Title
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Journal
The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation, 34(10)

ISSN
1053-2498

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Publication Date
2015-10-01

DOI
10.1016/j.healun.2015.05.002

Peer reviewed

HHS Public Access

Author manuscript

J Heart Lung Transplant. Author manuscript; available in PMC 2017 April 06.

Published in final edited form as:

J Heart Lung Transplant. 2015 October ; 34(10): 1318–1324. doi:10.1016/j.healun.2015.05.002.

Clinical Outcomes of Lung Transplantation in Patients with Telomerase Mutations

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Abstract

Background—Successful lung transplantation (LT) for patients with pulmonary fibrosis from telomerase mutations is limited by systemic complications of telomerase dysfunction including myelosuppression, cirrhosis, and malignancy. We describe clinical outcomes among 14 LT recipients with telomerase mutations.

Methods—Subjects underwent LT between February 2005 and April 2014 at 5 LT centers. We abstracted data from medical records, focusing on outcomes reflecting post-LT treatment effects likely to be complicated by telomerase mutations.

Results—The median age of subjects was 60.5 years (IQR 52.0–62.0), 64.3% were male, and the mean post-LT observation time was 3.2 years (SD ±2.9). Eleven subjects had a mutation in telomerase reverse transcriptase, 2 in telomerase RNA component, and 1 had an uncharacterized mutation. Ten subjects were leukopenic post-LT; leukopenia prompted cessation of mycophenolate mofetil in 5 and treatment with filgrastim in 4. Six subjects had recurrent lower respiratory tract infections (LRTI), 7 had acute cellular rejection (ACR) (A1), and 4 developed chronic lung allograft dysfunction (CLAD). Ten LT recipients developed chronic renal insufficiency and 8

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experienced acute, reversible renal failure. Three developed cancer, none had cirrhosis. Thirteen subjects were alive at data censorship.

Conclusions—The clinical course for LT recipients with telomerase mutations is complicated by renal disease, leukopenia prompting a change in the immunosuppressive regimen, and recurrent LTRI. In contrast, cirrhosis was absent, ACR was mild, and development of CLAD was comparable to other LT populations. While posing challenges, lung transplantation may be feasible for patients with pulmonary fibrosis due to telomerase mutations.

Keywords

Lung transplantation; telomerase mutations

Introduction

Lung transplantation can be life saving for patients with end-stage pulmonary fibrosis. While pulmonary fibrosis is most often idiopathic, it can also be the result of inhalational injuries, connective tissue diseases, and heritable genetic disorders(1). A rare, but increasingly recognized heritable form of pulmonary fibrosis is attributable to telomerase dysfunction(2). Telomerase is an enzyme that catalyzes the addition of telomeres to chromosomes; telomeres are repetitive DNA sequences that function to protect chromosomes from erosion(3). Telomerase activity is reliant upon several proteins and RNA including telomerase reverse transcriptase (TERT), telomerase RNA component (TERC), and dyskerin (DKC1) to stabilize the complex(3). Mutations in genes coding for these components can lead to telomerase dysfunction, telomere shortening, cellular senescence, and pulmonary fibrosis.

Much like idiopathic pulmonary fibrosis, pulmonary fibrosis due to mutations in telomerase is progressive and lethal(4). Furthermore, carriers of telomerase mutations are also predisposed to bone marrow dyscrasias(5), liver cirrhosis (6, 7), and malignancy(8). These extra-pulmonary complications pose challenges to successful lung transplantation due to the myelosuppressive, hepatotoxic, and carcinogenic effects of immunosuppressive medications required to maintain allograft function(9–11).

Despite increased recognition of pulmonary fibrosis due to telomerase mutations, knowledge of clinical outcomes of lung transplantation for this condition is limited to 2 cohort studies of 8 and 9 subjects by Silhan et al and Borie et al, accordingly, (12) (13) and a case report(14). Both Silhan and Borie reported a high incidence of serious hematologic and infectious complications, Silhan reported a high incidence of renal failure, and Borie reported a low median post transplant survival of 214 days. These concerning findings prompted us to examine a novel, larger cohort of 14 subjects, to characterize their clinical course after lung transplantation, and to identify pre-transplant risk factors for post-transplant complications.

