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Airway Complications after Lung Transplantation: Contemporary Survival and Outcomes

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ABSTRACT

INTRODUCTION: Airway complications are rare and cause increased morbidity and mortality post-lung transplantation (LT). We sought to examine risk factors associated with this complication and its impact on survival.

METHODS: We retrospectively evaluated United Network for Organ Sharing data from 2000 to 2012. A backward stepwise logistic regression was performed on recipient-, donor-, and transplant-related variables to select independent risk factors associated with airway complications and mortality. Survival was evaluated using the Kaplan-Meier method.

RESULTS: We evaluated 16,156 consecutive adult LT recipients, among whom 233 (1.4%) developed airway complications. Predictors of increased risk of airway complications included male gender (odds ratio [OR] 1.61, p=0.001), advancing recipient age (OR 1.02, p<0.001), and pre-transplantation admission to the intensive care unit (ICU) (OR 2.13, p< 0.001). The 30-day (89.6% vs. 96.2%, p-0.001), 90-day (69.9% vs. 93.1% p <0.001), one-year (54.6% vs. 84.4%, p<0.001), three-year (38.7% vs. 67.4%, p<0.001), and five-year (33.2% vs. 54.2%, p<0.001) survival rates were each significantly reduced in recipients with airway complications. Factors associated with an increased risk of one-year mortality included recipient age (hazard ratio [HR] 1.01, p<0.001), use of extracorporeal mechanical support (HR 1.5, p=0.01), diagnosis of cystic fibrosis (HR 1.22, p=0.01), glomerular filtration rate (GFR) 60-90 (HR 1.61, p<0.001), GFR <60 (HR 1.13, p=0.01), non ICU hospitalization (1.32, p<0.001), pre-transplantation ICU hospitalization (HR 2.54, p<0.001), donor with positive serology for cytomegalovirus (HR 1.16, p<0.001), and donor with a smoking history (HR 1.19, p<0.001). Double LT (HR 0.83, p<0.001) was associated with a decreased risk of death. COPD/emphysema was protective compared to idiopathic pulmonary fibrosis (HR 0.85, p=0.008).

CONCLUSION: Airway complications are associated with a significant mortality burden.

INTRODUCTION

Lung transplantation (LT) is the most effective treatment for end-stage pulmonary disease. Long-term survival is often determined by the development of chronic rejection or bronchiolitis obliterans syndrome.[1, 2] Short-term survival, however, may be considerably compromised by events such as airway complications (ACs), of which airway dehiscence has long been considered the most devastating.[3] The etiology of this complication has largely been attributed to the disruption of the bronchial circulation that occurs during LT.[4] The circulation is never fully restored and the anastomosis is believed to derive a new blood supply from the pulmonary circulation.[5, 6] Vascular compromise may develop and result in ischemia and possible necrosis of the airway. [4-6] This may manifest in a spectrum of varied complications ranging from focal stenosis to frank disruption of the airway.

Various intraoperative surgical techniques have been proffered to mitigate this risk.[7,8,9]. These have included deliberate shortening of the donor bronchus combined with the use of anastomotic techniques that telescope the donor bronchus into the recipient bronchus.[10,11] Several reports have described the use of a vascular muscle flap to buttress the bronchial anastomosis and promote neovascularization. [4, 10,11] None of these techniques, however, has been universally accepted and evidence of the efficacy of each remains equivocal. [12,13] The stable incidence of ACs over the past decade is further testament that a multifactorial etiology is at play. Nevertheless, data to articulate the risk factors for this post-LT complication to aid prevention are scarce.

We sought to evaluate these risk factors using a national data registry, with an aim to delineate those factors associated with ACs and elucidate their impact on survival.

METHODS

We reviewed data from the Scientific Registry of Transplant Recipients (SRTR) from the United Network for Organ Sharing (UNOS), evaluating a consecutive cohort of adult recipients (age >18 years) who underwent LT between January 2000 and December 2012. We excluded recipients who underwent multi-organ, combined heart-and-lung, or re-transplantations. The cohort was stratified into two groups, comprising those whose procedures were complicated by ACs and those without this complication. The primary outcome measured was mortality, with survival end points calculated at 30 days, 90 days, and one, three, and five years. Additionally, we evaluated cause of death within the cohort who developed ACs. Both patient-level data and transplantation center data were provided in a de-identified format. Our institutional review board approved this study (#PRO1301170212).

