
# The Impact of Airway Complications on Survival Among Lung Transplant Recipients

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## ABSTRACT

Introduction. Long-term outcomes of airway complications (AC) after lung transplantation are unknown. The incidence of AC varies from 1.6% to 32% with the related mortality rate of 2% to 4%. The management of most AC is based on endobronchial methods, including balloon bronchoplasty, endobronchial stent placement, and ablative techniques. The aim of the study was to assess the connection between airway complications treated by bronchial intervention (BI) and the survival of lung transplant recipients.

Materials and Methods. The single-center retrospective study reviewed the cases of 165 patients (63 women [38.18%], 103 men [61, 82%]; median age at referral for lung transplantations (LTx), 41 years [range, 15-68 years]). The cohort was stratified into 2 groups comprising those whose procedures were complicated by ACs and those without. The primary outcome measured was mortality, with survival endpoints calculated at 6 months.

Results. The comparison of the survival of recipients regarding underlying disease (cystic fibrosis [CF], chronic obstructive pulmonary disease [COPD], idiopathic pulmonary artery hypertension [IPAH], and others) with the use of the Kaplan-Meier estimator indicated that the only statistically significant ($P = .0194$) differences between patients who underwent BI and patients without BI performed were observed in CF patients (Fig 1). In any other diagnosis, the results were not statistically significant ($P > .05$).

Conclusions. Bronchoscopic intervention because of airway complications after lung transplantation are often-used procedures, but they have no impact on the survival of patients with cystic fibrosis.

THE rapid development in the efficacy of lung transplantation (LTx) in the past decades has resulted in noticeable improvement in overall outcomes and prolonged survival. According to the International Society for Heart and Lung Transplantation Registry, the average survival after a double lung transplantation (DLT) procedure is estimated at 7.8 years, in contrast to the single lung transplantation (SLT) with a survival set at the 4.8-year level [1]. The underlying disease is also one of the factors that affect survival after LTx. The 3-month mortality, after the procedure, in chronic obstructive pulmonary disease (COPD) or cystic fibrosis (CF) patients is the lowest (9%), whereas idiopathic pulmonary artery hypertension (IPAH) patients have a mortality rate at the highest level (23%) [2]. The occurrence of chronic rejection or bronchiolitis obliterans syndrome are determinant factors for long-term survival.

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However, short-term survival may be significantly threatened by incidence of airway complications (AC) [3–5]. The impact of AC on long-term outcomes is unknown, because of the general improvement of overall survival after LTx. The incidence of AC varies from 1.6% to 32% with the related mortality rate of 2% to 4% [1,6–8]. The management of most AC is based on endobronchial methods, including balloon bronchoplasty, endobronchial stent placement, and ablative techniques [9]. Unfortunately, recurrence of AC remains a source of persistent challenge. Up to 35% of patients with previous incidence of AC are prone to the occurrence of the second, and approximately 70% of recipients with a history of 2 will be at risk of 3 incidences or more [10].

The aim of the study was to assess the connection between AC treated by bronchial intervention (BI) and the survival of lung transplant recipients.

## MATERIALS AND METHODS

### Patients

The study design was single-center retrospective cohort research. We reviewed cases of 165 patients (63 women [38.18%], 103 men [61, 82%]; median age at referral for LTx, 41 years [range, 15-68 years]) who underwent LTx from April 2013 to June 2019 in the Silesian Center for Heart Diseases (Zabrze, Poland). Heart-lung transplantation and retransplantation recipients were excluded from the study.

The number of procedures of DLT was 104 (63.1%), and 62 (36.9%) operations of SLT were performed. The most common diagnoses were as follows: COPD (N = 45); CF (N = 43); IPAH (N = 20); interstitial lung disease (ILD; N = 51), which includes: idiopathic pulmonary fibrosis, sarcoidosis, histiocytosis, hypersensitivity pneumonitis, and lymphangioleiomyomatosis; and others (N = 6), including Osler-Weber-Rendu syndrome, Williams-Campbell syndrome, pulmonary veno-occlusive disease, bronchiectasis, and pulmonary embolism. The number of patients with at least 3-, 6- and 12-month survival was as follows: 143 (86.67%), 136 (82.43%), and 118 (71.52%) patients.