Methods

Study population

We performed a 5-center retrospective cohort study of 14 lung transplant recipients with telomerase mutations. The subjects were derived from 14 kindreds who underwent lung transplantation between February 21, 2005 and April 5, 2014. Clinical data was obtained by abstracting the medical record. The Institutional Review Board at each of the 5 centers approved the study.

Genetic analysis

Genetic sequencing of telomerase genes was available for 11 subjects (78.6%). For the 3 subjects without genetic testing, 1 had pulmonary fibrosis and a family history of pulmonary fibrosis and short telomeres, while the other 2 had pulmonary fibrosis and a sibling with a known telomerase mutation (1 in TERT and 1 in TERC). All telomerase mutations were identified before or after lung transplantation via direct DNA sequencing of genomic DNA either by a research laboratory (15) or by a clinical laboratory improvement amendment-certified genetics laboratory. Ten of the subjects who underwent DNA sequencing carried a mutation in TERT and 1 carried a mutation in TERC (Supplemental Table 1).

Outcomes of interest

Clinical outcomes of interest were pre- and post-transplant bone marrow dyscrasias, recurrent lower respiratory tract infections (LRTI), acute cellular rejection (ACR), chronic lung allograft dysfunction (CLAD), acute renal failure (ARF), chronic renal insufficiency (CRI), liver disease, and malignancy.

Statistical analyses

We used mean and standard deviation (SD) to describe normally distributed continuous variables and median and interquartile range (IQR) to describe not normally distributed continuous variables. We used the Fisher exact test to evaluate associations between dichotomous variables and Wilcoxon rank-sum test for continuous variables.

We defined pre-transplant bone marrow dyscrasias as presence of anemia (hemoglobin <13.0g/dL in men and <12.0g/dL in women), elevated mean corpuscular volume (>100.0 femtoliters), leukopenia (white blood cell count <3.4 $x10^9$/L), and thrombocytopenia (platelets <140.0 $x10^9$/L). We defined radiographic presence of usual interstitial pneumonia in accordance with American Thoracic Society guidelines(16). We defined post-transplant bone marrow dyscrasias as presence of anemia, leukopenia, and thrombocytopenia ≥30 days after transplant. We defined LRTI as presence of viruses, bacteria, or fungi in bronchoalveolar lavage fluid (BALF) and recurrent LRTI as 2 or more viral, bacterial, or fungal infections in ≤ 6 months (with the exception of persistent rhinovirus isolation). We defined ACR as ≥A1 on transbronchial biopsy in accordance with the International Society for Heart and Lung Transplantation (ISHLT) criteria (17). We defined primary graft dysfunction as presence of infiltrates on chest x-ray resembling pulmonary edema and development of hypoxemia within the first 72 hours of lung transplantation(18). Severity of primary graft dysfunction was graded according to ISHLT criteria(18). We defined CLAD as

presence of bronchiolitis obliterans syndrome (BOS) or restrictive allograft syndrome at least 6 months after lung transplantation in accordance with the ISHLT criteria (19). We defined BOS as presence of a sustained decline of at least 20% of peak forced expiratory volume at the end of the first second (FEV1) in the absence of other etiologies; we defined restrictive allograft syndrome as persistent decline in vital capacity and total lung capacity, infiltrates on thoracic high resolution CT scan (ground glass opacities, interstitial infiltrates, possible honeycombing), and upper lung zone predominant fibrotic changes. We defined ARF as an increase in serum creatinine by ≥1.5 times of baseline that occurred within the past 7 days and CRI as glomerular filtration rate <60mL/min/1.73 m^2 for ≥3 months. We defined transaminitis as aspartate transaminase ≥43U/L and/or alanine transaminase ≥61U/L, cholestasis as alkaline phosphatase ≥96U/L, and liver disease as presence of cirrhosis on imaging (ultrasound, CT scan, or MRI) or on liver biopsy. Lastly, we defined malignancy as presence of cancerous cells on biopsy.

