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ORIGINAL RESEARCH

Association of Oxygen Therapy with the Natural Disease Progression of Cystic Fibrosis: A Multi-State Model of the European Cystic Fibrosis Society Patient Registry

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On behalf of ECFSPR

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Background: Association between dependence on oxygen therapy (OT) and natural disease progression in people with cystic fibrosis (pwCF) has not been estimated yet. The aim of this study is to understand the prognosis for pwCF on OT, evaluating how the transition probabilities from being alive without lung transplantation (LTx) to LTx and to death, and from being alive after LTx to death change in pwCF with and without OT.

Methods: We used 2008–2017 data from the 35-country European CF Society Patient Registry. A multi-state model was fitted to assess the effects of individual risk factors on transition probabilities.

Results: We considered 48,343 pwCF aged from 6 to 50 years. OT (HR 5.78, 95% CI: 5.32–6.29) and abnormal FEV_1 (HR 6.41, 95% CI: 5.28–7.79) were strongly associated with the probability of having LTx; chronic infection with *Burkholderia cepacia* complex (HR 3.19, 95% CI: 2.78–3.67), abnormal FEV_1 (HR 5.00, 95% CI: 4.11–6.08) and the need for OT (HR 4.32, 95% CI: 3.93–4.76) showed the greatest association with the probability of dying without LTx. Once pwCF received LTx, OT (HR 1.75, 95% CI: 1.41–2.16) and abnormal FEV_1 (HR 1.63, 95% CI: 1.18–2.25) were the main factors associated with the probability of dying. An association of gross national income with the probability of receiving LTx and with the probability of dying without LTx was also found.

Conclusion: Oxygen therapy is associated with poor survival in pwCF with and without LTx; harmonization of CF care throughout European countries and minimization of the onset of pulmonary gas exchange abnormalities using all available means remains of paramount importance.

Keywords: cystic fibrosis, oxygen therapy, epidemiology, mortality, lung transplantation

Introduction

Improved diagnostics and treatment options have led to increased survival in people with cystic fibrosis (pwCF);[1] however, respiratory failure still represents the primary cause of morbidity and mortality. Chronic and recurrent respiratory infections damage the lungs progressively, leading eventually to chronic hypoxemia. A reduction in oxygen saturation is most likely to occur either during sleep or during exercise and before it becomes apparent at rest during

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the day.[2] Whether it is continuous, nocturnal or exertional, oxygen therapy (OT) is commonly prescribed in CF to normalize gas exchange, to relieve symptoms of dyspnea and fatigue and to delay the development of cor pulmonale.[3] Published studies regarding the use of oxygen in CF are primarily about the effects of nocturnal and ambulatory oxygen.[4] Despite the well-established benefit of supplemental oxygen in adults with severe hypoxemia who have chronic obstructive pulmonary disease (COPD),[5] there is little evidence to correlate OT in pwCF with either a reduction in mortality or the alleviation of symptoms.[4] Despite the clinical expectation that pwCF on OT are likely to have poor prognosis, to date, it remains unclear if OT is associated or not with the natural progression of the disease.[4]

The aim of this study was to evaluate how OT is associated with the course of CF disease, using a multi-state model which includes the transition probabilities from being alive without LTx to LTx and to death and from being alive after LTx to death. In addition, we also examined risk factors and comorbidities associated with these transitions.

Methods

Study Design

This observational cohort study used data from 2008 to 2017 from the European Cystic Fibrosis Society Patient Registry (ECFSPR), where each of the 35 member countries up to 2017 provided data under the existing ethical approval and data governance structures, in compliance with the Declaration of Helsinki. In 2017, the ECFSPR covered 35–99% of the CF population per country;[6] nine countries had <80% coverage (Armenia, Bulgaria, Croatia, Lithuania, Norway, Poland, Romania, Spain, Turkey and Ukraine).[6] The ECFSPR structure and operations have been previously described.[7] Participating pwCF signed an informed consent, including consent to use their data for future research. Demographic and clinical characteristics of the complete patient population were extracted from the ECFSPR. Standard ECFSPR definitions applied to all variables.[8] The study was approved by the ECFSPR Scientific Committee and by the ECFSPR Steering Committee (02/06/2019).

Statistics

To express the degree of lung damage, we use the forced expiratory volume in the first second (FEV_1) calculated using z-score from the Global Lung Initiative (GLI) reference equations;[9] information on ethnicity is not yet collected by the ECFSPR and for the purposes of the study we assumed that the pwCF were all Caucasian. FEV_1 was considered in the normal range when above the lower limit of normal (LLN), corresponding to a z-score of −1.64. Body mass index (BMI) was categorized according to the nutritional goal for CF, that is a BMI at or above 22 kg/m^2 (females) and 23 kg/m^2 (males) for those >18 years of age.[10] For pwCF ≤18 years of age we used BMI z-score computed on the CDC references,[11] with nutritional goal at or above 0 z-score.[10] Countries were classified into two groups (low versus high income) based on gross national income (GNI) per capita in 2017, obtained from the World Bank tables.[12]

We interpreted the course of CF disease as characterized by different types of events occurring after diagnosis. When considering CF from the perspective of respiratory disease, pwCF can die without having had LTx or can receive LTx and then die and we therefore used the multi-state model to estimate the transition probabilities of patients between these events (otherwise called *states*).[13] As summarized in Figure 1, pwCF could have been enrolled in the ECFSPR alive and without LTx, eventually being in a successive state (eg, alive with LTx, death without LTx), or they could have been enrolled alive with LTx, eventually transitioning to death with LTx. Furthermore, to assess the effect of individual risk factors on the transition probabilities from one state to the other, a multi-state regression model was fitted using age as timescale. The explanatory variables included in this model are: exposure to oxygen therapy, FEV_1 z-score (categorized as above or below the LLN, as recommended[14]); age at diagnosis (categorized as <1 year, 1–18 years, >18 years); sex, CFTR genotype (categorized as severe – with both alleles in class 1, 2 or 3, mild – with at least one allele in class 4 or 5, unknown); BMI nutritional goal; presence of diabetes treated with daily insulin; chronic *Pseudomonas aeruginosa* (PSA); chronic *Burkholderia cepacia* complex (BCC); use of pancreatic enzymes; history of pneumothorax; history of hemoptysis >250mL; GNI (low and high income countries).

