Heterogeneity in survival among adult cystic fibrosis patients with low lung function in the United States

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Abstract

Heterogeneity in survival among adult cystic fibrosis patients with low lung function in the United States

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Background

Lung transplantation (LTx) is frequently considered for patients with cystic fibrosis (CF) when FEV_1 reaches <30%. This study estimated transplant-free survival for patients with CF and FEV_1 <30% and identified predictors of transplant-free survival.

Methods

We conducted a retrospective cohort study using the Cystic Fibrosis Foundation Patient Registry, 1/1/2003-12/31/2013. Adult patients (≥18 years) with FEV_1 <30% prior to LTx were included. We performed Kaplan-Meier survival estimates censored at LTx. Multivariable Cox proportional hazard regression identified adjusted predictors of survival.

Results

There were 3,340 patients with FEV_1 <30%. Death without LTx occurred in 1,250 (37.4%); 945 (28.3%) underwent LTx; 924 (27.7%) remained alive without LTx at the end of the follow-up period; 221 (6.6%) were lost to follow-up. Median transplant-free survival after FEV_1 <30% was 6.6 years (95% CI 5.9-7.0). Adjusted predictors of mortality included (HR, 95% CI): supplemental oxygen use (2.1, 1.7-2.6), *B. cepacia* infection (1.8, 1.3-2.6), BMI ≤18 (1.6, 1.3-1.9), female sex (1.6, 1.2-2.0), CF-related diabetes on insulin (1.4, 1.2-1.8), and ≥1 exacerbations per year (1.7, 1.3-2.2; vs. 0 exacerbations).

Conclusions

Median survival is over 6.5 years for CF patients with FEV_1 <30%, exceeding prior survival estimates. There is substantial heterogeneity in survival, with some CF patients dying soon after reaching

this lung function threshold and others living for many years. For this reason, we conclude that FEV_1 <30% remains an important marker of disease severity for patients with CF, but we suggest FEV_1 value alone need not always trigger LTx evaluation.

Background

Cystic fibrosis (CF) is an autosomal recessive genetic disease that leads to dysfunction in multiple organ systems, including progressive respiratory failure causing death in approximately 80% of patients.[1, 2] Lung transplantation (LTx) is an option for treating end-stage lung disease in CF, and the International Society for Heart and Lung Transplantation (ISHLT) recommends referral for LTx evaluation when a patient has a 2-year predicted survival of <50%.[3] Referral for LTx evaluation is frequently considered in patients with CF once the forced expiratory volume in 1 second (FEV_1) is less than 30% of the predicted normal value.[3] This guideline is based on data from a single-center CF cohort from Toronto (patients eligible 1977-1989) that documented 2 year-survival falls to <50% once the FEV_1 reaches <30%; they also documented a high 2-year mortality for CF patients with hypoxemia, hypercarbia, older age and female sex.[4] In 1998, Milla et al. documented a median survival of 3.8 years among CF patients with FEV_1 <30% in a single-center cohort from Minneapolis eligible from 1975-1994.[5]

Survival in CF has been improving over time, but patients still experience a shortened lifespan due to progressive lung disease.[6, 7] Specifically focusing on patient survival prior to LTx (transplant-free survival) captures the natural history of CF-related lung disease and can inform decisions about the timing of referral and listing for LTx. A single-center study of 276 patients with cohort eligibility between 1990-2003 in London revealed that FEV_1 <30% was associated with a median transplant-free survival of 5.3 years.[8] Our hypothesis was that among CF patients with FEV_1 <30% in the United States (US), median survival likely exceeds 2 years. Additionally, we sought to identify predictors of survival among patients with low lung function, which could potentially better identify those patients most suitable for referral for LTx evaluation. We hypothesized that female sex [4, 9-11], pulmonary exacerbation frequency [10, 12, 13], low FEV_1 % predicted [10, 13], low body mass index (BMI) [4, 10], supplemental oxygen use [4], and colonization with *Burkholderia cepacia* [10, 14] would be associated with worsened survival, based on literature in CF patients with all ranges of lung function.