Missing data

Complete pre-transplant clinical data was available with a few exceptions. Duration of dyspnea before lung transplantation was unknown in 2 subjects, a complete blood cell count was unavailable in 1 subject, and development of premature gray hair was unknown in 6 subjects. Lastly, family history was unknown in 1 subject who was adopted.

Complete post-transplant clinical data was available in all but 1 subject. This subject's complete blood cell counts, liver function tests, and microbiologic cultures were unavailable due to a transition to an electronic medical record; furthermore, whether this subject required a change in lymphocyte anti-proliferative therapy is unknown. Development of chronic conditions such as CRI and CLAD could only be assessed in 12 of 14 subjects since one subject was censored within 46 days of transplant and another died 35 days after transplant. The deceased subject also could not be evaluated for post-transplant bone marrow dyscrasias because laboratory data >30 days after transplant was unavailable.

Post-transplant care

While the protocol for induction of immunosuppression varied from center to center, the maintenance regimen consisted of a calcineurin inhibitor, a lymphocyte anti-proliferative agent, and prednisone at all 5 centers [Supplement Table 2]. All subjects were treated with lifelong prednisone and tacrolimus; however, tolerance of lymphocyte anti-proliferative agents such as azathioprine and mycophenolate mofetil was variable due to leukopenia.

As part of routine care, all subjects underwent allograft surveillance including spirometry, high-resolution CT scan of the chest, and bronchoscopy with bronchoalveolar lavage and transbronchial biopsy at center-specific time points. The same studies were also performed at the discretion of treating physicians for changes in clinical condition. Subjects were monitored for presence of extra-pulmonary organ dysfunction with routine laboratory assessment of the complete blood cell count, metabolic panel, and liver panel. Lastly, serum drug levels were monitored to target center specific troughs [Supplement Table 3].

Results

The median age at the time of lung transplant was 60.5 years (IQR 52.0–62.0), 64.3% of subjects were male, and the majority had a family history of pulmonary fibrosis (92.3%) [Table1]. All subjects had radiographic evidence of pulmonary fibrosis pre-transplant, however, only 42.9% had definite usual interstitial pneumonia pattern. The mean follow up time was 3.2 years (SD ±2.9) [Table 2]. Twelve subjects had a bilateral lung transplant (85.7%). Thirteen subjects were alive at the time of censorship (92.9%) and 1 died of a massive pulmonary embolism 35 days after lung transplant (7.1%) [Table 2].

Pre-transplant bone marrow dyscrasias were mild; none of the subjects had leukopenia, 4 had anemia (lowest hemoglobin: 10.4g/dL), and 1 had thrombocytopenia (platelet count: 102.0 $x10^9$/L). After lung transplant, leukopenia developed in 10 subjects (83.3%) [Table 2]. Notably, 9 of these 10 subjects became leukopenic within the first 6 months of transplant and 4 required Filgrastim therapy. Intolerance of lymphocyte anti-proliferative agents developed in 5 subjects due to leukopenia (38.5%) [Table 2]. However, we found no association between this intolerance and ACR (p=1.00) or CLAD (p=0.18). All subjects remained chronically anemic post-transplant; however, only 2 required blood transfusions outside of the perioperative period as well as erythropoietin therapy. Lastly, while 5 subjects developed thrombocytopenia (41.7%), none required platelet transfusions. Presence of pre-transplant bone marrow dyscrasias did not appear to predict post transplant dyscrasias; we found no association between pre-transplant dyscrasias and post-transplant leukopenia (p=1.00).

