

Medication Nonadherence After Lung Transplantation in Adult Recipients

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Background. Our objective was to identify potential avenues for resource allocation and patient advocacy to improve outcomes by evaluating the association between recipient sociodemographic and patient characteristics and medication nonadherence after lung transplantation.

Methods. States US adult, lung-only transplantations per the United Network for Organ Sharing database were analyzed from October 1996 through December 2006, based on the period during which nonadherence information was recorded. Generalized linear models were used to determine the association of demographic, disease, and transplantation center characteristics with early nonadherence (defined as within the first year after transplantation) as well as late nonadherence (years 2 to 4 after transplantation). Outcomes comparing adherent and nonadherent patients were also evaluated.

Results. Patients ($n = 7,284$) were included for analysis. Early and late nonadherence rates were 3.1% and

10.6%, respectively. Factors associated with early nonadherence were Medicaid insurance compared with private insurance (adjusted odds ratio [AOR] 2.45, 95% confidence interval [CI]: 1.16 to 5.15), and black race (AOR 2.38, 95% CI: 1.08 to 5.25). Medicaid insurance and black race were also associated with late nonadherence (AOR 2.38, 95% CI: 1.51 to 3.73 and OR 1.73, 95% CI: 1.04 to 2.89, respectively), as were age 18 to 20 years (AOR 3.41, 95% CI: 1.29 to 8.99) and grade school or lower education (AOR 1.88, 95% CI: 1.05 to 3.35). Early and late nonadherence were both associated with significantly shorter unadjusted survival ($p < 0.001$).

Conclusions. Identifying patients at risk of nonadherence may enable resource allocation and patient advocacy to improve outcomes.

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In 2011, more than 1,800 lung transplantations were performed in the United States alone [1]. Despite improvements in outcomes after lung transplantation, the 1-year survival remains close to 80% and the median survival is only 5.5 years. Despite immunosuppressive drugs, 35% of adult recipients still have at least one episode of acute rejection within the first year [2].

Adherence to medical therapy has repeatedly been shown to be associated with improved outcomes among solid-organ transplant recipients [3–8]. Despite this, nonadherence is a persistent and costly problem in the overall transplantation population [6]. A 2007 meta-analysis found that the incidence of nonadherence was 19% to 25% per year [9]. Of the studies analyzed, only a few reported on lung transplant recipients [10–13]. More recent studies have suggested similar rates of nonadherence in patients who received a lung transplant compared with other solid-

organ transplants [14–19]. Furthermore, nonadherence was more common among patients who experienced bronchiolitis obliterans syndrome [20, 21].

Despite this body of evidence regarding the importance of medication adherence in lung transplant recipients, a paucity of literature exists regarding risk factors for nonadherence in this patient population. Furthermore, medication nonadherence has been recognized as not only related to factors on an individual level but also results from failings of the health system related to health access, cost, and communication [22–25]. Our objective was to evaluate the association between recipient sociodemographic and disease characteristics and the incidence of nonadherence after lung transplantation using a cohort of all lung transplantations performed in the United States. A secondary objective was to report the survival implications of nonadherence after lung transplantation.

Patients and Methods

The Institutional Review Board at Duke University Medical Center approved this study.

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Study Population

The Organ Procurement and Transplantation Network's national computerized database as maintained by the United Network of Organ Sharing (UNOS) was used for this analysis [26]. This contains data regarding every organ donation and transplantation event occurring in the United States since October 1, 1987 [1]. The dataset used for the present study included lung transplantations performed through December 31, 2011, with follow-up through March 31, 2012. All adult (≥ 18 years) lung transplant recipients were included for analysis. Multiple organ, en block, lobar, and repeat transplantations were excluded. The study period included transplantations performed from October 1996 through December 2006 based on the time period during which nonadherence information was recorded in the UNOS database. To be included in the study, patients had to have a follow-up visit after transplantation documenting the presence or absence of evidence of noncompliance with immunosuppressive medication during this follow-up period that compromised the patient's recovery within the first 4 years after transplantation (this is a yes/no field on the Adult Thoracic Transplant Recipient Follow-Up Worksheet [Office of Management and Budget approved form number 0915-0157]). Patients with unknown or missing adherence information were excluded.