Demographic and clinical features of the studied group are presented in Table 1.

### Airway Complications

Many types of AC can be distinguished. In our study, we focused on bronchial stenosis.

For the purpose of the analysis, AC were defined as serious stenosis requiring the use of BI.

### Statistical Analysis

All statistical analyses were performed in IBM SPSS 25.0, R 3.5.3 and Statistica 10.0 software (StatSoft, Inc., Tulsa, Okla, United States). *P* levels lower than .05 were deemed statistically significant. For survival analysis, we used Cox regression and Kaplan-Meier survival analysis with Gehan's Wilcoxon test or log-rank test. To analyze demographic and clinical features of the studied group, the Student *t* test was used.

The cohort was stratified into 2 groups comprising those whose procedures were complicated by ACs and those without. The primary outcome measured was mortality, with survival of at least 6 months.

**Table 1. Demographic Features of Studied Group Presented as Mean ± Standard Deviation**

| | AC (n = 63) | No-AC (n = 102) | *P* Value |
|---|---|---|---|
| **Recipient related** | | | |
| Age, years | 40.49 ± 13.63 | 41.41 ± 14.69 | .689 |
| Female sex | 26 (41.27%) | 37 (36.27%) | .521 |
| Diagnosis | | | |
| CF | 19 (30.16%) | 24 (23.53%) | .123 |
| COPD | 22 (34.92%) | 23 (22.55%) | |
| ILD | 13 (20.63%) | 38 (37.25%) | |
| IPAH | 6 (9.52%) | 14 (13.73%) | |
| Other | 3 (4.76%) | 3 (2.94%) | |
| BMI, kg/m$^2$ | 20.63 ± 3.63 | 21.25 ± 4.2 | .332 |
| GFR, mL/(min×1.72 m$^2$) | 116.62 ± 44.09 | 112.54 ± 49.42 | .595 |
| HGB, mmol/L | 11.47 ± 3.29 | 12.15 ± 3.09 | .190 |
| RBC, mln/mL | 4.91 ± 0.61 | 5.02 ± 0.77 | .352 |
| HTC | 43.42 ± 6.08 | 42.44 ± 5.3 | .281 |
| FEV1*, % | 28.15 ± 18.39 | 28.25 ± 18.79 | .983 |
| FVC*, % | 43.7 ± 14.33 | 44.31 ± 20.71 | .887 |
| **Donor related** | | | |
| Age, years | 38.23 ± 12.17 | 35.67 ± 12.21 | .204 |
| Female gender | 13 (30.23%) | 28 (41.18%) | .245 |
| BMI, kg/m$^2$ | 23.81 ± 2.98 | 23.38 ± 2.61 | .425 |
| Cause of death | | | |
| Brain hemorrhage | 20 (46.51%) | 40 (57.97%) | .541 |
| Head trauma | 20 (46.51%) | 23 (33.33%) | |
| Stroke | 1 (2.33%) | 3 (4.35%) | |
| Other | 2 (4.65%) | 3 (4.35%) | |
| **Transplant related** | | | |
| Waiting time, days | 231.41 ± 218.47 | 279.62 ± 327.59 | .260 |
| CIT in SLT, hours | 5.09 ± 1.08 | 6.24 ± 2.19 | .238 |
| CIT in DLT, hours | 8.86 ± 2.21 | 8.43 ± 2.06 | .411 |
| **1-year follow-up** | | | |
| GFR, mL/(min×1.72 m$^2$) | 53.72 ± 22.06 | 58.81 ± 30.22 | .297 |
| RBC, mln/mL | 3.82 ± 0.52 | 3.85 ± 0.53 | .743 |
| HGB, mmol/L | 7.16 ± 0.98 | 7.07 ± 0.92 | .598 |
| HCT | 0.35 ± 0.05 | 0.34 ± 0.04 | .447 |
| FEV1*, % | 59.91 ± 20.69 | 76.55 ± 24.12 | .002 |
| FVC*, % | 74.57 ± 22.96 | 81.6 ± 19.3 | .154 |
| **5-year follow-up** | | | |
| GFR, mL/(min×1.72 m$^2$) | 49.73 ± 25.09 | 52.96 ± 26.8 | .678 |
| RBC, mln/mL | 4.14 ± 0.77 | 4.5 ± 0.77 | .128 |
| HGB, mmol/L | 7.73 ± 1.42 | 8.01 ± 1.08 | .437 |
| HCT | 0.37 ± 0.06 | 0.38 ± 0.05 | .360 |
| FEV1*, % | 45.64 ± 17.96 | 83.9 ± 21.79 | < .001 |
| FVC*, % | 71 ± 18.73 | 84.6 ± 11.13 | .061 |