Presence of oxygen supplementation is collected by the ECFSPR as oxygen therapy during the year of follow-up; this variable was included in the model as a time-dependent variable since a subject can enter the registry and not be on

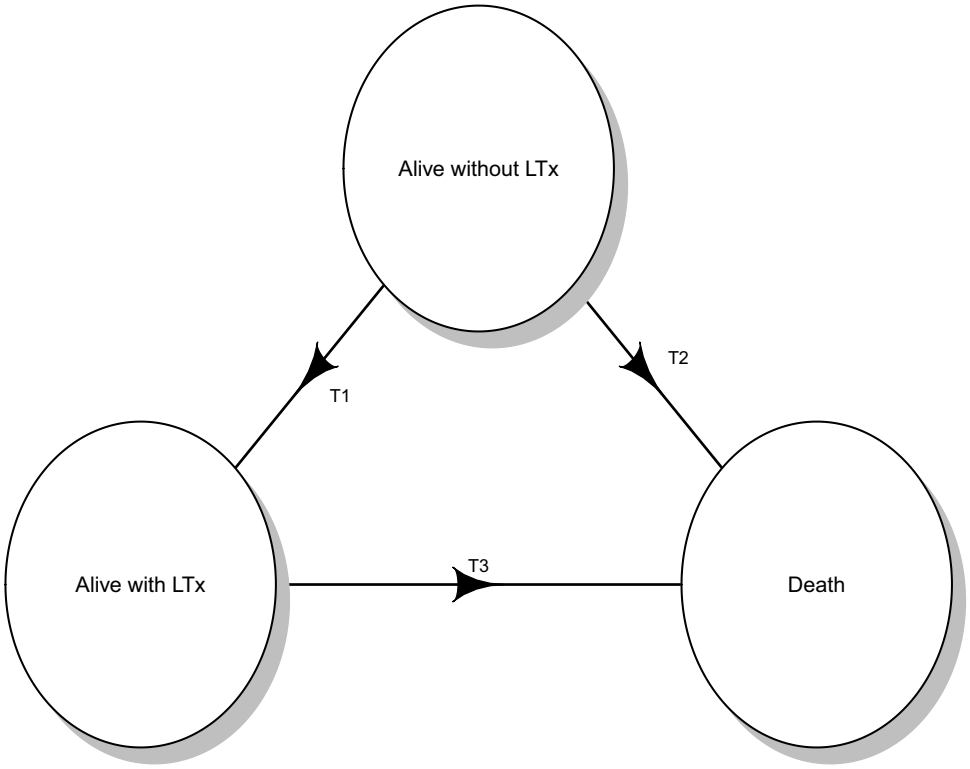

Figure 1 Multi-state model for pwCF: arrows denote direction of transition probabilities (T): from alive without LTx to alive with LTx (T1) or to death (T2); and from alive with LTx to death (T3).

oxygen therapy and then begin oxygen therapy during follow-up; this change is taken into account in the model. On the other hand, all other variables are included in the model considering their value at baseline, that is the time of entry in the registry.

The results of the regression model are provided for each transition in terms of Hazard Ratio (HR), with 95% confidence intervals (95% CI) and p-value. Regarding missing data, we performed a case-wise complete analysis. Categorical data are presented as number and percentage (computed excluding missing data). Analyses were done with the open-source software R Core Team, version 3.6.2 with the mstate[15] package added.

Results

For the years 2008–2017, the ECFSPR collected information on 62,367 pwCF from 35 countries. For the purpose of this study, we considered 48,343 individuals between the ages of 6 and 50 with verified lung transplantation status. Of these, 46,951 were alive without LTx and 1392 were alive with LTx at enrollment in the ECFSPR. During follow-up 2392 received LTx, 2234 died without LTx and 753 died after LTx. Overall, median follow-up time for those alive without LTx to LTx is 10.9 (95% CI: 10.8 to 11) years and 11 (95% CI: 10.8 to 11) years for pwCF who died without LTx. Follow-up time for those who received LTx and died is 12.8 (95% CI: 10.6 to 16) years.

As summarized in Table 1, pwCF on OT had more severe features of CF disease: 59% had been diagnosed with CF within the first year of life; 34% and 7% were diagnosed between 1–18 and >18 years old, respectively. We report an uneven distribution of pwCF on OT between countries with high versus low incomes (Figure 2), with the odds of being in OT at baseline reduced by 19% (OR 0.81, 95% CI: 0.72 to 0.91) for pwCF living in countries with low income.

Low-income nations registered higher use of OT from 2011, which may be attributable to additional nations joining the ECFSPR, namely Ukraine, Romania, North Macedonia and Lithuania. In particular, for pwCF aged 12–24 and 25–34 living in low-income countries, consistently higher oxygen utilization was reported than for pwCF in high-income countries.