Methods

We performed a retrospective cohort study using the Cystic Fibrosis Foundation (CFF) Patient Registry (CFFPR), with data available between January 1, 2003 and December 31, 2013. The CFFPR

captured demographic and encounter-based clinical data for approximately 81-84% of persons with CF the US in 2012.[15] This project was approved by the University of Washington Institutional Review Board and the CFF Registry Committee (Bethesda, MD). Adult patients (age ≥18 years), who had not yet undergone LTx, were included in the analyses based on a lung function (FEV_1) cutoff of FEV_1 <30% at cohort entry. Only lung function measurements recorded during "stable" encounters were considered for eligibility. "Stable" encounters were identified as visits that occurred in clinic, and were not labeled as "home IV" or "hospital" encounters. After 2010, a pulmonary exacerbation indicator was added to the Cystic Fibrosis Foundation Patient Registry and a "stable" encounter was also required to have "absent" marked for the pulmonary exacerbation indicator. Patients were deemed lost to follow-up if their last encounter was more than 1 year prior to the end of the dataset (December 31, 2013). Patient follow-up was censored at the encounter during which LTx was documented, at loss to follow-up or at the end of the study. An indicator variable for LTx was created utilizing data from two separate covariates in the CFFPR; date of LTx is assumed to be the encounter date when LTx status is updated (update to LTx status occurs at the patient's "annual visit").

Our primary analysis was determination of median transplant-free survival with censoring at the time of LTx, using Kaplan-Meier estimates of the survival function. We also determined the incidence rate of death prior to LTx and median time to LTx for patients with FEV_1 <30%. Univariate Cox proportional hazard (PH) regression was first performed (FEV_1 % predicted, continuous and 5% intervals; calendar time (by year); entry age; female sex; height; BMI less than or equal to 18 – continuous BMI violated PH; F508del genotype; pancreatic insufficiency; number of pulmonary exacerbations in the year prior to eligibility; categorized pulmonary exacerbations [0 versus ≥1]; supplemental oxygen requirement – continuous, nocturnal or exertional; any supplemental oxygen requirement; *Burkholderia cepacia* infection; CF-related diabetes on insulin; end-stage renal disease on dialysis; pneumothorax requiring a chest tube; hemoptysis; cirrhosis; osteoporosis; depression; Medicaid insurance; high school education; white race; marital status – married, living together), and then a multivariable model was constructed, adding covariates to the model if their univariate p-value was <0.10. All covariates were then included in the final multivariable model regardless of significance. Tests for violation of PH assumption were performed with Schoenfeld residuals. If the PH assumption failed, the covariate was either categorized or

was modeled as strata in the multivariate Cox PH regression. Time-varying effects were tested for FEV_1 % predicted.

Sensitivity analyses were performed to obtain median survival among patients with: FEV_1 <30% without censoring at LTx; FEV_1 <30% among those who never undergo LTx; and FEV_1 <30% among those who will undergo LTx. Additional sensitivity analyses were performed using two additional FEV_1 cut-points during stable clinical encounters (not marked as pulmonary exacerbation or hospitalization): (1) FEV_1 <30% during two consecutive years; and (2) FEV_1 <25% once. Survival analysis using Kaplan-Meier estimates was performed to obtain transplant-free median survival in these additional cohorts with more severe lung disease. Additionally, median survival was estimated for patients stratified by covariates that were significant in the multivariate Cox regression model. Finally, a sensitivity analysis was performed to identify the number of pulmonary exacerbations per year, during the year prior to reaching FEV_1 <30%, that is associated with a clinically significant shortened median survival.

Table 1: Characteristics of 3,340 patients with cystic fibrosis at the time of their first stable measurement of FEV_1 <30%, 2003-2013