Abbreviations: AC, airway complications; BMI, body mass index; CF, cystic fibrosis; CIT, cold ischemic time; COPD, chronic obstructive pulmonary disease; DLT, double lung transplantation; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GFR, glomerular filtration rate; HCT, hematocrit; HGB, hemoglobin; ILD, interstitial lung disease; IPAH, idiopathic pulmonary artery hypertension; RBC, red blood cells; SLT, single lung transplantation.
*Evaluated for patients after DLT only.

## RESULTS

Before analyzing the impact of bronchial interventions on survival among lung transplant recipients, the multivariate

**Table 2. Cox Proportional Hazard Model**

| Parameter | Parameter Assessment | SE | $\chi^2$ | *P* Value | HR | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Sex (female) | -0.320 | 0.761 | 0.176 | .674 | 0.726 | 0.163 | 3.229 |
| Age (years) | 0.020 | 0.035 | 0.342 | .559 | 1.021 | 0.953 | 1.093 |
| Donor's age (years) | 0.003 | 0.024 | 0.017 | .896 | 1.003 | 0.957 | 1.051 |
| CIT (hours) | 0.305 | 0.228 | 1.791 | .181 | 1.357 | 0.868 | 2.121 |
| Operation after 2018 | -2.303 | 1.249 | 3.400 | .065 | 0.100 | 0.009 | 1.156 |
| Time on waiting list > 365 days | 0.001 | 0.001 | 0.864 | .353 | 1.001 | 0.999 | 1.003 |
| Diagnosis | | | | | | | |
| CF | 0.903 | 1.056 | 0.212 | .441 | 0.600 | 0.073 | 4.896 |
| COPD | -1.340 | 0.957 | 0.732 | .633 | 0.365 | 0.077 | 1.730 |
| Other | | | | .204 | | | |
| Intervention in the first year after LTx | 0.021 | 0.028 | 0.569 | .451 | 1.021 | 0.967 | 1.078 |

Abbreviations: CF, cystic fibrosis; CI, confidence interval; CIT, cold ischemic time; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LTx, lung transplantation; SE, standard error.

analysis was performed to assess risk factors of mortality in the studied group. Multivariate Cox regression assessed that BI in the first year after LTx in addition to other factors incorporated are not statistically significantly associated with increased mortality as presented in Table 2. When it comes to the Kaplan-Meier survival analysis with log-rank test, comparing patients who underwent bronchoscopic intervention with the group with no BI, we did not observe any statistically significant differences ($P > .05$). The same analysis was also performed with Gehan's Wilcoxon test ($P > .05$) as the better method for evaluating mortality at early time points; however, it also remained statistically insignificant (Fig 1).

Four analyses were done for the comparison of the survival of recipients regarding underlying disease (CF, COPD, IPAH, and ILD) with the use of the Kaplan-Meier estimator, which indicated that the only statistically significant ($P = .0194$) differences between patients who underwent BI and patients without BI performed were observed in CF patients (Fig 2). In any other diagnosis, the results were not statistically significant ($P > .05$).