Table 1 Main Demographic and Clinical Characteristics of the 48,343 Considered pwCF

	Total N=48343		Room Air N=45408		Oxygen Therapy N=2935		OR (95% CI)	P-value
	Missing	n (%)	Missing	n (%)	Missing	n (%)		
Sex (male)		25,516 (52.78%)		24,103 (53.08%)		1413 (48.14%)	0.82 (0.76–0.88)	<0.001
Age								
6–11		18,036 (37.31%)		17,702 (38.98%)		334 (11.38%)	(reference)	
12–24		17,708 (36.63%)		16,482 (36.30%)		1226 (41.77%)	3.94 (3.49–4.46)	<0.001
25–34		7775 (16.08%)		6941 (15.29%)		834 (28.42%)	6.37 (5.60–7.26)	<0.001
35–50		4824 (9.98%)		4283 (9.43%)		541 (18.43%)	6.69 (5.82–7.71)	<0.001
CFTR genotype								
Mild		6158 (12.74%)		6004 (13.22%)		154 (5.25%)	(reference)	
Severe		33,813 (69.94%)		31,613 (69.62%)		2200 (74.96%)	2.71 (2.31–3.21)	<0.001
Unknown		8372 (17.32%)		7791 (17.16%)		581 (19.80%)	2.91 (2.43–3.49)	<0.001
FEV_1 z-score < LLN	6581	20,923 (50.10%)	6154	18,572 (47.31%)	427	2351 (93.74%)	16.68 (14.22–19.70)	<0.001
BMI < *nutritional goal*	3605	28,751 (64.27%)	3330	26,493 (62.96%)	275	2258 (84.89%)	3.30 (2.97–3.69)	<0.001
Chronic *Pseudomonas aeruginosa*	11,912	11,388 (31.26%)	10,840	10,135 (29.32%)	1072	1253 (67.26%)	4.95 (4.49–5.47)	<0.001
Use of pancreatic enzymes	2552	37,638 (82.20%)	2326	35,061 (81.38%)	226	2577 (95.13%)	4.47 (3.76–5.35)	<0.001
CFRD	4095	5920 (13.38%)	3636	4899 (11.73%)	459	1021 (41.24%)	5.28 (4.85–5.75)	<0.001
Chronic *Burkholderia cepacia* complex	12,095	1032 (2.85%)	11,035	907 (2.64%)	1060	125 (6.67%)	2.64 (2.16–3.18)	<0.001
Pneumothorax	5718	341 (0.80%)	4968	234 (0.58%)	750	107 (4.90%)	8.85 (6.99–11.14)	<0.001
Hemoptysis (>250mL)	5337	912 (2.12%)	4592	720 (1.76%)	745	192 (8.77%)	5.35 (4.53–6.30)	<0.001

Notes: The number of patients and the percentage (in brackets) were reported unless otherwise stated. Functional grouping as mild/severe was based on published data from the CFTR2 project (www.cftr2.org).
Abbreviations: CFTR, Cystic Fibrosis Transmembrane Regulator; CFRD, Cystic Fibrosis-related Diabetes; FEV_1, Forced Expiratory Volume in the first second; LLN, lower limit of normal; BMI, Body Mass Index.

