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 hepato-pulmonary 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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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. 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.

**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 recipients.

**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 waiting 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.
Operative Details

Two patients underwent Roux-en-Y cholecchojunostomy, whereas 10 underwent cholecchocholectomy. 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 sticture, 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), or severe liver dysfunction (2).

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 methyprednisolone. 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).

| Infections during transplant hospitalization | 58.33% (7/12)* |
|------------------------------------------------|----------------|
| 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.

TABLE 2.
Infections during initial hospitalization for transplantation

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 34.67 (SD, 12.34) minutes for left lung allografts (Table 4). Average warm ischemia times were 36.33 (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 transplantation. All patients received bilateral orthotopic lung transplant on the same day.
| 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 |
|   | Basiliximab (20 mg) Methylprednisolone (1000 mg) | Tacrolimus | Prednisone (5 mg) | Mycophenolate (1000 mg BID) |   | No | No | BOS - 4 years, 7 months, 22 days |
|---|---------------------------------|---------|----------------|-----------------|---|---|---|---------------------------------|
| 6 | 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 |
| 7 | 1 mo, 27 d                      | No      | No             | Died of primary liver graft dysfunction—1 mo, 27 d |
| 8 | 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 | None                            | No      | No             | Alive—3 y, 7 mo, 6 d |
| 10| 5 mo: lung minimal ACR, A1Bx, treated with steroids | No      | No             | Alive—3 y, 6 mo, 30 d |
| 11| 2 mo: lung minimal ACR, A1B0, treated with steroids | No      | No             | Alive—2 y, 1 mo, 20 d |
| 12| None                            | No      | No             | Alive—1 y, 7 mo, 11 d |

*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.
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. 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). 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.
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, pre-transplant colonization with multidrug-resistant organisms in patients with CF and need for broad-spectrum antibiotics for perioperative prophylaxis. Yi et al 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. Additionally, patients with CF are at especially high risk of infection with *Pseudomonas aeruginosa* or *Burkholderia cepacia*. 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. 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. 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.
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.\textsuperscript{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 liver 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.\textsuperscript{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 thrombocytopenic 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.\textsuperscript{14} Of our patients, 2 underwent Roux-en-Y cholecystocholedochostomy, whereas 10 underwent cholecystocholedochostomy. Neither patient who underwent Roux-en-Y cholecystocholedochostomy had CF. Of the 10 patients who had cholecystocholedochostomy, 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 isolated liver transplantations.\textsuperscript{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\textsuperscript{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).\textsuperscript{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.

REFERENCES

1. Klima LD, Kowdley KV, Lewis SL, et al. Successful lung transplantation in spite of cystic fibrosis-associated liver disease: a case series. J Heart Lung Transplant. 1997;16:934–938.
2. Zimmerman AA, Howard TK, Huddleston CB. Combined lung and liver transplantation in a girl with cystic fibrosis. Can J Anaesth. 1999;46:571–575.
3. Como V, Dezza MC, Lucianetti A, et al. Combined double lung-liver transplant for cystic fibrosis without cardio-pulmonary by-pass. Am J Transplant. 2007;7:2433–2438.
4. Bäckman S, Javela K, Koluvalu AM, et al. Successful liver and lung transplantation in patients with severe IgA deficiency, high anti-IgA concentration and a history of anaphylactic transfusion reaction. Transfus Med. 2014;24:251–253.
5. Ceulemans LJ, Manbaliu D, Verslype C, et al. Combined liver and lung transplantation with extended normothermic lung preservation in a patient with end-stage emphysema complicated by drug-induced acute liver failure. *Am J Transplant*. 2014;14:2412–2416.

6. Couetil JP, Houssin DP, Soubrane O, et al. Combined lung and liver transplantation in patients with cystic fibrosis. *Am J Transplant*. 2014;14:2412–2416.

7. Arnon R, Annunziato RA, Miloh T, et al. Liver and combined lung and liver transplantation for cystic fibrosis: analysis of the UNOS database. *Pediatr Transplant*. 2011;15:254–264.