Variable Definitions

The UNOS database includes donor, recipient, and transplantation-related characteristics. To describe our study cohort, we included the following characteristics: age; sex; race; cause of lung failure; diabetes; hypertension; creatinine; body mass index, steroid use before transplantation that required life support at the time of transplantation; Lung Allocation Score (available after May 2005); days on the waitlist; insurance carrier; education level; smoking history; type of transplantation; human leukocyte antigen mismatch level; donor/recipient sex, race, and cytomegalovirus (CMV) mismatch; total ischemic time (hours); transplantation year; and transplantation center volume.

PREDICTOR VARIABLES. Predictor variables for analysis were determined a priori based on factors previously demonstrated in the literature to affect medication adherence [8, 16, 25, 27–29]. These variables included recipient age, sex, race, smoking history, insurance carrier, education level, cause of lung failure, comorbidities, year of transplantation, and transplantation center volume.

OUTCOME MEASURES AND FOLLOW-UP. The primary outcome variable was nonadherence with immunosuppressive medications. This was separately assessed for nonadherence within the first year (termed early nonadherence) and nonadherence during years 2 to 4 (termed late nonadherence). To be included in an analysis for a given postoperative period (early or late) a patient must have had definitive documentation of the presence or absence of nonadherence during that time. Overall survival for patients with nonadherence was also assessed in comparison with patients without nonadherence.

Outcome data for each patient were ascertained from the date of transplantation until patient death, date of last follow-up, or the end of study period (March 31, 2012).

Study Design and Statistical Analysis

We performed a retrospective, observational cohort analysis of lung transplant recipients subject to inclusion/exclusion criteria as described in the sections above. Baseline characteristics were described for the overall study population, with medians and interquartile range (IQR) reported for continuous variables and proportions (frequency, percentage) for discrete variables.

Multivariable logistic regression was performed to assess the association between predictor variables defined in the section above and nonadherence with immunosuppressive medications. Logistic regression models were performed separately for early and late nonadherence. The late nonadherence models included transplantations before year 2003 to allow adequate follow-up time to assess late nonadherence. Continuous variables included in the model (recipient age, year of transplantation, and transplantation center volume) were assessed for linearity with respect to the outcome measures. Only recipient age demonstrated a nonlinear relation and was accordingly stratified by age 18 to 20 years, 21 to 50 years, and 51 years and older.

To assess survival implications of nonadherence, unadjusted patient survival rates for early and late nonadherence were estimated using the product-limit (Kaplan-Meier) method [30] and compared with control subjects using the log-rank test. Patients with early nonadherence were excluded from the analysis of late nonadherence to isolate the association of late nonadherence with survival.

Statistical analyses were performed using JMP Version 10.0 (SAS Institute Inc, Cary, NC) and R version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria). For all comparisons, *p* values less than or equal to 0.05 were considered statistically significant, and all tests were two sided.

Results

Study Population and Baseline Characteristics

A total of 7,284 lung transplant recipients met the inclusion and exclusion criteria of this study (Fig 1). Median recipient age was 54 years (IQR, 44 to 60 years), whereas median donor age was 29 years (IQR, 20 to 44 years) (Table 1). Most of the lung transplant recipients were white ($n = 6,472$, 88.9%), whereas 490 (6.7%) recipients were black, 233 (3.2%) recipients were Hispanic. Private insurance/self-payment was the most frequent recipient insurance at time of transplantation ($n = 4,556$, 63.0%) followed by Medicare ($n = 1,789$, 24.7%) and Medicaid ($n = 529$, 7.3%) (Table 2).

Early and Late Nonadherence

Factors associated with early nonadherence were Medicaid insurance (adjusted odds ratio [AOR] compared

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