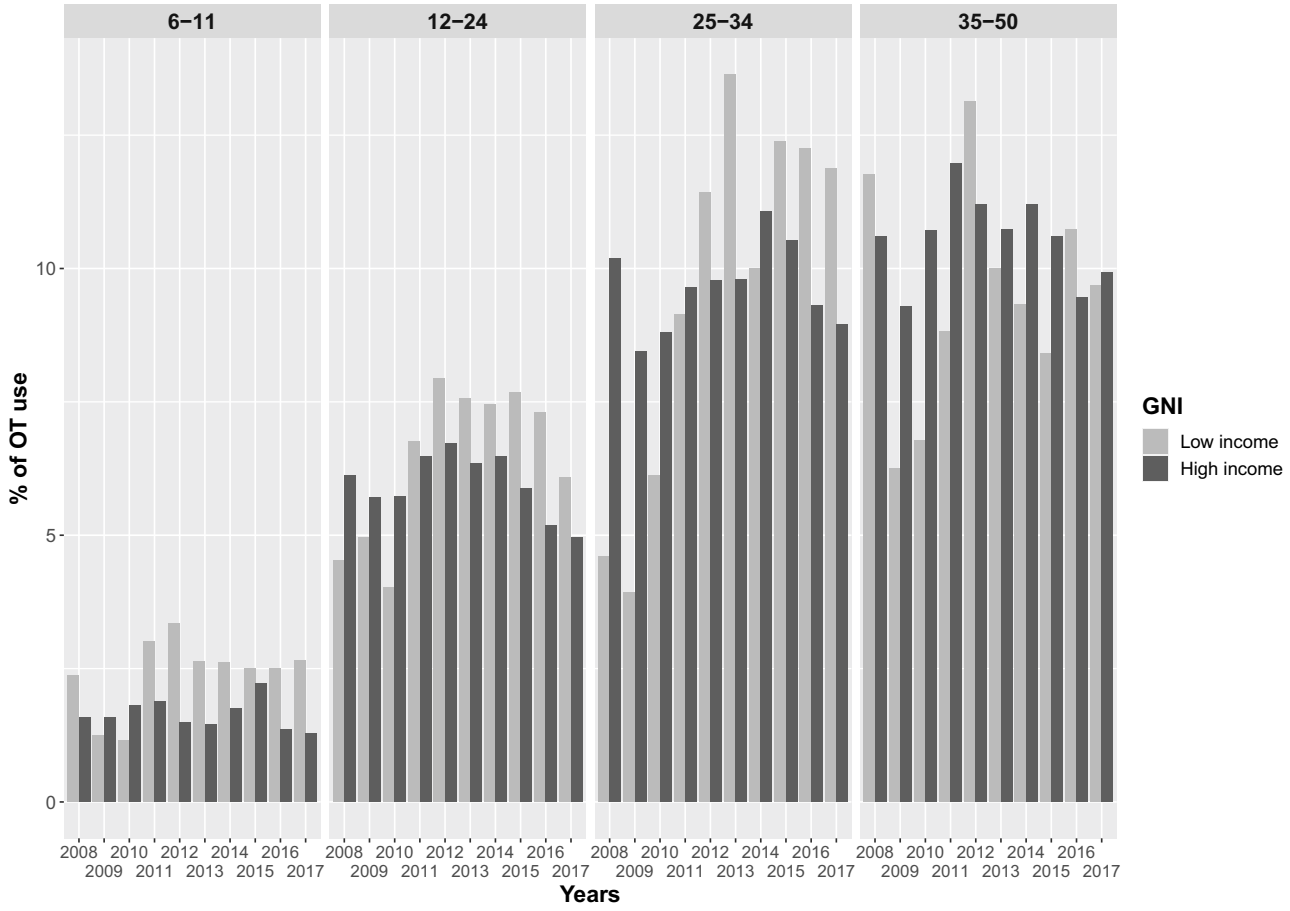

Figure 2 Percentage of pwCF on OT, stratified by year of follow-up, age class and economic status. Low income: Albania, Armenia, Bulgaria, Czech Republic, Greece, Croatia, Hungary, Latvia, Lithuania, North Macedonia, Republic of Moldova, Poland, Portugal, Romania, Russian Federation, Serbia, Slovak Republic, Slovenia, Turkey, Ukraine; high income: Austria, Belgium, Denmark, France, Germany, Ireland, Israel, Italy, Luxembourg, The Netherlands, Norway, Spain, Sweden, Switzerland, United Kingdom.

By adjusting the multi-state model for all of the features of CF disease mentioned above, pwCF on oxygen therapy showed worse transition probabilities (Figure 3). For example, the probability of receiving LTx by 50 years old is 17.5 (95% CI: 10.5–29.2)% and the chance of dying by age 50 without LTx is 81.1 (95% CI: 72.6–90.6)% for those individuals who start OT at 20 years of age. On the other hand, pwCF without oxygen supplementation at 20 years old have 20.3 (95% CI: 15.1–27.2)% and 34.7 (95% CI: 29.2–41.1)% probability, respectively. Even after LTx, pwCF in OT at 20 years old show 87.7 (95% CI: 80.3–95.7)% probability of dying by age 50 compared to 69.8 (95% CI: 58.6–83.2)% for pwCF not on OT at 20 years old (Figure 3, lower panels).

Table 2 summarizes the strength of association between selected covariates and transitions from one state to another. FEV_1< LLN (HR 6.41, 95% CI: 5.28–7.79) (Supplemental Figure 1) and oxygen therapy (HR 5.78, 95% CI: 5.32–6.29) (Figure 3) are strongly associated with the probability of undergoing LTx, whereas males (HR 0.81, 95% CI: 0.74–0.87) and people living in a low-income country (HR 0.63, 95% CI: 0.52–0.76) are less likely to receive LTx. This can be seen further in Figure 4, where cumulative probabilities for pwCF living in high and low-income countries are consistently separated, whether they had OT or not at age 20. Transition probabilities stratified by GNI are identical when assessing the risk of death after receiving LTx, which is higher for those who were on OT.

There was evidence for a strong association between FEV_1 < LLN and being on oxygen therapy and the transition probability of dying without LTx (Table 2). Chronic infection with BCC represented a risk factor for the survival probability (HR 3.19, 95% CI: 2.78–3.67), whereas male sex showed 17% lower risk of death (HR 0.83, 95% CI: 0.75–0.91) compared to females (Supplemental Figure 2). Individuals who were diagnosed with CF after the first year of life had 21% lower risk of death (HR 0.79, 95% CI: 0.72–0.88).