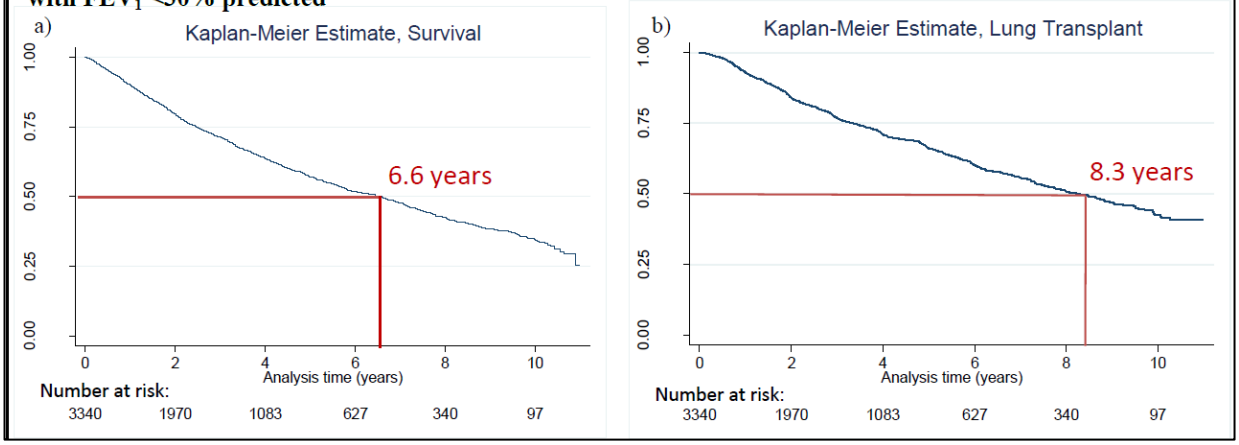
Age at eligibility – mean (SD), years	33.2 (10.1)
Female sex	1444 (43.2)
Race, white vs. non-white	3220 (96.4)
FEV_1 at eligibility - % predicted (SD; min-max)	25.6 (3.9; 4.3-29.9)
Acute exacerbations per year – N (SD; min-max)[1]	1.8 (1.7; 0-11)
Sputum culture positive	
Pseudomonas aeruginosa[2]	2681 (80.3)
Burkholderia cepacia complex[3]	205 (6.1)
Nontuberculous mycobacterium[3]	41 (1.2)
Supplemental oxygen[4]	1154 (34.6)
Noninvasive mechanical ventilation[5]	167 (5.0)
BMI at eligibility – kg/m^2 (SD)	20.4 (3.7)
BMI ≤ 18	721 (21.6)
CF-related diabetes on insulin[3]	879 (26.3)
F508del mutation status	
Non-F508del	245 (7.3)
Heterozygous F508del	1106 (33.1)
Homozygous F508del	1427 (42.7)
Unknown[6]	562 (16.8)
Pancreatic insufficiency[7]	3046 (91.2)
CF-related liver cirrhosis	91 (2.7)
Renal failure requiring dialysis	24 (0.7)
Osteoporosis	325 (9.7)
Pneumothorax requiring chest tube	74 (2.2)
Hemoptysis	100 (3.0)
Depression	769 (23.0)
Marital Status	
Married	1253 (37.5)
Living Together	228 (6.8)
High school graduate	2719 (81.4)
Medicaid insurance	1304 (39.0)

Data are presented as No. (%) unless indicated otherwise. Missing <1% unless indicated otherwise. Covariate values are observed at the time of eligibility for the FEV_1<30% cohort.
[1] number of pulmonary exacerbations requiring IV antibiotics during the year prior to FEV_1<30% [2] *Pseudomonas* culture data missing for 172 (5.2%) [3] positive if documented as present, otherwise recoded to negative [4] supplemental oxygen continuous or nocturnal [5] noninvasive mechanical ventilation data missing for 1923 (57.6%) [6] over 75% of non-genotyped patients entered the cohort by 2007 [7] pancreatic insufficiency if patient is documented to take pancreatic enzymes
FEV_1 = forced expiratory volume in 1 second, SD = standard deviation, BMI = body mass index, CF = cystic fibrosis

Results

The analysis included 3,340 patients with FEV_1 <30% who had not yet undergone LTx. The average age of patients meeting eligibility was 33.2 years old (Table 1). The cohort was predominantly white, with over 80% having graduated from high school and 38% married. Thirty-five percent required supplemental oxygen (continuously or at night) at the time of eligibility.

Figure 1: Kaplan Meier Estimates for survival (panel a) and time to lung transplant (panel b) for patients with FEV_1 <30% predicted



Of the 3,340 patients in the analysis, 1,250 (37.4%) later died without LTx, 945 (28.3%) underwent LTx, 924 (27.7%) remained alive without LTx at the end of follow-up, and 221 (6.6%) were lost to follow-up. Median transplant-free survival after FEV_1 <30% was 6.6 years (95% CI 5.9-7.0); median time to transplant for patients who did not die was 8.3 years (95% CI 7.6-8.9) after FEV_1 <30% (Figures 1 and 2). Incidence rate of death among patients with FEV_1 <30% predicted was 109.5 per 1,000 person-years.

