10	NR	100%	NR
Freischlag et al, 2017	12	100%	91.7%	71.3%

NR, not reported.

occurring in the liver. The rate of acute liver rejection in this series was lower than the national reported acute rejection rate of 15% to 25% in liver-alone patients.[25,26] With the exception of 1 patient who had primary graft failure within 90 days, all of the liver allografts were functioning at the end of this study among the surviving patients. Most of the reported graft complications in our and previous studies were secondary to lung graft dysfunction. In this study, 3 patients developed BOS as a long-term complication of their lung allografts, with 2 patients dying from complications of BOS and 1 patient requiring a lung retransplant. Nationally, lung allografts develop chronic rejection at a much higher rate than liver allografts. The lung's proclivity to chronic rejection does call into question the best long-term utilization of liver grafts.

Best surgical practices are still being determined in this relatively rare patient population. The majority of reported literature, including the majority of cases in this series, implant the lungs before the liver to fit within the accepted cold ischemic times for different organs. However, the rise of lung normothermic perfusion has made "liver-first" a possibility.[14] It has been hypothesized that if liver allografts were transplanted first, they would be able to absorb donor-specific HLA antibodies, help with coagulation status, and/or prevent biliary stricture. However, our "liver-first" patient had numerous initial complications including biliary stricture, immune thrombocytic purpura, and needed hepatic artery embolization for hemoperitoneum (Table 3). Although the patient successfully recovered, further investigation into this technique is required. Debate also remains on whether or not to perform a Roux-en-Y reconstruction of the bile duct, especially in patients with CF.[14] Of our patients, 2 underwent Roux-en-Y choledochojejunostomy, whereas 10 underwent choledochodochostomy. Neither patient who underwent Roux-en-Y choledochojejunostomy had CF. Of the 10 patients who had choledochocholedochostomy, 1 patient had a biliary leak, and another had a biliary stricture (Table 4).

Multiorgan allocation is a complex but necessary ethical issue in transplantation. An LLT recipient with a relatively lower MELD will receive lungs and a liver allocated from the same donor regardless of waitlist status of the liver. These patients had a high LAS which resulted in transplantation but a lower mean MELD than would be expected from isolated liver transplantation.[18,27] This approach has previously been critiqued because it bypasses liver-only patients with higher MELD scores and, thus, may result in higher waitlist mortality from liver complications. Further, there is thought in the field that livers might be better used in liver-alone patients compared with LLT patients due to the shorter survival and higher incidence of chronic lung allograft rejection compared with liver-alone. Allograft utilization in particular is a difficult question to objectively address in this small population. However, in heart-liver transplantation, Goldberg et al[28] found that although transplant is delayed for liver transplant waitlist candidates bypassed by heart-liver recipients, they do not have excess mortality compared with 3 sets of matched controls. While bypassing liver-alone patients might not affect their survival, remaining on the waitlist is significantly detrimental to survival for LLT patients compared with either liver- or lung-only waitlist patients. Expected 3-year survival for patients listed for LLT was 41.0% compared with 61.4% for liver-alone and 58.9% for lung-alone. Overall, transplantation showed a significant survival benefit for patients listed for LLT (hazard ratio, 0.53; 95% CI, 0.29-0.96; $P = 0.04$).[18] We hold that LLT remains a viable and necessary option in a select group of patients.

Our study has several limitations. This is a single-center review with verification of data from UNOS. As such, it is a retrospective analysis and may suffer from selection bias for LLT. Another limitation is the small number of patients available in this rare transplant population, and inferences from observational data are difficult to make. This limits our ability to pinpoint the exact causes of graft failure or causes of mortality on a systemic level. The evidence is also unclear concerning what patient risk factors increase the risk of graft failure and mortality due to the small patient cohort.

CONCLUSIONS

An improved understanding of outcomes after LLT is imperative to determine whether dual allocation of organs to a single recipient is justifiable. Here we present one of the largest single-institution series in the United States. Our study is the most recent to focus solely on LLT in patients with multiple indications with all recipients using calcineurin inhibition-based immunosuppression therapy. Lung-liver transplantation at our center had a similar long-term survival rate to other major LLT series and isolated BOLT. This series additionally provides a granular look at infectious and rejection complications after LLT. Combined with extant published reports demonstrate that LLT is a viable option for patients with end-stage liver and lung disease with survival similar to lung transplantation alone. Prospective, multicenter data collection will be helpful in determining the future of organ allocation in this unique population.

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