Statistical analysis

Baseline characteristics of the two cohorts were compared. Continuous variables were compared using the Student t-test for those with normal distribution and the Wilcoxon rank-sum test for those without. Categorical variables were compared using the chi-squared test. We performed survival analysis using the Kaplan-Meier method and log rank test. We specifically calculated 30-day, 90-day, one-, three-, and five-year survival post-LT. To evaluate survival after an AC, we calculated conditional survival contingent upon surviving at least one year post-transplantation. A multivariate Cox proportional hazard model was used to estimate the risk of death one year after LT between the two cohorts.

In order to evaluate the impact of the introduction of the lung allocation score (LAS) on survival, we divided the study period into “before” and “after” the introduction, which occurred in May 2005. We compared the incidence of AC in both eras. A similar multivariate Cox proportional

hazard model was used to estimate the risk of mortality after transplantation in both eras. Variables with biological plausibility, significance in univariate analysis, and supporting literature were included in the multivariate model. These included recipient age, race, gender, diabetes, pulmonary diagnosis, mechanical ventilator (MV) support, extracorporeal membrane oxygenation (ECMO) support, renal function, donor age, donor cytomegalovirus (CMV) infection, donor smoking, intensive care unit (ICU) hospitalization, donor-recipient ABO mismatch, HLA mismatch, and type of LT (unilateral or bilateral).

In order to identify predictors of AC, we fitted a multivariable logistic regression with ACs as the primary outcome. Once again, variables with biological plausibility, those significant in univariate analysis, and those with proven literature support were included in a stepwise backward selection method, with $p<0.2$ used as a cut-off for inclusion. We used imputation techniques to account for missing values for study variables using the Stata MICE functionality under the assumption that missing information did not occur at random within the dataset. [14] Mean and median values are displayed with standard deviation and interquartile ranges, respectively. Hazard ratios (HR) and odds ratios (OR) are presented with their 95% confidence intervals (CI). A two-tailed $p < 0.05$ value was considered statistically significant. All the analyses were performed on Stata 12.0 (StataCorp, College Station, TX).

RESULTS

A total of 16,156 consecutive adult LT recipients were included in the analyses. This group comprised 233 (1.4%) who developed AC post-transplantation and 15,923 (98.6%) who did not. The two groups were similar in most baseline characteristics, but differed in recipient age, need

for MV support, need for ECMO support, pre-transplantation admission to ICU, and type of LT (single vs. double LT). (Table 1)

The 30-day (89.6% vs. 96.2%, p<0.001), 90-day (69.9% vs. 93.3%, p<0.001) one-year (54.6% vs. 84.4%, p<0.001), three-year (38.7% vs. 67.4%, p<0.001), and five-year (33.2% vs. 54.2%, p<0.001) actuarial survivals were each significantly lower for recipients whose procedures had been complicated by ACs (Figure 1). The five-year conditional survival, contingent on surviving one-year post-transplantation, was similar between the two groups. (60.8% vs. 64.20, p=0.15) (Figure 2).

Males had a higher risk of developing AC compared to females (OR 1.61, 95% CI 1.22-2.14). Advancing recipient age was also associated with marginally increased risk of AC (OR 1.01, 95% CI 1.01-1.02). Other predictors of AC included pre-transplant ICU hospitalization (OR 2.13, 95% CI 1.39-3.29) and double LT (OR 1.97 [1.41-2.76]). Additionally, patients with pulmonary diagnoses other than idiopathic pulmonary fibrosis, COPD, or cystic fibrosis had an increased risk of AC (OR 1.38, 95% CI 1.00-1.91) (Table 2). When we accounted for the number of anastomoses per recipient, we found no difference in the rate of AC between bilateral LT (172/19662 = 0.87%) and single LT (61/6325 = 0.96%) (p=0.49).

In multivariate analysis, patients with AC were three times more likely to die within one year (HR 3.38, 95% CI 2.76-4.13). Other predictors of one-year mortality included recipient age (HR 1.10, 95% CI 1.01-1.02), ECMO support (HR 1.51, 95% CI 1.14-2.03), diagnosis of COPD (HR 0.85, 95% CI 0.77-0.95), and cystic fibrosis (HR 1.22, 95% CI 1.08-1.36). Furthermore, non-ICU (HR 1.32, 95% 1.13-1.54) and ICU hospitalization prior to LT (HR 2.54, 95% CI 2.23-2.90), increasing donor age (HR 1.002, 95% CI 1.00-1.01), donor CMV infection (HR 1.16, 95% CI

1.06-1.26), and a positive donor smoking history (HR 1.19, 95% CI 1.10-1.32) were each predictors of one-year mortality. (Table 3)

When the study period was stratified into two eras based on introduction of the LAS, the incidence of AC was marginally higher in the latter era (early era 62/5,270 [1.2%] vs. latter era 171/10,886 [1.6%] p=0.049). In the adjusted analysis, the risk of one-year mortality for recipients who developed AC in the early and latter era was four times (HR 4.09, 95% CI 2.87-5.82) and three times (HR 3.13, 95% CI 2.45-4.01) higher than in those without AC, respectively (Table 4). A multivariate analysis restricted to the latter era showed no relationship between LAS and AC (OR 0.99, 95% CI 0.98- 1.00, p=0.15).