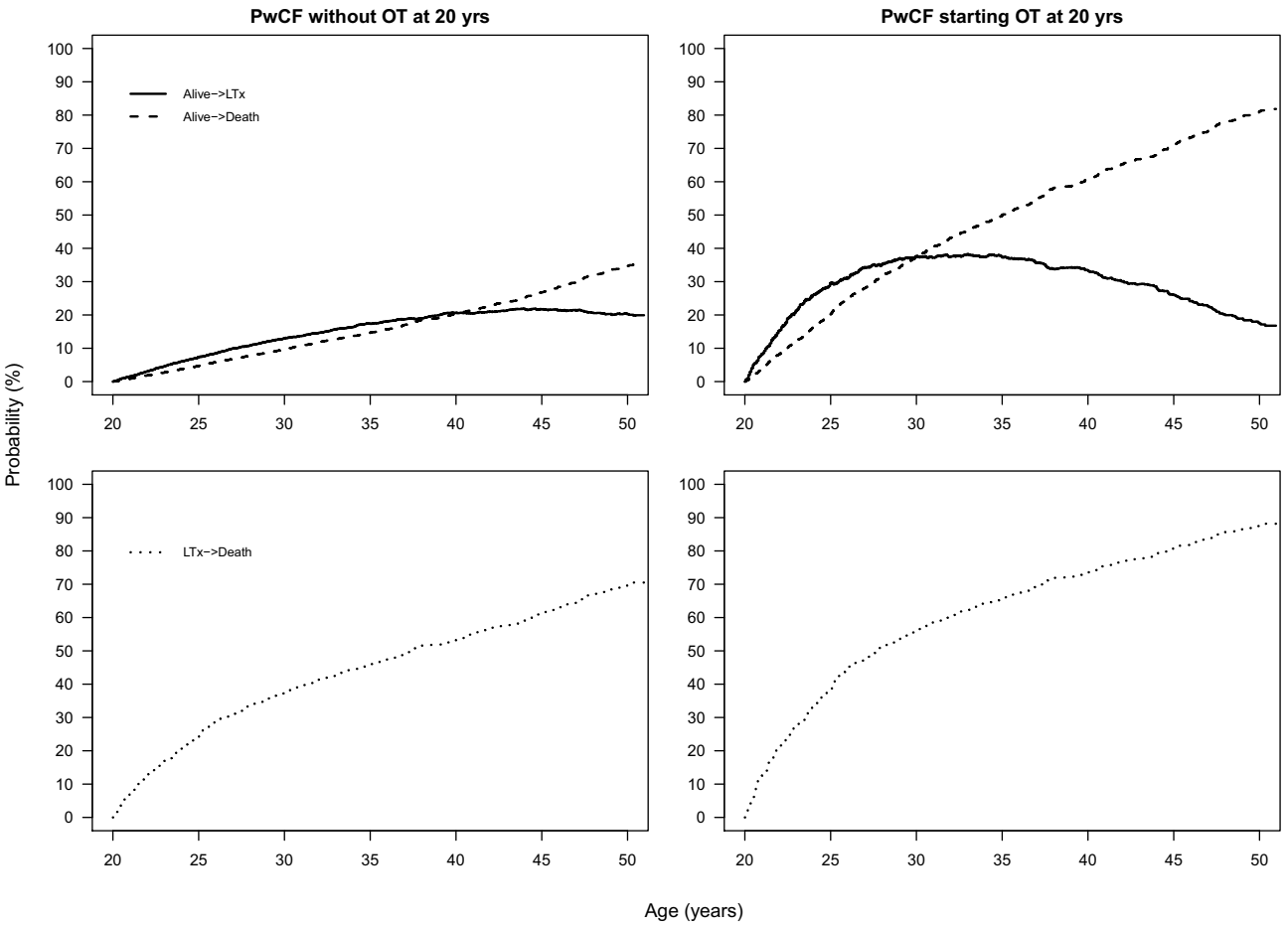

Figure 3 Probabilities of moving from state 1 (alive without LTx) to state 2 (alive with LTx) or state 3 (death) (upper panels) and probabilities for pwCF moving from state 2 to state 3 (lower panels), according to treatment with supplemental oxygen in pwCF at 20 years of age. Adjusting covariates are held constant at the most frequent occurrence.

The fitted multi-state model also shows that after LTx, oxygen therapy (HR 1.75, 95% CI: 1.41–2.16) and FEV_1<LLN (HR 1.63, 95% CI: 1.18–2.25) almost doubled the risk of death. Additionally, severe disease, characterized by CF-related diabetes (HR 1.39, 95% CI: 1.15–1.67), pancreatic insufficiency (HR 2.44, 95% CI: 1.26–4.70) and a history of hemoptysis (>250mL) (HR 1.44, 95% CI: 1.06–1.96), increases the risk of death (Table 2). On the other hand, a late CF diagnosis, between 1 and 18 years of age, is associated with a significantly reduced probability of dying in pwCF who had LTx (HR 0.82, 95% CI: 0.67–0.99). There is no evidence for an association between BMI (Supplemental Figure 3) and *Pseudomonas aeruginosa* infection (Supplemental Figure 4) and the risk of death after LTx.

We also found evidence of differences between HRs for OT among transition probabilities (Table 2): when pwCF were alive without LTx the HR of OT for death was lower than the HR of OT for LTx (P<0.001); for pwCF alive with LTx, the HR of OT for death was lower compared to the HR of OT for death in pwCF alive without LTx (P<0.001).

Discussion

Cystic fibrosis is a multisystem disease. Although there have been steady and significant improvements in median survival over the past decades,[16–18] most of the comorbidities and premature mortality in pwCF are due to chronic respiratory infection and subsequent respiratory failure; approximately, 20% of individuals develop severe lung disease by the age of 30.[19] Our findings show that 6.1% of pwCF in the present study are on OT, a key factor associated with transition probabilities between states in pwCF either with or without LTx. Oxygen treatment for CF exacerbations is similar to the initial oxygen treatment for COPD exacerbations,[20] whereas chronic oxygen therapy is prescribed in pwCF

Table 2 Adjusted Hazard Ratio (HR) for the Transition Probabilities from the Multi-State Model