Twelve of 14 subjects were censored ≥ 6 months after transplant (85.7%), 11 of whom had accessible microbiologic data. These 11 subjects were evaluated for recurrent LRTIs. Six subjects had recurrent LRTI (54.5%) of whom 5 had recurrent bacterial infections, 5 had recurrent fungal infections, and 3 had both [Table 2]. Notably, viral infections, other than cytomegalovirus (CMV), were never isolated from BALF. One subject shed CMV, but never developed CMV pneumonitis. The most commonly isolated pathogens included *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Aspergillus* species. Mycobacterial infections occurred less frequently than recurrent fungal or typical bacterial infections (15.4% vs 45.5% and 45.5%, accordingly); *Mycobacterium abscessus* was isolated in BALF of 1 subject and *Mycobacterium bovis* in BALF of another. One subject developed *Candida tropicalis* empyema requiring drainage and decortication. We found no association between leukopenia and recurrent LRTI (p=1.00). We also found no association between recurrent LRTI and CLAD (p=0.55).

Subjects were surveyed for ACR via bronchoscopy with transbronchial biopsies. There were 12 episodes of ACR identified in 7 subjects; all episodes were graded A1. Only 2 of the 7 subjects who developed ACR did not tolerate lymphocyte anti-proliferative agents (28.6%); the remaining 5 subjects developed ACR despite a standard, three-drug immunosuppressive regimen. We found no association between ACR and lymphocyte anti-proliferative agent intolerance (p=1.00).

Subjects censored ≥6 months after lung transplantation were screened for development of CLAD (n=12/14, 85.7%). Chronic lung allograft dysfunction developed in 4 subjects (33.3%) and all 4 had bronchiolitis obliterans syndrome [Table 2]. The median time to development of CLAD was 3.1 years (IQR=1.0–6.0). One subject developed CLAD within the first year likely due to antibody-mediated rejection and 2 subjects developed CLAD after 5 years of transplant. We found no association between CLAD and known risk factors for CLAD including ACR, recurrent LRTI, and grade 2 or 3 primary graft dysfunction (p=0.59, 0.55, and 0.33, accordingly).

Most subjects showed evidence of renal dysfunction after lung transplantation. Eight subjects had at least 1 episode of ARF (57.1%) and 10 developed CRI (83.3%) [Table 2]. One subject required temporary renal replacement therapy (7.1%); however, none required permanent hemodialysis [table 2]. Liver abnormalities, particularly transaminitis and cholestasis, were also common, however, none of the subjects developed cirrhosis despite frequent exposure to voriconazole. Lastly, 3 subjects were diagnosed with a malignancy (21.4%), 2 with squamous skin cancer and 1 with post-transplant lymphoproliferative disorder (PTLD).

Discussion

In this 5-center retrospective case series we describe the clinical outcomes of 14 lung transplant recipients with telomerase mutations. After lung transplant, subjects commonly developed bone marrow dyscrasias characterized by leukopenia, anemia, and thrombocytopenia. Infections were common and often recurrent, while ACR, when diagnosed, was always minimal in severity. Lung function was acceptable and the proportion of subjects with CLAD was comparable to the general lung transplant population (20). Surprisingly, we found no association between recurrent LRTI and CLAD or ACR and CLAD, however, this finding must be interpreted in context of a small sample size. Chronic renal failure was more common than expected, however, no one required permanent hemodialysis (21). Additionally, although transaminitis and cholestasis were common, no one developed fulminant liver failure or cirrhosis. Lastly, malignancy was limited to squamous skin cancer and PTLD, both of which are well-documented and often treatable complications of lung transplantation(21, 22). This case series suggests that lung transplantation, while posing challenges, remains a feasible option for select patients with pulmonary fibrosis due to telomerase mutations.