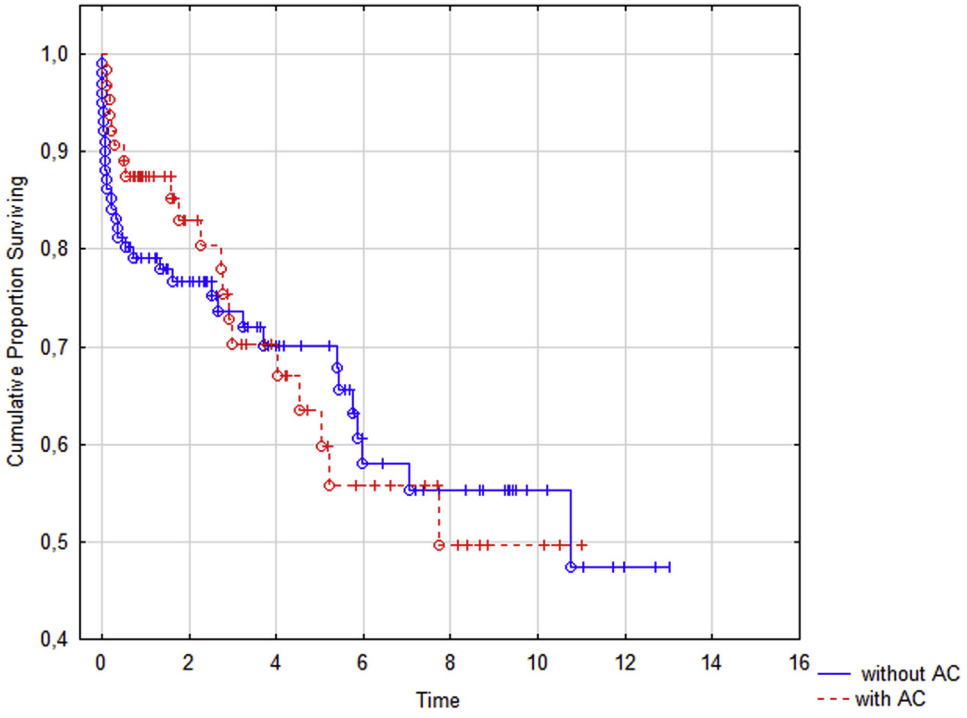


**Fig 1.** Kaplan-Meier estimator with Gehan's Wilcoxon test comparing patients with and without AC.

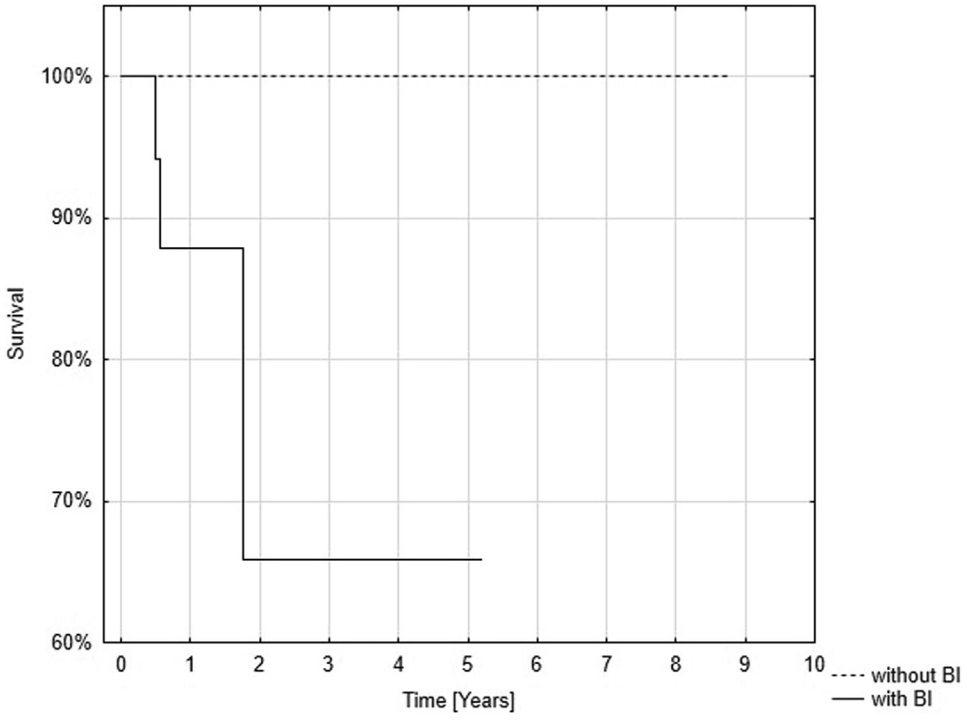


**Fig 2.** Kaplan-Meier estimator conditional on survival to 3 months. Survival in cystic fibrosis with or without bronchoscopic intervention ($P = .01938$).

Moreover, any statistically significant differences were not observed between the survival of patients who underwent SLT with/without BI ($P = .582$) or DLT with/without BI ($P = .1439$). Given the longer condition of survival in the DLT group, respectively 3 and 8 years, the results of predicted survival (patients without BI/patients with BI) are presented as follows: 95% and 88%/95% and 58%.

In terms of patients with BI, who were divided into groups of single lung recipients (SLR) or double lung recipients (DLR), the Kaplan-Meier estimator with 6 months, in addition to 1-year conditions on survival, remained statistically insignificant (as follows: $P = .2039$; $P = .094$). The results of the estimator with consideration of 1-year conditions on survival (SLR/DLR): 3-year survival was 95%, 97%; 5-year survival was 90.5%, 97%, and 8-year survival was 59%, 96%.

The result of Kaplan-Meier estimator on the 6-month conditional survival regarding the 4 groups of patients (SLR without BI; SLR with BI; DLR without BI, and DLR with BI) also remained statistically insignificant ($P = .65$).

## DISCUSSION

Despite improvement in organ preservation, immunosuppression treatment, and surgical techniques over the last decades, anastomotic airway complications are an important cause of morbidity after lung transplantation, and their influence on long-term survival remains unknown. Bronchoscopic examination is a gold standard for establishing a diagnosis of proximal airway complication after LTx.