	Alive without LTx–>Alive with LTx		Alive without LTx–>Death		Alive with LTx –>Death	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Exposure to oxygen therapy	5.78 (5.32–6.29)	<0.001	4.32 (3.93–4.76)	<0.001	1.75 (1.41–2.16)	<0.001
FEV_1 z-score (<LLN vs ≥ LLN)	6.41 (5.28–7.79)	<0.001	5.00 (4.11–6.08)	<0.001	1.63 (1.18–2.25)	0.003
Age at diagnosis						
1–18 years vs <1 year	0.96 (0.88–1.05)	0.342	0.79 (0.72–0.88)	<0.001	0.82 (0.67–0.99)	0.043
>18 years vs <1 year	0.85 (0.67–1.08)	0.185	0.60 (0.46–0.78)	<0.001	0.53 (0.28–1.00)	0.051
Sex (male vs female)	0.81 (0.74–0.87)	<0.001	0.83 (0.75–0.91)	<0.001	0.95 (0.79–1.13)	0.547
CFTR Genotype						
Severe vs mild	1.76 (1.35–2.28)	<0.001	1.07 (0.83–1.37)	0.611	0.62 (0.36–1.07)	0.086
Unknown vs mild	1.67 (1.27–2.19)	<0.001	2.55 (1.98–3.28)	<0.001	1.03 (0.58–1.84)	0.909
BMI nutritional goal (< nutritional goal vs ≥ nutritional goal)	2.20 (1.94–2.49)	<0.001	1.33 (1.18–1.50)	<0.001	1.00 (0.77–1.31)	0.975
CFRD (yes vs no)	1.11 (1.01–1.23)	0.029	1.63 (1.47–1.81)	<0.001	1.39 (1.15–1.67)	0.001
Chronic *Pseudomonas aeruginosa* (yes vs no)	1.25 (1.14–1.37)	<0.001	1.78 (1.60–1.98)	<0.001	0.93 (0.77–1.12)	0.438
Chronic *Burkholderia cepacia complex* (yes vs no)	1.00 (0.82–1.21)	0.967	3.19 (2.78–3.67)	<0.001	0.90 (0.54–1.50)	0.689
Use of pancreatic enzymes (yes vs no)	1.71 (1.35–2.15)	<0.001	1.72 (1.37–2.18)	<0.001	2.44 (1.26–4.70)	0.008
History of pneumothorax (yes vs no)	1.92 (1.55–2.39)	<0.001	1.62 (1.24–2.12)	<0.001	0.87 (0.53–1.44)	0.595
History of hemoptysis >250mL (yes vs no)	1.77 (1.53–2.05)	<0.001	1.08 (0.88–1.32)	0.470	1.44 (1.06–1.96)	0.021
Country (low vs high income)	0.63 (0.52–0.76)	<0.001	1.94 (1.69–2.23)	<0.001	0.99 (0.58–1.67)	0.965

Notes: Data are presented as hazard ratios with 95% Confidence Intervals (CI). Functional grouping as mild/severe was based on published data from the CFTR2 project (www.cftr2.org).
Abbreviations: FEV_1, Forced Expiratory Volume in the first second; LLN, lower limit of normal; CFTR, Cystic Fibrosis Transmembrane Regulator; CFRD, Cystic Fibrosis-related Diabetes; BMI, Body Mass Index.

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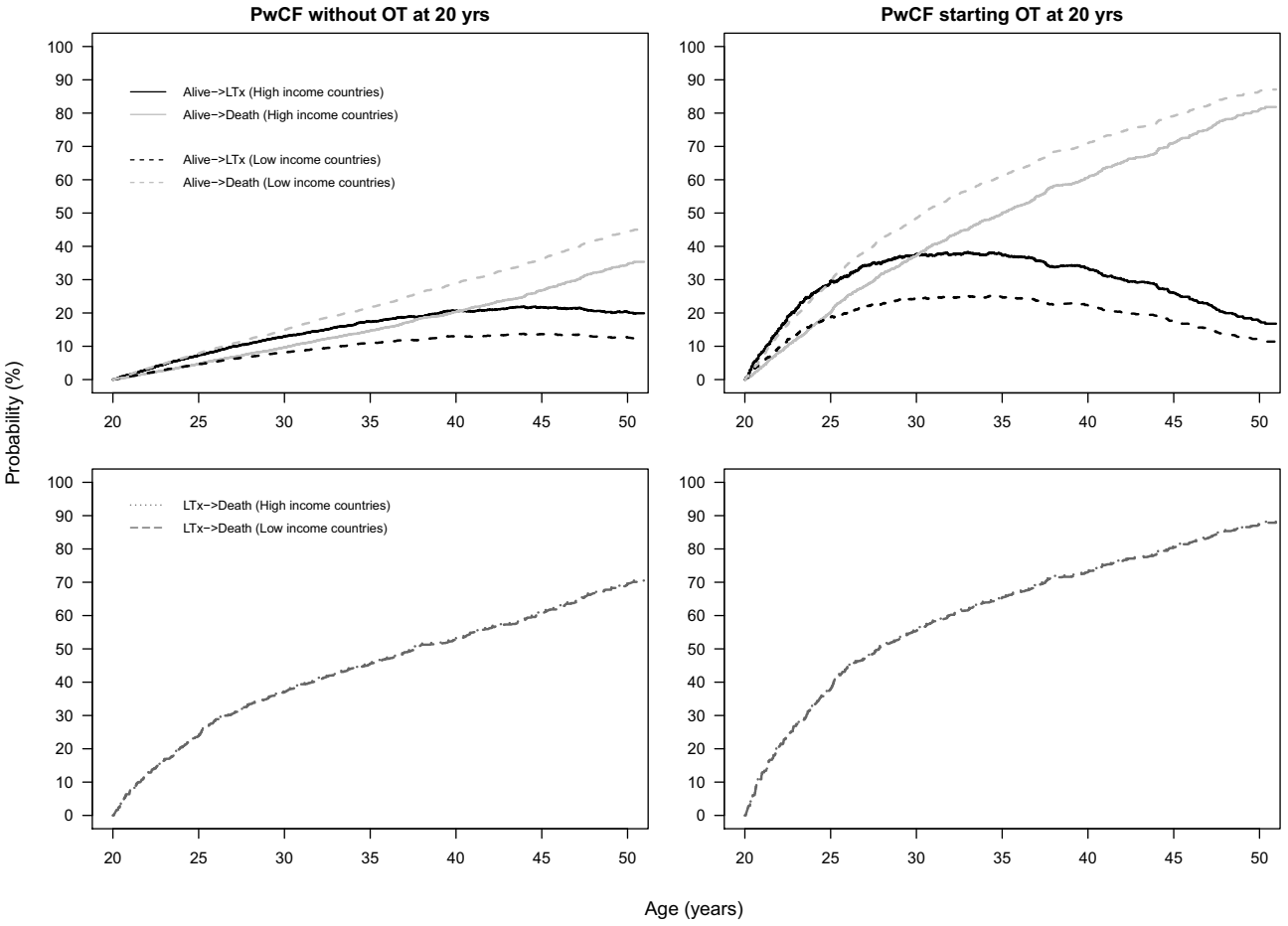