The hypoplastic bone marrow of TERT or TERC mutation carriers can often maintain adequate hematopoiesis under normal conditions but may be more susceptible to toxic environmental and drug exposures(23). This observation is supported by the high incidence of post-transplant bone marrow dyscrasias in this cohort and in previously published studies by Silhan and Borie(12, 13). Subjects in Silhan's and Borie's cohorts had severe post-transplant bone marrow dyscrasias, with all 8 subjects requiring blood transfusions in the former and myelodysplastic syndrome with pancytopenia contributing to the deaths of 4 of 6 deceased subjects in the latter. In contrast, of the 13 subjects described in this cohort, only 2 required recurrent transfusions and bone marrow dyscrasias did not contributed to the mortality of the 1 deceased subject. This difference between the 3 cohorts may stem from

varying degrees of pre-transplant bone marrow involvement as illustrated by the presence of thrombocytopenia in 5 of 8 subjects in Silhan's cohort, 7 of 9 subjects in Borie's cohort, and only 1 of 13 subjects in this cohort. However, since the pre-transplant peripheral blood cell count is not a reliable surrogate for degree of bone marrow abnormalities, perhaps, patients with telomerase mutations would benefit from more aggressive screening for subclinical disease by bone marrow biopsy before transplant as was done by George et al(24). In addition, careful adjustment of myelosuppressive medications after transplant may mitigate hematologic complications.

Despite frequent intolerance of lymphocyte anti-proliferative agents, significant ACR was absent and recurrent LRTIs were common. While speculative, this surprising finding may be related to immunosenescence induced by telomerase dysfunction. Lymphocytes, the primary drivers of ACR, have a unique requirement for clonal expansion and are reliant upon the telomerase to avoid senescence and apoptosis(25); thus, telomerase dysfunction may compromise lymphocyte clonal expansion thereby reducing risk of ACR and increasing risk of infection. In fact, a 8.5-fold higher mortality from infectious disease was identified in a cohort of normal adults >60 years of age with short telomeres(26). Larger studies of patients with telomerase mutations are needed to validate this concept of immunosenescence, particularly as it relates to intolerance of lymphocyte anti-proliferative agents, the risk of ACR, and the LRTIs after lung transplantation.

Although risk factors for CLAD were common, allograft function remained acceptable and the proportion of subjects with CLAD was comparable to the general lung transplant population(20). ACR is the most consistently described risk factor for CLAD(27), thus the absence of moderate or severe ACR may have been protective in this cohort. Animal models of bronchiolitis obliterans syndrome demonstrate T-cell mediated lymphocytic airway inflammation with ongoing stimulation of T-cells and activation of the airway epithelium stimulation by the cytokine interferon-γ(28). The activated airway epithelium generates a profibrotic milieu that eventually results in bronchiolar obliteration(29). Thus, compromised clonal T-cell expansion in transplant recipients with telomerase mutations may result in reduced epithelial activation, reduced epithelial fibrosis, and a reduced risk of CLAD.

Even though there is no known association between renal disease and telomerase mutations in individuals without organ transplantation, ARF and CRI developed in the majority of subjects (57.1% and 83.3%, accordingly [Table 2]). However, the severity of renal disease was lower in this cohort than in Silhan's; only 1 of our subjects required renal replacement therapy in comparison to Silhan's 5 ($p=0.01$)(12). The etiology of this predisposition toward renal failure is not known, but may be related to compromised tolerance of perioperative renal insults and nephrotoxic calcineurin inhibitors required for allograft maintenance. Unfortunately, less nephrotoxic alternatives to calcineurin inhibitors, such as inhibitors of the mammalian target of rapamycin, may not be tolerated due to the myelosuppressive effects of this drug class(30).

This cohort study is limited by its descriptive nature, small sample size, and absence of a control group. Furthermore, it is limited by selection bias since patients with significant bone marrow dyscrasias or multi-organ dysfunction would not have undergone lung

transplantation. However, this is the largest case series to date to describe the clinical outcomes of lung transplant recipients with telomerase mutations and expands our knowledge of a unique patient population with an unusual genetic condition.