Figure 2: Number of lung transplants and deaths each year after FEV_1 <30%

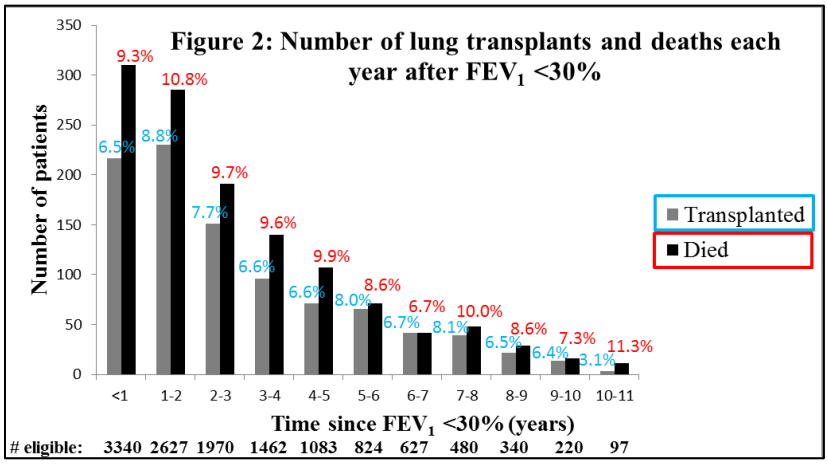


Table 2: Sensitivity analyses of median survival for patients with different lung disease severity and differing survival analysis methods

FEV1 cutoff	Number of subjects	Median survival (95% CI)	Number of deaths
<30% once	3,340	6.6 years (5.9 -7.0)	1,250
<30% once, not censored at transplant	3,421	6.7 years (6.4-7.1)	1,530
<30% once, excluded if ever-transplanted	2, 389	4.5 years (4.3-4.9)	1,250
<30% once, only if ever-transplanted[1]	1,032	---	280
<30% in two consecutive years	1,818	5.2 years (4.8-5.6)	693
<25% once	2,214	4.8 years (4.4-5.1)	876

[1] at the end of study follow-up, only 39.6% of eligible patients had died; analysis is not censored at transplant; 5-year survival is 82.3% (79.6-84.8%) and 10-year survival is 60.4% (56.2-64.3%)

Sensitivity analyses revealed median survival of 6.7 years (95% CI 6.4-7.1 years) for patients with FEV_1 <30% when there was no censoring at LTx, which is almost exactly the same as the estimate from the model with censoring at LTx (Table 2). When patients were excluded if they eventually undergo LTx, median transplant-free survival decreases and when patients are only considered if they eventually undergo LTx median transplant-free survival increases markedly (Table 2). Further sensitivity analyses showed a median survival of over 5 years for patients with two consecutive years of FEV_1 <30% predicted and a median survival of nearly 5 years for patients with FEV_1 <25% predicted at cohort entry.

Univariate Cox PH analysis

Table 3: Relative mortality in patients with cystic fibrosis and low lung function in relation to demographic, anthropometric, and clinical characteristics – univariate Cox proportional hazards regression results

Covariate	HR (95% CI)
FEV1 % predicted, per 1% increase[1]	0.94 (0.92-0.95)**
FEV1 % predicted, 5% intervals[1]	0.73 (0.68-0.78)**
Calendar year of first FEV_1 < 30%[1]	0.91 (0.89-0.93)**
Entry age (years)	1.00 (1.00-1.01)
Female sex	1.39 (1.24-1.55)**
Height (inches)	0.95 (0.94-0.96)**
BMI ≤18	1.68 (1.49-1.90)**
F508del mutation status	
Heterozygous[2]	1.20 (0.95-1.53)
Homozygous[2]	1.30 (1.03-1.65)*
Unknown[2]	2.06 (1.60-2.64)**
Pancreatic insufficiency[3]	1.05 (0.86-1.27)
# pulmonary exacerbations [1,4]	1.28 (1.24-1.31)**
1 or more exacerbations (versus none)[1]	1.99 (1.73-2.29)**
Supplemental oxygen[1,5]	2.96 (2.64-3.32)**
Any supplemental oxygen[1,6]	2.90 (2.59-3.25) **
Burkholderia cepacia[7]	1.99 (1.65-2.41) **
CFRD, on insulin	1.70 (1.50-1.91) **
ESRD, on dialysis	4.04 (2.53-6.45) **
Pneumothorax[8]	1.75 (1.22-2.49) *
Hemoptysis	1.44 (1.04-1.98) *
Cirrhosis	2.08 (1.59-2.74) **
Osteoporosis	1.50 (1.26-1.80) **
Depression	1.71 (1.53-1.92) **
Medicaid Insurance	1.67 (1.50-1.87) **
High school graduate[9]	0.78 (0.63-0.98) *
White[10]	0.95 (0.72-1.26)
Marital status	
Married[11]	0.74 (0.65-0.84) **
Living Together[11]	1.08 (0.87-1.34)
Non-invasive ventilation[12]	3.14 (2.49-3.96) **
Smoking[12]	1.41 (0.89-2.24)