Figure 4 Probabilities to move from state 1 (alive without LTx) to state 2 (alive with LTx) or state 3 (death) (upper panels) and probabilities for pwCF to move from state 2 to state 3 (lower panels), according to GNI in pwCF at 20 years of age. Adjusting covariates are held constant at the most frequent occurrence.

to relieve symptoms of dyspnea and fatigue and to delay the development of right heart failure.[3] The last systematic review on OT for CF reported that OT should be reserved for those individuals with objective evidence of hypoxemia, either at rest while awake or during either exercise or sleep.[4] To date, there are no published studies that have been able to establish whether OT alleviates symptoms or, most importantly, is associated with natural disease progression. In the ECFSPR, from 2008 to 2017, oxygen therapy was recorded as any use of oxygen in the year; therefore, in this study it was considered to be a proxy of a significant clinical event that marked not only a hypoxemic episode but also the initial failure of the respiratory system to cope with the higher metabolic demands imposed by the disease.

Recently, the Cystic Fibrosis Foundation (CFF) identified supplemental oxygen requirement as a clinical milestone for LTx referral since it was found to be repeatedly associated with death without LTx in pwCF.[21] Supplemental oxygen was a predictor of death without LTx (HR 2.1, 95% CI: 1.7–2.6) in 3340 adult patients with CF with FEV_1<30% in the United States of America (US).[22] An earlier Canadian study of 673 individuals who were followed between 1977 and 1989 identified PaO_2 lower than 55mmHg as a risk factor for death within two years.[23] Dependence on supplemental oxygen seemed to indicate decreased survival also in children with CF selected for LTx in the US during the period from 1992 to 2002.[24] Adult patients requiring supplemental oxygen were identified as having an increased risk of death while on the waiting list for LTx (1.07, 95% CI: 1.00–1.14) in one US study conducted between 2005 and 2013,[25] and a study from the French CF Registry identified long-term oxygen therapy as a prognostic factor associated with death or LTx within 4 years in adults.[26] Overall, our study demonstrates how oxygen therapy is associated not only with the probability of dying without LTx, conceived as a competitive event against the probability of receiving LTx, but also with the probability of dying after LTx. This outcome indicates that a high degree of attention should be devoted to pwCF

immediately after they show signs of respiratory system failure in order to maintain adequate gas exchange, independent of age or severity of lung disease. It is well documented that respiratory failure does not only occur in end-stage lung disease; before becoming chronic, respiratory failure is episodic, occurring during exercise or during sleep, even in stable clinical conditions. Abnormalities in arterial blood gas pressure are more manifest during exercise and sleep but can also occur during daytime activities when symptoms of lung disease are exacerbated. Therefore, oxygen supplementation becomes a marker of the severity of the disease and does affect survival, even after LTx, as shown in the present study. This indicates that, rather than early referral of pwCF to LTx centers, which are not specialized CF centers, multidisciplinary teams (MDT) at CF clinics should optimize diagnostic methods for the detection of early markers of alterations in pulmonary gas exchange and intervene therapeutically. At the very minimum, MDTs should implement potentiating therapies as soon as oxygen supplementation is required and before respiratory failure becomes chronic.

Our findings reinforce the importance of FEV_1 as a marker of CF disease across the three transition probabilities, even if z-score is used instead of percent of predicted. The idea that pwCF are at risk just because FEV_1 falls to below an arbitrary cut-off point of percent of predicted is increasingly being questioned. The CFF recently recommended initiating discussions on LTx when pwCF present with a FEV_1 below 50% of predicted,[21] since the previously accepted indicator of FEV_1 <30% predicted as a marker of shortened survival seems no longer appropriate,[22,23,27–29] especially when considering that some reference equations used before the implementation of GLI may overestimate lung function.[30] On the whole, FEV_1 z-score below −1.64 should indicate to the MDT that they need to address the issue with urgency and intervene with more frequent follow-up and optimization of therapy, including regular physical activity and exercise which have been demonstrated to increase survival.[31,32] Striving to maintain the FEV_1 of pwCF within normal ranges should be a common goal for all MDTs.

Regarding the role of other covariates in the transition probabilities between the different states, we found evidence of an association between chronic BCC infection and the probability of dying without LTx. This association is possibly inflated by BCC being listed so far as a contraindication for LTx in most countries. Until now, BCC has been considered a significant barrier to the success of LTx in pwCF:[21] data from the Canadian CF Registry and the US CFF Patient Registry showed that the risk of death after first lung transplantation increased if pwCF were infected with BCC before transplantation (HR 1.40, 95% CI: 1.03–1.91),[33] but this was not found in our data (HR 0.90, 95% CI: 0.54–1.50).

A significant difference in survival between the sexes is however apparent in our study. For females with CF, there is an increased risk of dying without LTx and also after LTx. As reported elsewhere,[21] this survival difference disappears in those alive with LTx who later die. With regard to age at diagnosis, pwCF with a late diagnosis have significant lower hazards of death, before or after LTx, which is likely due to a mild course of CF disease.