In conclusion, the clinical course of lung transplant recipients with telomerase mutations is complicated by bone marrow dyscrasias with lymphocyte anti-proliferative agent intolerance and a predisposition toward renal disease. However, in contrast to other reports, both bone marrow abnormalities and renal dysfunction remained mild in most subjects. Furthermore, while recurrent LRTIs were common, ACR, when identified, was minimal. Lastly, allograft function remained reasonable and the proportion of subjects with CLAD was comparable to the general lung transplant population. Lung transplantation is feasible for some patients with telomerase mutations; a structured comparison to other lung transplant recipients would help shed better light on the outcomes of lung transplantation in patients with this rare genetic condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Tokman's salary was funded by the National Institute of Health T32 training grant. The Nina Ireland Program Lung Health provided funding for statistical analysis. We would like to thank Dr. Fernando Torres for providing the surveillance and immunosuppressive protocols at University of Texas Southwestern.

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Table 1

Clinical characteristics before lung transplant.

	Subjects with Available Data*	N (%)
Age at transplant (years) [Median, IQR]	14	60.5 (52.0–62.0)
Male	14	9 (64.3%)
Age at onset of dyspnea (years) [Mean, SD]	12	50.9 (±9.4)
Family history of pulmonary fibrosis	13	12 (92.3%)
Premature gray hair (<30 years old)	8	3 (37.5%)
Current or past tobacco use	14	4 (28.6%)
Bone marrow dyscrasia	13	5 (38.5%)
Leukopenia (white blood cell count <3.4 x10^9/L)	13	0
Anemia (hemoglobin <13g/dL in men, <12g/dL in women)	13	4 (30.8%)
Elevated mean corpuscular volume (>100fL)	13	2 (15.4%)
Thrombocytopenia (Platelets <140x10^9/L)	13	1 (7.7%)
Genetic Mutation	11	
TERT [a]	11	10 (90.9%)
TERC [b]	11	1 (9.1%)
Radiographic pattern on thoracic CT scan [c]	14	
Definite UIP [d]	14	6 (42.9%)
Possible UIP [e]	14	2 (14.3%)
Inconsistent with UIP [f]	14	6 (42.9%)

* Missing data:

-Age at onset of dyspnea unknown in 2 subjects.

-Family history unknown in 1 subject who was adopted.

-Development of premature gray hair unknown in 6 subjects.

-Presence or absence of pre-transplant bone marrow dyscrasias unknown in 1 subject due to a transition to an electronic medical record.

-3 subjects did not undergo genetic testing. One subject had pulmonary fibrosis and a family history of pulmonary fibrosis and short telomeres, the second had pulmonary fibrosis and a sibling with a known TERT mutation, and the third had pulmonary fibrosis and a sibling with a known TERC mutation.

[a] TERT: telomerase reverse transcriptase

[b] TERC: telomerase RNA component

[c] The radiographic pattern of fibrosis was defined in accordance with American Thoracic Society guidelines.

[d] Thoracic CT evidence of definite usual interstitial pneumonia (UIP): sub-pleural, basal predominant reticular abnormality, honeycombing with or without traction bronchiectasis, absence of features listed as inconsistent with UIP pattern.

[e] Thoracic CT evidence of possible UIP: sub-pleural, basal predominant reticular abnormality, absence of features listed as inconsistent with UIP pattern.

[f] Thoracic CT evidence of a pattern inconsistent with UIP: upper or mid-lung predominance, peribronchovascular predominance, extensive ground glass abnormality, profuse micronodules, discrete cysts, diffuse mosaic attenuation/air-trapping, consolidation in bronchopulmonary segment(s)/lobe(s).

Table 2

Clinical characteristics after lung transplant.