DISCUSSION

Following LT, long-term outcomes are predominantly determined by the incidence of chronic rejection or bronchiolitis obliterans syndrome. Short-term outcomes, however, may be influenced by various factors and concerted efforts are required to mitigate the risks associated with each of these. ACs, though rare, are a significant driver of early post-transplant mortality, which we have also demonstrated, within the first 90 days.[2] In this report, we estimate the incidence of AC as approximately 2%. Albeit a comparatively small risk, it bears an almost three times increased risk of death and an over 30% reduction in cumulative survival. However, this risk is somewhat attenuated if the recipient survives the first year.

Airway complications have long been suspected to be a function of the disruption in circulation that occurs during LT. The dual native circulation derived from the bronchial arteries is interrupted and the pulmonary artery and transplantation only surgically restores the low

pressure pulmonary deoxygenated arterial circulation in a retrograde fashion. The anastomosis is theoretically susceptible to ischemia and hypoxic injury. [4,13] Several surgical techniques have been described to mitigate this risk.[4, 15,16] These have included the use of a vascularized pedicle such as omentum, pericardium, peribronchial, or intercostal tissue wrapped around the anastomosis. Randomized trials, however, showed no reduction in the incidence of ACs with the use of these pedicles. [17] Shortening the bronchial donor stump to two cartilaginous rings from the secondary carina has also been generally considered a means of minimizing the territory of ischemia but, once again, without consensus. [4,18]

The technique of bronchial artery revascularization, however, showed a significant reduction in ACs with at least partial restoration of bronchial flow on postoperative angiography. [3, 4, 17-20] The technical detail and cumbersomeness of this latter approach, however, has limited its appeal. The deliberate intussusception and telescoping of the bronchial anastomoses has also been described as a potential solution. [4, 9, 10, 18-20] This technique, however, was found to increase the risk of airway stenosis by up to 50% and has largely been abandoned. Though each of these techniques has been described in an attempt to improve anastomotic healing and decrease the risk of ACs as a whole, none has been independently proven to offer any durable remedy.

By performing an era analysis, we were able to evaluate whether interventions in the early 2000s may have resulted in different outcomes when compared to the latter half of the past decade. We found, however, that the incidence has not changed over the past 12 years and the apparent higher incidence for double LTs compared to single LTs is neutralized once the data are analyzed per anastomosis. As such, our understanding of post-LT bronchial re-

vascularization remains somewhat incomplete and continues to evolve. Preclinical canine studies demonstrated that bronchial artery circulation slowly regenerates by angiogenesis following LT.[21] Computed tomographic angiographic studies have, however, failed to demonstrate the re-vascularization of the bronchial circulation by secondary intention and indeed, the transplanted bronchial mucosa has been confirmed by autopsy studies to remain comparatively hypoxic for many months post-LT. [13, 21,22] The introduction of the LAS did not herald a reduction in the incidence of AC. On the contrary, the incidence increased. It is plausibly the result of the increased consideration of older, sicker recipients and the increased impetus for double as opposed to single LT that has characterized the past decade, but has now increased the absolute number of anastomoses being performed per recipient, and with it the number of possible complications. In this vein, we observed an increased risk of AC in male recipients with advancing age admitted to the ICU. We also observed an increased mortality in those who required ICU and post-transplant ECMO support. These observations concur with published evidence regarding outcomes in critically ill recipients with end stage advanced pulmonary disease.[23,24]

This study has a number of limitations. First, this was a retrospective analysis of a national database with variability in the quality of the data submitted from various centers. Second, our analysis was limited to patients with advanced lung disease who received transplants; we have no clinical data regarding those who developed airway compromise unrelated to LT. Third, the data analyzed here pertains only to centers in the United States and are not generalizable to transplant centers around the world. Fourth, variations in surgical practice and their associated temporal trends are not accurately captured in the data. However, we divided the entire period into two equal halves to estimate trends. Fifth, the data does not take into consideration any variations in clinical pathways, organ preservation, antimicrobial, or immunosuppressive protocols with the assumption made that these exerted an equal influence throughout the study

period. Finally, we were restricted to evaluating the binary presence or absence of AC without a uniform definition that might more accurately stratify the spectrum of the complication.

