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Original Article

Predictors of non-referral of patients with cystic fibrosis for lung transplant evaluation in the United States☆

Kathleen J. Ramos [a,*], Bradley S. Quon [b], Kevin J. Psoter [c], Erika D. Lease [a], Nicole Mayer-Hamblett [d,e,f], Moira L. Aitken [a], Christopher H. Goss [a,d,f]

[a] University of Washington Medical Center, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Seattle, WA, United States
[b] Centre for Heart Lung Innovation, University of British Columbia and St. Paul's Hospital, Vancouver, BC, Canada
[c] Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States
[d] Seattle Children's Hospital, Seattle, WA, United States
[e] University of Washington, Department of Biostatistics, Seattle, WA, United States
[f] University of Washington, Department of Pediatrics, Seattle, WA, United States

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Abstract

Background: Lung transplantation is an intervention that improves survival for adult patients with cystic fibrosis (CF). Some patients with CF are never referred for lung transplant evaluation despite meeting physiologic criteria for referral.
Methods: We performed a retrospective analysis of adult patients (≥18 years of age) in the Cystic Fibrosis Foundation Patient Registry (CFFPR), eligible for their first evaluation for lung transplantation during the years 2001–2008 based on FEV1 < 30% predicted in two consecutive years.
Results: Within the CFFPR, 1240 patients met eligibility criteria. Eight hundred and nine (65.2%) were referred for lung transplant evaluation, and 431 (34.8%) were not referred. In a multivariable model, Medicaid insurance (OR 1.79, 95% CI 1.29–2.47), older age (per 5 year increase; OR 1.25, 95% CI 1.13–1.39), lack of high school graduate education (OR 2.27, 95% CI 1.42–3.64), and *Burkholderia cepacia* complex sputum culture positivity (OR 2.48, 95% CI 1.50–4.12) were associated with non-referral, while number of pulmonary exacerbations (OR 0.93, 95% CI 0.87–0.99) and supplemental oxygen use (OR 0.59, 95% CI 0.43–0.81) were associated with increased referral.
Conclusions: Despite meeting lung function criteria for lung transplant evaluation, 35% of patients with CF had not yet been referred to a lung transplant center. Predictors of non-referral included markers of low socioeconomic status, older age and *B. cepacia* complex sputum culture. Further work is needed to understand the outcomes for non-referred patients in order to refine referral recommendations in this population.

Keywords: Cystic fibrosis; Lung transplantation; Referral

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFFPR, Cystic Fibrosis Foundation Patient Registry; CI, confidence interval; FEV_1, forced expiratory volume in 1 s; FPL, federal poverty level; ISHLT, International Society for Heart and Lung Transplantation; LAS, lung allocation score; LTx, lung transplantation; min, minutes; NPPV, noninvasive positive pressure ventilation; OR, odds ratio; SD, standard deviation; SE, standard error; SES, socioeconomic status; UNOS, United Network for Organ Sharing; US, United States.

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* Corresponding author at: Division of Pulmonary and Critical Care Medicine, University of Washington Medical Center, Box 356522, 1959 NE Pacific Street, Seattle, WA 98195, United States. Tel.: +1 206 616 8378; fax: +1 206 685 8673.
E-mail address: ramoskj@uw.edu (K.J. Ramos).

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1. Background

Progressive respiratory failure causes death in approximately 80% of patients with cystic fibrosis (CF) [1–3]. Lung transplantation (LTx) is a treatment option for certain patients with CF and end-stage lung disease. CF is currently the third most common indication for LTx in the United States (US) [4]. Appropriate candidates for LTx have advanced lung disease with impaired quality of life and are adherent to medical recommendations, while lacking contraindications to transplant. Patients deemed good candidates for LTx are referred to a lung transplant center. The evaluation for LTx involves: assessing a patient's indication for transplant; identifying potential contraindications or barriers to transplant; and providing the patient with information about the LTx process [5]. If the candidate is determined to be appropriate for lung transplantation, he/she is placed on the United Network for Organ Sharing (UNOS) waitlist in rank-order by lung allocation score (LAS). The LAS was adopted in May 2005 in the US in an attempt to maximize net benefit of transplant, considering a patient's waitlist urgency and 1-year post-transplant survival.

