

The ripple effect of a complication in lung transplantation: Evidence for increased long-term survival risk

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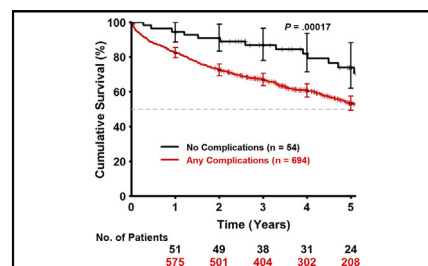
ABSTRACT

Objective: Lung transplantation is a life-saving procedure for patients who have end-stage lung disease. The frequency and severity of complications have not been fully characterized. We hypothesized that early in-hospital, postoperative complications decrease long-term survival.

Methods: We retrospectively identified in-hospital complications in lung transplant recipients, from the period January 2007 to October 2013. Complications were graded using the extended Accordion Severity Grading System (ASGS). Complications were categorized by event and organ system. Survival analysis was performed ($P < .05$) using a time-dependent model.

Results: Among 748 eligible patients, 3381 independent in-hospital, postoperative complications occurred in 92.78% of patients. Median follow-up was 5.4 years. Complications associated with significant decrease in 5-year survival were: renal (hazard ratio [HR] 2.58, 95% confidence interval [CI] 1.40-4.48); hepatic (HR 4.08, 95% CI 2.86-5.82); cardiac (HR 1.95, 95% CI 1.56-2.45). The maximum ASGS of ≥ 5 (18.5% vs 73.8%), and the weighted ASGS sum >10 (2.5% vs 73.8%), were found to be significant predictors of long-term survival. Multivariate analysis identified a weighted ASGS sum of >10 , and renal, cardiac, and vascular complications as predictors of decreased long-term survival.

Conclusions: Rigorous delineation of complications after lung transplantation showed that grade 5 ASGS in-hospital postoperative complications, and a weighted ASGS sum >10 , were independent predictors of decreased long-term survival well beyond the initial perioperative period. These results may identify important targets for best practice guidelines and quality-of-care measures after lung transplantation. (J Thorac Cardiovasc Surg 2016; ■:1-10)



Time-dependent survival curves for patients who have any postoperative complications, versus none.

Central Message

Grade ≥ 5 ASGS in-hospital postoperative complications, and a weighted ASGS sum of >10 were independent predictors of long-term survival.

Perspective

The overall 90-day postoperative course influences long-term survival. Both severity of the intervention needed to overcome a complication, and having many less-severe complications, have negative effects on long-term survival. These results support the need to establish best-practice guidelines outlining the best way to avoid complications, particularly during the initial period.

Advancements in operative techniques and postoperative management have greatly evolved and served to improve survival outcomes after lung transplantation surgery during the past 3 decades.^{1,2} Despite these improvements, however, 5-year survival of patients undergoing lung transplantation remains in the range of 55%. Some argue³ that

survival rates have plateaued in 2005, owing to a change in candidate selection from the implementation of the lung allocation score. Nevertheless, our goal should be to identify methods in which we can improve medical care given to these patients to push the field forward and improve outcomes.

An evolving literature suggests that postoperative course is correlated with long-term survival.^{4,5} High-volume centers performing lung resection surgery have decreased perioperative morbidity rates, compared with

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Abbreviations and Acronyms

ASGS = Accordion Severity Grading System
 CCI = Charlson Comorbidity Index
 CI = confidence interval
 HR = hazard ratio
 ICD-9 = International Classification of Diseases, 9th edition

lower-volume centers, indicating potentially more-effective management of postoperative complications that affect long-term survival. Using the American College of Surgeons National Surgical Quality Improvement Program Database, Ghaferi and colleagues^{6,7} attributed a 2.5-fold-higher mortality rate in the “worst” hospitals to their much higher failure-to-rescue rates. They proposed standardization of the management of postoperative complications as an effective strategy in decreasing variability in mortality after major surgery, across institutions.^{6,7}