**p-value <0.001; *p-value <0.10, covariates included in the multivariable analysis
[1] Violation of proportional hazards assumption [2] Reference group has non-F508del mutations [3] Pancreatic insufficiency defined as documentation of pancreatic enzyme use [4] Number of exacerbations requiring IV antibiotics in the year prior to FEV_1 <30% [5] Continuous or nocturnal use of oxygen [6] Any use of oxygen, including continuous, nocturnal, with exacerbations or PRN [7] Sputum infection with *Burkholderia cepacia* complex [8] Pneumothorax that required a chest tube [9] High school graduate education or higher [10] Race includes white, compared to non-white race [11] Reference group is not married and not living together with a partner [12] Non-invasive mechanical ventilation and smoking status were missing in >50% of observations; missing values were imputed with "0", which assumes a lack of ventilation and a lack of smoking, respectively, if it is not documented; these variables were not included in multivariate analyses due to high proportion missing FEV1= forced expiratory volume in 1 second; BMI = body mass index; CFRD= CF-related diabetes; ESRD = end-stage renal disease

revealed a significant association of nearly all of the tested covariates with transplant-free survival (Table 3). There was evidence of a time-varying effect of FEV_1 % predicted on survival (p<0.001), and calendar time also violated the PH assumption, therefore multivariable analyses were stratified by FEV_1 (in 5% increments) and calendar time. After adjustment for confounding using multivariable Cox PH regression stratified by calendar time and FEV_1, several predictors of mortality were identified (Table 4). The strongest adjusted predictors of death included supplemental oxygen use (HR 2.1, 95% CI 1.7-2.6), and *B. cepacia* infection (HR 1.8, 95% CI 1.3-2.6). Importantly, patients with BMI ≤18, female sex, and CF-related diabetes on insulin were also at an increased risk of death. Genotype information is likely an indirect proxy for calendar time in this cohort because >75% of non-genotyped patients entered the cohort by 2007. Number of pulmonary exacerbations per year, in the year prior to reaching FEV_1 <30%, was also associated with the risk of death; patients with 1 or more exacerbations per year were at a 70% increased risk of death (HR 1.7, 95% CI 1.3-2.2) when compared to patients with no pulmonary exacerbations. In a sensitivity analysis, we evaluated the adjusted risk of death and median survival for increasing number of pulmonary exacerbations and identified ≥5 exacerbations per year (compared to 0-4 exacerbations) as associated with a 2 year median survival (Table 5).

Table 4: Multivariable Cox Proportional Hazards regression analysis of predictors of mortality in patients with cystic fibrosis and low lung function*

Covariate	HR (95% CI)	p-value
Female sex	1.55 (1.21-2.01)	**0.001**
Height (inches)	1.00 (0.97-1.04)	0.796
BMI ≤18	1.57 (1.28-1.94)	**<0.001**
F508del mutation status		
Heterozygous[1]	1.19 (0.80-1.78)	0.394
Homozygous[1]	1.25 (0.84-1.85)	0.273
Unknown[1]	1.86 (1.21-2.84)	**0.004**
1 or more pulmonary exacerbations[2]	1.71 (1.34-2.18)	**<0.001**
Supplemental oxygen[3]	2.08 (1.68-2.57)	**<0.001**
Burkholderia cepacia[4]	1.81 (1.29-2.55)	**0.001**
CFRD, on insulin	1.44 (1.17-1.79)	**0.001**
ESRD, on dialysis	2.24 (0.76-6.56)	0.141
Pneumothorax[5]	0.98 (0.54-1.78)	0.941
Hemoptysis	0.80 (0.45-1.42)	0.445
Cirrhosis	1.10 (0.67-1.82)	0.702
Osteoporosis	1.07 (0.78-1.46)	0.671
Depression	1.15 (0.92-1.43)	0.210
Medicaid Insurance	1.16 (0.95-1.41)	0.154
High school graduate[6]	1.05 (0.73-1.51)	0.784
Marital status		
Married[7]	0.71 (0.57-0.88)	**0.002**
Living Together[7]	0.86 (0.58-1.28)	0.458
Global Proportional Hazards test		0.8900