To the best of our knowledge, this is the first report that characterizes the risk factors for AC and relates this to survival. It affords us a better understanding of this rare and complex complication, for which specific management warrants a comprehensive multidisciplinary approach to prevent early post-LT mortality. We hope that these data will form the basis for further investigations into anastomotic techniques and local post-transplant therapies for patients at risk for this serious complication.

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Table 1 Baseline characteristic of patients who developed airway complication and no airway complicationscontrolsNo airway complications

	Control No complications dehiscence(n=**15,923**)	Airway dehiscencecomplications (**n=233**)	P-value
Recipient-related			
Age , years (sd)	57(47-63)	58(48-63)	0.33
Male, gender (%)	8,930/15,923(56.1)	158/233(67.8)	<0.001
White (%)	13,608/15,921 (85.5)	198/233(85.0)	0.39
Body Mass Index, Kg/m^2(sd)	24.8(4.7)	25.0(4.9)	0.46
Diabetes (%)	2,385/15,798(15.1)	39/231(16.9)	0.45
Diagnosis(%)			0.09
Idiopathic pulmonary fibrosis	4,900/15,923(30.8)	75/233(32.2)	
COPD/Emphysema	5,146/15,923(32.3)	58/233(24.9)	
Cystic fibrosis	2,096/15,923(13.2)	34/233(14.6)	
Pulmonary hypertension	478/15,923(3.0)	8/233(3.4)	
Other	3,781/15,923(23.8	66/233(28.3)	
Mechanical Ventilator(%)	711/15,923(4.5)	23/233(9.9)	<0.001
ECMO support (%)	144/15,923(0.9)	8/233(3.4)	<0.001
eGFR, ml/min/1.73m^2(sd)	101.2(45.4)	100.4(47.1)	0.80
Chronic steroid use(%)	7,400/15,370(48.2)	114/215(53.0)	0.16
Donor -related			
Age, years(IQR)	31(21-45)	27(20-44)	0.06
Male, gender	9,542/15,923(59.9)	138/233(59.2)	0.83
Pulmonary Infection(%)	5,624/15,867(35.4)	93/232(40.1)	0.14
Transplant related			
Admission to ICU(%)	934 /15,923(5.9)	31/233(13.3)	<0.001
Graft ischemic time, hours (sd)	5.0(1.7)	5.1(1.6)	0.31
Waiting time, days (IQR)	118(32-370)	118(25-346)	0.58
Bilateral transplant(%)	9,659/15,923(60.7)	172/233(73.8)	<0.001

*other diagnosis include thoracic diagnosis other than Chronic obstructive pulmonary disease, emphysema, cystic fibrosis and idiopathic pulmonary fibrosis.

sd:standard deviation, COPD: Chronic obstructive pulmonary disease , eGFR: estimated glomerular filtration rate, IQR: Inter quartile range, CMV: cytomegalovirus, ICU: Intensive care unit.

Table 2. Predictors of Airway Complications

Variables	Odds Ratio 95% CI	P-value
Recipient Age, per year	1.02(1.00-1.03)	0.01
Male Recipient	1.61(1.22-2.14)	0.001
Idiopathic pulmonary fibrosis	Reference(1)	
Other pulmonary diagnosis	1.38(1.00-1.91)	0.048
Bilateral transplant	1.97(1.41-2.76)	<0.001
Medical condition at admission		
Non hospitalization	Reference (1)	
Non-ICU hospitalization	1.73(1.11-2.71)	0.02
ICU hospitalization	2.13(1.39-3.29)	0.001

*other diagnosis include: thoracic diagnosis other than Chronic obstructive pulmonary disease, emphysema, cystic fibrosis and idiopathic pulmonary fibrosis.
ICU: Intensive care unit.