In addition, center volume may have a strong association with improved survival, even beyond the initial perioperative period of 30 days in many fields, including thoracic surgery and transplantation.⁸⁻¹² Recently, our group demonstrated a negative association between in-hospital complications and 5-year overall and cancer-specific survival in patients undergoing lung resection surgery for stage I non-small cell lung cancer using the Surveillance, Epidemiology, and End Results (SEER) database.⁵ Others¹⁰ have demonstrated equivalent incidences of individual postoperative complications in high-volume centers after lung transplantation, but they have identified these same high-volume centers as best equipped for minimizing adverse effects of complications on short- and long-term survival. Similar associations were identified between postoperative complications and survival in cardiac and renal transplant recipients.^{9,11} These important findings highlight the need for further in-depth analysis into an intriguing aspect of surgical management of complications after high-risk procedures.

Complication types such as infections have been extensively studied in the lung transplantation literature.^{13,14} However, few reports have rigorously examined the overall postoperative complications profile of lung transplant recipients. The purpose of the current study is to identify and create the postoperative complication profile for this population. Further, we sought to investigate the relationship between long-term survival and the way in which it is influenced by each adverse event during the postoperative course. Using the Accordion Severity Grading System (ASGS) to assess severity, we hypothesized that in-hospital, postoperative complications have an independent, negative impact on long-term survival.

METHODS**Data Sources**

The University of Pittsburgh Medical Center Transplant Patient Management System database was utilized to identify patients suitable for this study. Prior to extracting data, institutional review board approval was obtained to ensure patient confidentiality. Between January 2007 and October 2013, a comprehensive database on all postoperative complications was prospectively recorded on all 748 patients transplanted at that time. Follow-up included the day of transplantation until death or censoring on August 31, 2015. No patient was lost to follow-up for postoperative complications or mortality.

Data Variables

All variables were obtained from the University of Pittsburgh Medical Center Cardiothoracic Transplant database. These included, among others, demographics such as comorbidities and diagnosis, characteristics of the surgical procedure, cause of death, and annotated in-hospital postoperative complications occurring within 90 days of surgery. Comorbidities were quantified using the Charlson Comorbidity Index (CCI).¹⁵ In-hospital complications up to 90 days were included in the analysis to achieve a comprehensive list of complications while excluding medical events that may have been unrelated to the surgery or postoperative course. Postoperative complications that occurred outside of the initial 90 days, including outside-hospital events resulting in readmission, were excluded from this study, owing to the relative ambiguity of their origin. Adverse events were identified via chart review by a dedicated team of database professionals and adjudicated by a lung transplantation surgical-quality committee prior to updating of patient profiles in the database. The date of occurrence was verified as that between the day of surgery and the date of discharge, prior to labeling them as in-hospital postoperative complications.

Following a methodologic approach that paralleled our previous work, 94 postoperative complications were identified based on International Classification of Diseases, 9th edition (ICD-9) diagnostic definitions, as well as findings in the literature, and classified into categories⁵ (Table 1). No additions to the ICD-9 diagnostic codes were necessary. Our primary outcome measure was 1-, 3-, and 5-year overall survival, in keeping with other similar published reports.^{10,11,16}

Accordion Severity Grading System

The extended ASGS version was chosen to classify adverse events. This standardized system quantifies the severity of complications, based on the magnitude of intervention (treatment for complications) necessary to overcome the event.¹⁷ Details illustrating the course of complications, as well as the extent of treatment the patients underwent, were obtained directly from chart review and included in the database. Grades from the ASGS were weighted based on the burden of total morbidity, as quantified by Porembka and colleagues.¹⁸ Analysis of the ASGS grades included patients' highest-graded in-hospital postoperative complications, as well as the sum of their weighted ASGS scores, as previously described.

Statistical Analysis

Cox proportional hazard models were used to test the univariate associations between time-independent covariates, such as demographics, operative characteristics, comorbidities, and post-transplant survival. The Cox model, with time-dependent covariates, mainly postoperative complication categories, was used to test for univariate and multivariate associations with survival. Survival curves were estimated via counting processes in Cox regression models with time-dependent covariates. Data were analyzed using the R environment for statistical analysis and graphics,¹⁹ particularly the survival package.²⁰

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