*Analysis adjusted for all covariates listed in the table; analysis stratified by calendar time and FEV_1 at baseline (in 5% increments) due to PH violation. Statistically significant p-values are shown in **bold**. [1] Reference group has no F508del mutations [2] Number of exacerbations requiring IV antibiotics in the year prior to FEV_1 <30%, modeled as 1 or more exacerbations per year versus no exacerbations [3] Continuous or nocturnal use of oxygen [4] Sputum infection with *Burkholderia cepacia* complex [5] Pneumothorax that required a chest tube [6] High school graduate education or higher [7] Reference group is not married and not living together with a partner

FEV_1= forced expiratory volume in 1 second; BMI = body mass index; CFRD= CF-related diabetes; ESRD = end-stage renal disease

Table 5: Sensitivity analysis to determine number of pulmonary exacerbations associated with clinically significant shortened median survival			
	Adjusted HR[1]	Median survival (95% CI)	p-value
≥1 exacerbation/year No exacerbations	1.71 (1.34-2.18) Ref	5.1 years (4.9-5.6) 9.6 years (8.3-10.3)	<0.001
≥2 exacerbations/year 0-1 exacerbation/year	1.64 (1.34-1.99) Ref	4.0 years (3.5-4.3) 8.5 years (7.9-9.4)	<0.001
≥3 exacerbations/year 0-2 exacerbations/year	1.59 (1.29-1.97) Ref	3.2 years (2.7-3.5) 7.9 years (7.3-8.5)	<0.001
≥4 exacerbations/year 0-3 exacerbations/year	1.68 (1.29-2.19) Ref	2.6 years (2.2-3.0) 7.3 years (6.9-7.8)	<0.001
≥5 exacerbations/year 0-4 exacerbations/year	1.93 (1.37-2.72) Ref	2.0 years (1.7-2.5) 7.0 years (6.5-7.4)	<0.001
Median survival ≤2 years is the recommended time for referral for lung transplant evaluation and is, therefore, clinically important [1]When categorized pulmonary exacerbations entered into final multivariate Cox proportional hazards (PH) regression in place of continuous measure of pulmonary exacerbations, stratified by calendar time and FEV_1 in 5% increments, there is no violation of the PH assumption			

Median survival estimates for patients stratified by sex reveal an impressive survival gap among patients with FEV_1 <30% predicted (Table 6); stratification by other significant covariates also demonstrates important differences among patients with low BMI, supplemental oxygen requirement, B. cepacia complex in sputum, and CF-related diabetes on insulin.

Table 6: Median survival estimates for CF patients with FEV_1 <30% predicted, stratified by covariates of interest		
	Median survival (95% CI)	p-value
Females Males	5.1 years (4.6-5.8) 7.2 years (6.7-8.0)	<0.001
BMI ≤18 BMI >18	4.2 years (3.7-4.5) 7.4 years (6.9-7.9)	<0.001
Supplemental oxygen No supplemental oxygen	3.1 years (2.8-3.4) 8.3 years (7.8-9.1)	<0.001
B. cepacia complex No *B. cepacia* complex	2.8 years (2.4-3.9) 6.9 years (6.4-7.3)	<0.001
CFRD, on insulin No CFRD	4.3 years (3.7-4.7) 7.4 years (6.9-7.9)	<0.001
BMI = body mass index; CFRD= CF-related diabetes		

Discussion

In this nationwide US cohort of CF patients during 2003-2013, median transplant-free survival after the development of advanced lung disease with an FEV_1 <30% was 6.5 years. While this level of survival is greater than that seen in earlier years in similar persons with CF, there remains about a 10% per year

probability of death once the FEV_1 has fallen below 30%; as shown in Figure 2, this risk of death does not seem to decline much over time. We have identified several important baseline predictors of death among CF patients with low lung function. These include both static and variable patient characteristics, including female sex, BMI ≤18, supplemental oxygen requirement, number of pulmonary exacerbations in the prior year, and the presence of *B. cepacia* infection and CF-related diabetes requiring insulin.