Table 3.Multivariable Cox regression for 1-year mortality after transplantation

Variables	Hazard Ratio(95% CI)	p-value
Airway complications	3.38(2.76-4.13)	<0.001
Age, per year	1.01(1.01-1.02	<0.001
Male	1.08(0.99--1.18)	0.07
White	Reference(1)	
Black	0.90(0.77-1.05)	0.18
Hispanic	0.96(0.79-1.16)	0.68
Other	0.86(0.63-1.18)	0.37
Diabetes	0.99(0.89-1.17)	0.93
ECMO support	1.51(1.14-2.03)	0.01
Idiopathic pulmonary fibrosis	Reference (1)	
COPD/Ephysema	0.85(0.77-0.95)	0003
Cystic fibrosis	1.22(1.08-1.36)	0.01
Other	1.06(0.87-1.29)	0.55
eGFR >90 ml/min/1.	Reference(1)	
eGFR between 60 and 90 ml/min/1.73m^2	1.61(1.42-1.83)	<0.001
73m^{2}eGFR <60 ml/min/1.73m^2	1.13(1.03-1.23)	0.01
Donor age, per year	1.002(0.99-1.01)	0.08
Donor CMV infection	1.16(1.11-1.24)	0.001
Donor smoking	1.19(1.10-1.32)	0.001
Non hospitalization	Reference (1)	
Non ICU hospitalization	1.32(1.13-1.54)	<0.001
ICU hospitalization	2.54(2.23-2.90)	<0.001
ABO mismatch	1.130.99-1.30)	0.08
Bilateral lung transplant	0.86(0.79-0.94)	<0.001

*other diagnosis include: thoracic diagnosis other than Chronic obstructive pulmonary disease, emphysema, cystic fibrosis and idiopathic pulmonary fibrosis.

COPD: Chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration rate, CMV: cytomegalovirus, ICU: Intensive care unit.

Table 4 Multivariate analysis 1-year mortality for controls vs patients with airway complications vs no airway complications before and after the introduction of lung allocation score

		Hazard Ratio*	p-value
Before LAS	No Airway ComplicationsControls	1	
	Airway Complicationsdehiscence	4.10(2.87--5.82)	<0.001
After LS	No Airway complicationControls	1	
	Airway Complicationsdehiscence	3.13(2.45-4.01)	<0.001

*adjusting for race diabetes recipient age, gender, body mass index, extracorporeal membrane oxygenation support, recipient renal function, diagnosis, donor age, donor smoking status, donor CMV infection, type of hospitalization, ABO match type.

Figure 1. Kaplan Meier 5- year Survival curve for patients with Airway complications and No Airway complication

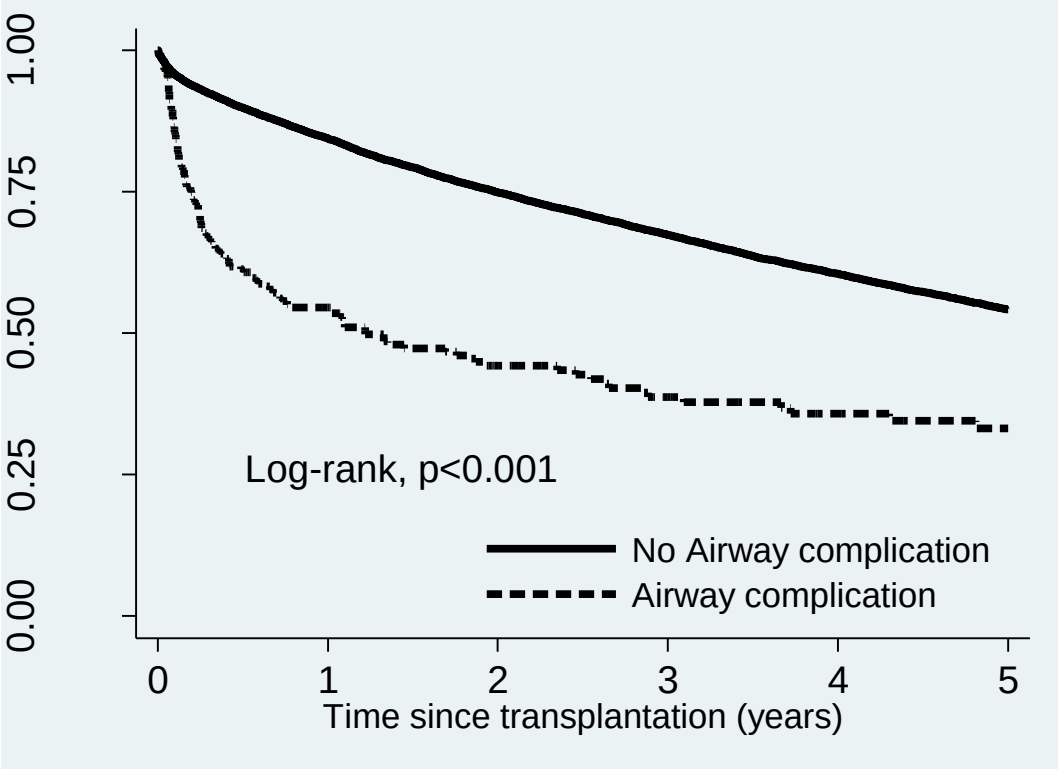

Figure 2. 5-year survival contingent on surviving first year for patients with Airway complication versus no Airway complication