8. Prasheed RM, McNeil KD, Watson CJ, et al. Combined transplantation of the heart, lung, and liver. *Lancet*. 2001;358:812–813.

9. Barshes NR, DiBardino DJ, McKenzie ED, et al. Combined lung and liver transplantation: the United States experience. *Transplantation*. 2005;80:1161–1167.

10. Grannas G, Neipp M, Hooerer MM, et al. Indications for and outcomes after combined lung and liver transplantation: a single-center experience on 13 consecutive cases. *Transplantation*. 2008;85:524–531.

11. Yi SG, Burroughs SG, Loebbe M, et al. Combined lung and liver transplantation: analysis of a single-center experience. *Liver Transpl*. 2014;20:46–53.

12. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. *J Am Stat Assoc*. 1958;53:457–481.

13. Herrmann U, Dockter G, Lammert F. Cystic fibrosis-associated liver disease. *Best Pract Res Clin Gastroenterol*. 2010;24:585–592.

14. Ceulemans LJ, Strypstein S, Neyrinck A, et al. Combined liver-thoracic transplantation: single-center experience with introduction of the ‘liver-first’ principle. *Transpl Int*. 2016;29:715–726.

15. Stewart S, Fishbein MC, Snell GI, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. *J Heart Lung Transplant*. 2007;26:1229–1242.

16. Chapman JR, Webster AC, Wong G. Cancer in the transplant recipient. *Cold Spring Harb Perspect Med*. 2013;3: pii: a015677.

17. Chandok N, Watt KD. Burden of de novo malignancy in the liver transplant recipient. *Liver Transpl*. 2012;18:1277–1289.

18. Wolf JH, Sulewski ME, Cassuto JR, et al. Simultaneous thoracic and abdominal transplantation: can we justify two organs for one recipient? *J Am Transplant*. 2013;13:1806–1816.

19. Organ Procurement, Transplantation Network. Organ Procurement and Transplantation Network Lung Kaplan-Meier Patient Survival Rates For Transplants Performed: 2008–2016. 2017.

20. Barshes NR, DiBardino DJ, McKenzie ED, et al. Combined liver and thoracic transplantation with extended normothermic lung preservation in a patient with end-stage emphysema complicated by drug-induced acute liver failure. *Am J Transplant*. 2014;14:2412–2416.

21. Bothe P, Archer L, Anderson RL, et al. Pseudomonas aeruginosa colonisation of the allograft after lung transplantation and the risk of bronchiolitis obliterans syndrome. *Transplantation*. 2008;85:771–774.

22. Baker AW, Lewis SS, Alexander BD, et al. Two-phase hospital-associated outbreak of Mycobacterium abscessus: investigation and mitigation. *Clin Infect Dis*. 2017;64:902–911.

23. Martini T, Howell DN, Palmer SM. Acute cellular rejection and humoral sensitization in lung transplant recipients. *Semin Respir Crit Care Med*. 2010;31:179–188.

24. Yusen RD, Edwards LB, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-third adult lung and heart-lung transplant report—2016; focus theme: primary diagnostic indications for transplant. *J Heart Lung Transplant*. 2016;35:1170–1184.

25. Fisher RA, Cotterell AH, Maluf DG, et al. Adult living donor versus deceased donor liver transplantation: a 10-year prospective single center experience. *Ann Hepatol*. 2009;8:298–307.

26. Maluf DG, Stravitz RT, Cotterell AH, et al. Adult living donor versus deceased donor liver transplantation: a 6-year single center experience. *Am J Transplant*. 2005;5:149–156.

27. El Mir S, Lake J. Current status of liver allocation in the United States. *Gastroenterol Hepatol (NY)*. 2016;12:166–170.

28. Goldberg DS, Reese PP, Amaral S, et al. Reframing the impact of combined heart-liver allocation on liver transplant wait-list candidates. *Liver Transpl*. 2014;20:1356–1364.