	Subjects with Available Data*	N (%)
Follow up time (years) [Mean, SD]	14	3.2 (±2.9)
Bilateral lung transplant	14	12 (85.7%)
Alive at data censorship	14	13 (92.9%)
Primary graft dysfunction (Grade 2 or 3)	14	1 (7.1%)
Bone marrow dyscrasia ≥30 days after lung transplant	12	12 (100.0%)
Leukopenia (white blood cell count <3.4 x10^9/L)	12	10 (83.3%)
Filgrastim therapy	12	4 (33.3%)
Anemia (hemoglobin <13g/dL in men, <12g/dL in women)	13	13 (100.0%)
Recurrent transfusions	13	2 (15.38%)
Erythropoietin therapy	13	2 (15.38%)
Thrombocytopenia (platelets <140x10^9/L)	12	5 (41.7%)
Change in lymphocyte anti-proliferative therapy	13	5 (38.5%)
Recurrent lower respiratory tract infections (≥2 in 6 mo)	11	6 (54.5%)
Bacterial	11	5 (45.5%)
Fungal	11	5 (45.5%)
Viral	11	0 (0.0%)
Polymicrobial	11	3 (27.3%)
Acute cellular rejection [a]		
A1	14	7 (50.0%)
A2	14	0
A3	14	0
A4	14	0
Chronic lung allograft dysfunction [b]	12	4 (33.3%)
BOS 0p[c]	12	1 (25.0%)
BOS 1	12	0
BOS 2	12	2 (50.0%)

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	Subjects with Available Data*	N (%)
BOS 3	12	1 (25.0%)
Restrictive allograft Syndrome	12	0
Time to BOS (years) [Median, IQR]	4	3.1 (1.0–6.0)
Renal Disease		
Acute renal failure [d]	14	8 (57.1%)
Chronic renal insufficiency [e]	12	10 (83.3%)
Transient renal replacement therapy	14	1 (7.1%)
Permanent renal replacement therapy	14	0
Liver Disease		
Transaminitis [f]	13	11 (84.6%)
Cholestasis [g]	13	5 (38.5%)
Cirrhosis [h]	14	0
Malignancy[i]	14	3 (21.4%)

*Missing data:

-Presence or absence of bone marrow dyscrasias ≥30 days after transplant was unknown in 2 subjects due to death 35 days after lung transplant in 1 and a transition to an electronic medical record in the other.

- Need to change lymphocyte anti-proliferative therapy was unknown in 1 subject due to a transition to an electronic medical record.

-Development of recurrent lower respiratory tract infections was unknown in 1 subject due to a transition to an electronic medical record. Two subjects were transplant within 90 days of data censorship and did not have repeated bronchoscopic surveillance for lower respiratory tract infections. Due to the time proximity of data censorship to lung transplantation, these 2 subjects were also not assessed for development of chronic lung allograft dysfunction or chronic renal insufficiency.

-Presence or absence of transaminitis or cholestasis was unknown in 1 subject due to a transition to an electronic medical record.

[a]Grading of acute cellular rejection (characterized by perivascular and interstitial mononuclear cell infiltrates):

A0: none

A1: minimal

A2: mild

A3: moderate

A4: severe

[b]Chronic lung allograft dysfunction defined as presence of bronchiolitis obliterans syndrome or restrictive allograft syndrome at least 6 months after lung transplantation

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[c] BOS: Bronchiolitis obliterans syndrome. Grading of BOS:

BOS 0: Forced expiratory volume at the end of the first second (FEV1) >90% of baseline

BOS 0-p: FEV1 81–90% of baseline

BOS 1: FEV1 66–80% of baseline

BOS 2: FEV1 51–65% of baseline

BOS 3: FEV1 ≤50% of baseline

[d] Acute renal failure: increase in serum creatinine of ≥1.5 times baseline that occurred within the past 7 days.

[e] Chronic renal insufficiency: glomerular filtration rate <60mL./min/1.73 m^2 for ≥3 months.

[f] Transaminitis: aspartate transaminase ≥43 U/L and/or alanine transaminase ≥61 U/L

[g] Cholestasis: alkaline phosphatase ≥96 U/L

[h] Cirrhosis diagnosed on the basis of liver biopsy or radiographic results (ultrasound, CT scan, or MRI of the liver).

[I] Two with squamous skin cancer and 1 with post-transplant lymphoproliferative disorder.