The International Society for Heart and Lung Transplantation (ISHLT) recommends referral for lung transplant evaluation when a patient has a 2- to 3-year predicted survival of <50% [6]. Historically, forced expiratory volume in 1 s (FEV_1) <30% of the predicted value was considered the strongest independent predictor of 2-year mortality in patients with CF, but this finding has not been uniform. [7–9] FEV_1 < 30% predicted has been an ISHLT-recommended indication for consideration of referral for lung transplant evaluation since 1998 [10]. Several other clinical factors have also been recommended for consideration of referral, including a rapid decline in FEV_1 despite optimal therapy, 6-minute walk distance <400 m, development of pulmonary hypertension, or clinical decline (pulmonary exacerbations with intensive care unit admission, refractory or recurrent pneumothorax, life-threatening hemoptysis not controlled by embolization), particularly if present prior to a fall in FEV_1 to below 30% predicted [6].

Despite meeting current medical indications for referral for transplant evaluation, some CF patients are not referred to a lung transplant center for evaluation. Listing for LTx for patients with CF (once referred to a transplant center) has been shown to differ based on socioeconomic status (SES), including Medicaid insurance status and driving time to nearest lung transplant center [11]. We hypothesized that markers of low SES would also be associated with non-referral of CF patients for lung transplant evaluation. The purpose of this study was to identify predictors of non-referral for lung transplant evaluation in CF patients with advanced lung disease.

2. Methods

The Institutional Review Board at the University of Washington determined that this research has Exempt Status based on the proposed project's use of a de-identified data set, the US Cystic Fibrosis Foundation Patient Registry (CFFPR). Our request to use data from the CFFPR was reviewed and accepted by the Cystic Fibrosis Foundation.

2.1. Study population and data source

We performed a retrospective cohort study to evaluate predictors of non-referral for lung transplant evaluation in patients with CF using the CFFPR. The CFFPR captures demographic and encounter-based clinical data for approximately 85–90% of the US CF population [1]. Inclusion criteria for this study included: age 18 years and older with a valid residential zip code, eligible for first lung transplant evaluation during the years 2001–2008 based on FEV_1 < 30% predicted for two consecutive years when clinically stable (Fig. 1). The physiologic inclusion criterion for this study was intended to capture an extreme phenotype for CF patients, those likely to be referred for lung transplant evaluation based on current ISHLT recommendations [6]. Subjects with less than two years of lung function data or with a prior lung transplant evaluation were excluded. Once meeting the eligibility requirement, the patient's lung transplant referral status was ascertained from the CFFPR.

2.2. Outcome and exposures

The primary outcome of interest was non-referral (yes/no) for lung transplant evaluation, irrespective of the decision to list for transplant following a referral. The primary covariates of interest focused on SES. Receipt of any Medicaid insurance at the time of eligibility for lung transplant was our primary indicator of low SES and a common proxy for low SES in the CF literature [12]. We also examined other markers of low SES, including educational attainment (high school graduate vs. did not complete high school), median household income based on the patient's residential ZIP code [relative to the 2000 federal poverty level (FPL)] and driving time to the nearest lung transplant center, defined as the driving time from the center of the patient's residential zip code to the nearest adult lung transplant center [11].

Additional covariates included demographics (race, age, gender), markers of disease severity (FEV_1% predicted, number of acute exacerbations [requiring intravenous antibiotics] per year, *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex sputum culture status, use of supplemental oxygen or noninvasive positive pressure ventilation [NPPV], body mass index [BMI, kg/m^2], insulin-requiring CF-related diabetes), comorbidities (CF-related liver cirrhosis with associated portal hypertension, renal failure requiring dialysis, osteoporosis, depression, tissue-proven cancer, smoking), adherence to medical follow-up (frequency of outpatient visits per year), and LAS implementation period (pre-2005, 2005 or later). Covariate values were ascertained in the same year as the patient met physiologic inclusion criteria. Current clinical recommendations include quarterly clinical visits for all CF patients; therefore, having fewer than four outpatient visits per year was used as a marker of non-adherence. There was significant missing data for