Prior studies evaluating survival in patients with CF have documented increased risk of death among patients with lower FEV_1 % predicted [10, 13], lower BMI [4, 10], reduced PaO2 [4], increased number of pulmonary exacerbations [10, 12, 13], *B. cepacia* infection [10, 14], and female sex [4, 7, 9-11], and our study confirms these earlier findings but now in a population of patients with low lung function. Although predicting death for an individual patient is notoriously difficult to do [10, 13], our sensitivity analyses evaluating median survival among specific cohorts with low lung function highlight the persistent gender gap in survival in more recent years, the high mortality associated with a supplemental oxygen requirement and BMI ≤18, and the dismal prognosis for patients with *B. cepacia*; importantly, despite the increased risk of death, the lower bounds of the 95% confidence intervals for median survival exclude 2 years in these specific cohorts. Additionally, we show that patients who have reached the threshold of FEV_1 <30% and have 5 or more pulmonary exacerbations per year have a median survival of 2 years, which is the current recommended threshold for referral for LTx evaluation [3]. Describing median survival for these cohorts allows clinicians to have a practical interpretation of the relative risk of mortality for their patients and emphasizes certain traits that should increase the concern for potential deterioration and prompt referral for LTx evaluation.

We did a variety of sensitivity analyses to address different approaches to survival analysis in patients with CF who will potentially undergo LTx. In order to answer the question about the timing of LTx referral, transplant-free survival with censoring at the time of LTx most closely estimates the amount of time a patient is expected to live with advanced lung disease without LTx. In analyses not censored at LTx, survival estimates cannot help with decisions about the timing of LTx referral; analyses that include post-LTx survival data add to our understanding of overall life expectancy when LTx is included with all other available treatment options [6]. Excluding from analysis all patients who will eventually undergo LTx [8] induces selection bias because there is an inherent difference in patients who are not transplanted when

compared to the general population of CF patients; additionally, when making clinical decisions for an individual patient when their FEV_1 reaches <30% predicted there is no way to know if they will never be transplanted unless an absolute contraindication exists. As demonstrated in our sensitivity analysis, including only the patients who will eventually undergo LTx induces selection bias and immortal time bias because patients must necessarily live long enough to get to LTx and must be good candidates to undergo LTx; these biases are also present in the estimate of time to LTx for patients who did not die.

Limitations

This study has important limitations. First, although the CFFPR captures data on a large number of variables for most patients with CF in the US, our study is limited to the variables included in the database. Unfortunately, certain variables of clinical and scientific interest (i.e. presence of pulmonary hypertension, PaO2/PaCO2, or an indicator for non-adherence) are not captured in the registry. *B. cenocepacia* is the only known genomovar associated with increased mortality [14], but the species are not differentiated in the CFFPR until 2010 and our study necessarily combines all species in the *B. cepacia* complex. Second, we only assessed covariates at cohort entry, which limits their interpretation in a population with extended survival. Third, there is some difficulty with capturing death in the CFFPR if a patient is post-LTx. Loss to follow-up is approximately 2% per year for all patients in the CFFPR, but approaches 7% for patients who have undergone LTx. Such losses to follow-up likely represent informative censoring. Additionally, Kaplan-Meier estimates of survival are based on the assumption of uninformative censoring at the time of LTx, but it is clear that patients who undergo LTx are not similar to those who remain in the cohort. Fourth, there could be an element of selection bias in our cohort because the exclusion of patients who reach FEV_1 <30% only during exacerbation(s) could lead to the exclusion of patients who died or underwent LTx prior to a "stable" FEV_1 <30%; such patients likely represent a minority, but are important to acknowledge when considering generalizability of these results. Finally, the choice of the primary end-point as transplant-free survival is novel in the CF literature, but it is the necessary choice when attempting to address the natural history for patients with CF and advanced lung disease prior to intervention with LTx. The current model only applies to those who have not yet been transplanted at the time of cohort entry and it should be noted that LTx and death are competing risks in this population. The hazard ratios presented represent the hazard of death if a patient is not transplanted.

Conclusions

The current study demonstrates a median survival over 6.5 years for CF patients with FEV_1 <30%, exceeding prior survival estimates. The strongest predictors of death in this cohort with low lung function included supplemental oxygen use, the presence of *B.cepacia* complex infection, BMI ≤18, and female sex. This study highlights the heterogeneity among patients with FEV_1 <30%, with some patients dying soon after reaching this threshold and others living for many years. For this reason, we conclude that FEV_1 <30% remains an important marker of disease severity for patients with CF, but we suggest FEV_1 value alone need not always trigger LTx evaluation.

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