It is reported that up to 33% of patients after lung transplantation demonstrated abnormal findings by routine bronchoscopy and also the need for interventions [11]. About two-thirds of patients with anastomotic complications have associated airway symptoms [10]. According to available literature, patients with AC after LTx had a higher mortality rate than patients without AC, and endobronchial therapy of these complications reduced early mortality [9,11].

The current study shows that there is no statistical difference in survival in patients with bronchoscopic intervention and without these procedures, except for patients with CF.

Yserbyt et al similarly reported no statistically significant differences in overall survival between patients that suffered from AC compared to others, aside from patients suffering from AC didn't develop chronic lung allograft dysfunction more often than the controls, nor did they develop severe stages of bronchiolitis obliterans syndrome more often [12]. According to Yacoub et al, patients with CF tend to retain purulent secretions after transplantation more than in other patients without CF, which initiates the development of excessive granulation tissue response at the anastomotic site [13,14]. Retention of secretions might also contribute to the development of necrosis, granulation, or microabscesses along the suture line, which can lead to partial dehiscence.

Our study has several limitations. First, the study is retrospective, and the experience changed over the time with more transplantations performed in the last years. The transplantations were also performed by 2 different surgical teams. Also, the immunosuppression therapy was different.

## CONCLUSIONS

Bronchoscopic interventions because of airway complications after lung transplantation are frequent procedures. They seem to have no impact on the short-term survival among patients who received transplants because of chronic obstructive pulmonary disease, primary pulmonary hypertension, and interstitial lung diseases. Lung transplant recipients because of CF seem to be the exception, as the number of BI influence their survival.

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