Our study also investigated whether GNI was associated with the probability of survival with or without LTx in pwCF. In a recent study, survival across Europe was found to be influenced by socioeconomic factors.[34] It is therefore relevant that we also found a statistical association between GNI and the probability of receiving LTx, which is lower for pwCF living in low-income European countries, and a statistical association between GNI and the probability of dying without LTx, which is higher for pwCF living in low-income European countries. This finding underpins the inequalities in CF healthcare across Europe. How CF standards of care are implemented differs across Europe, as does how OT is considered and managed. OT for pwCF is reimbursed in most European countries except for Bulgaria, Moldova, Serbia, Russia and Ukraine. In Latvia, the therapy is only reimbursed for adults.[6] There is further disparity around access to transplant programs and in some countries there is no access at all.[21] As reported by the US, socioeconomic status influences outcomes for patients awaiting LTx; however, social disparities might affect LTx outcomes only before transplantation.[25] Our findings did not demonstrate that GNI is associated with death after LTx either. Overall, clinical features associated with a poor outcome after LTx remain previous exposure to OT, FEV_1<LLN, the presence of cystic fibrosis-related diabetes (CFRD), use of pancreatic enzymes and history of hemoptysis.

Future actions are needed to ensure equal access to recommended standards of care for pwCF in European countries and, in particular, reimbursement of OT and access to advanced therapeutic regimes such as LTx. Harmonization of how OT is prescribed for pwCF is of utmost importance; it is currently based on evidence from people with COPD which means our understanding of the true significance of the variable oxygen therapy during the year of follow-up collected by ECFSPR is unknown. Redefining how this variable is collected may also help us to understand more about the effect of oxygen usage, whether it be administered intermittently, such as during pulmonary exacerbation, overnight or during

exercise, or on a long-term basis. Gathering additional information about OT in the future, for the 2935 pwCF included in the present study, could also shed more light onto how and for what OT has been prescribed.

Altogether, our results bring to the literature that OT and FEV_1 below LLN are associated with a worse transition probability towards death, with or without LTx. However, bearing in mind that FEV_1 is just one indication of CF lung disease it could be appropriate to model survival probabilities by exploring other, more sensitive markers of lung disease, such as lung clearance index (LCI).[35–37] The decision to include LCI as a variable in the ECFSPR from 2018 onwards is therefore rather appropriate since it can help to diagnose earlier stage lung disease than if only a decrease in FEV_1 is considered; this has promising implications for future prognostication in CF, as recently presented elsewhere.[38] We hope it is, or will become, available and reimbursed in as many countries as possible.

Despite the Copernican revolution that has been ignited by highly effective CFTR modulator therapies, many pwCF still do not have, and are unlikely to have in the near future, access to these new drugs, either because of their genotype or due to country-specific health policies.[39] It is therefore imperative that CF MDTs recognize early-stage pulmonary disease using the latest and most sensitive diagnostic methods and technology available, and treat it as soon as symptoms are manifest.

Limitations and Strengths

This study has limitations: it is limited to the variables included in the ECFSPR database; data were collected before 2018, the year in which the ECFSPR started to record data about CFTR modulator therapies (though we can estimate, looking at data from 2018[40] that less than 16% of pwCF included in the present analysis took one of the CFTR modulator therapies before 2018 and thus the bias on the overall probabilities is small); we considered OT as present from its first occurrence onwards, thus assuming that respiratory failure was irreversible. There is no way, however, given how this variable was collected by the ECFSPR, to understand how pwCF were exposed to OT or the rationale behind its administration and we therefore acknowledge that we made a strong assumption. We have considered the need for oxygen supplementation, even just once, as an indicator that the respiratory system is profoundly compromised by the disease. On the other hand, this could be deemed to be one of the strengths of the study since we demonstrate that the prescription of OT can be regarded as a red flag and turning point, for the worse, in the course of CF disease.

Another strong point of this study is that it is based on high-quality data[41,42] from a large population of pwCF from 35 countries and data were analyzed using a technique that allowed us to model the transition from one condition to another as an extension of competing risk models. In addition, our findings corroborate the relevance of using FEV_1 z-score based on the GLI equations as a marker of CF-disease severity. These equations eliminate age, sex and height bias and provide a more standardized approach to measuring lung function than the traditional method of percent of predicted.

Conclusion

With the statistical evidence presented in this study, we have demonstrated that treatment with oxygen therapy, abnormal FEV_1, presence of CFRD and use of pancreatic enzymes are all features of CF that consistently affect the transition probabilities of surviving, with or without LTx. Since prognosis is also determined by economic disparities at a country level, which in turn affect standards of care and the availability of diagnostic and therapeutic instruments, we strongly recommend that the harmonization of CF care throughout the countries in Europe remains of paramount importance to the CF community, to prevent by all possible means, as much as possible, the onset of respiratory failure.

Abbreviation

pwCF, people with Cystic Fibrosis; OT, Oxygen therapy; COPD, Chronic Obstructive Pulmonary Disease; LTx, Lung Transplantation; ECFSPR, European Cystic Fibrosis Society Patient Registry; CF, Cystic Fibrosis; FEV_1, Forced Expiratory Volume in the first second; GLI, Global Lung Function; LLN, Lower Limit of Normal; BMI, Body Mass Index; GNI, Gross National Income; CFTR, Cystic Fibrosis Transmembrane conductance Regulator; PSA, *Pseudomonas aeruginosa*; BCC, *Burkholderia cepacia* complex; HR, Hazard Ratio; IQR, Interquartile Range; CFF, Cystic Fibrosis Foundation; MDTs, Multi-Disciplinary Teams; CFRD, Cystic Fibrosis-related Diabetes; LCI, lung clearance index.

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Author Contributions

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