CHEST Online Supplement

Survival and Lung Transplant Outcomes for Individuals With Advanced Cystic Fibrosis Lung Disease Living in the United States and Canada

An Analysis of National Registries

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e-Appendix 1.

Methods:

US registry merge

Record Linkage between United Network for Organ Sharing (UNOS) and the Cystic Fibrosis Foundation (CFF) Patient Registry (CFFPR) was completed utilizing the LinkPlus software, a record linkage software freely available from the US Centers for Disease Control (CDC). The CFFPR contains information for approximately 81-84% of individuals with CF in the United States (US)1. The UNOS Registry contains information about 100% of patients listed for lung transplant in the US2. Patients were matched on last name, birth date, sex, first name, middle initial and zip code (when available). Phonetic last name (NYSIIS), birth date, and gender were used as blocks. Matching was done using probabilistic matching and matches needed to have a match score of 10 or higher to be accepted (eFigure 1). The match score is calculated as the probability of two true matches agree on a variable divided by the probability that false matches would randomly agree[3]. Base probability of names was determined using the 1990 Census.

6,821 unique matches were made. 250 (3.7%) heart transplants were excluded to bring the total down to 6,571 lung transplant matches. 135 patients with a transplant year in the CFFPR were not matched to any record in UNOS. We found that there were 198 deaths in the CFFPR that were missing from the UNOS data, and 891 deaths in the UNOS registry that are missing from the CFFPR. If there was a death date in both registries, we used UNOS as the 'gold standard' date. However, if a transplant date is AFTER the death date recorded in CFFPR, we assume that these are likely mismatched cases and we use the CFF information as the correct information. If a transplant date was recorded in CFFPR and not recorded in UNOS, we considered this a mismatch and used the transplant date from CFF. There were some patients who had duplicate records in UNOS, pertaining to times when they were

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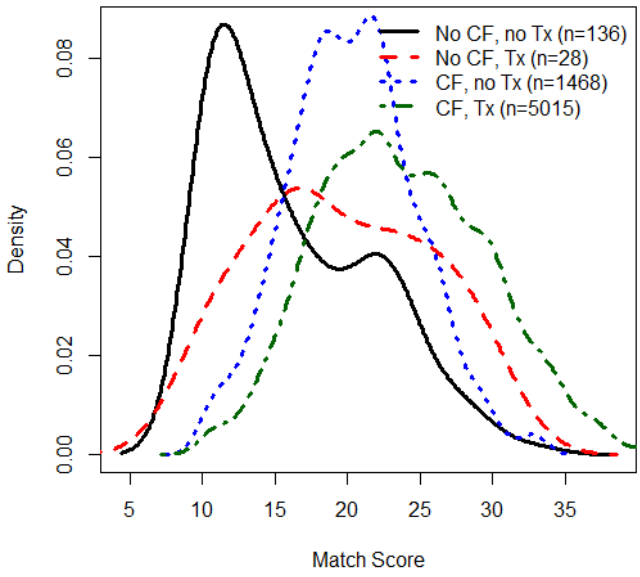
1 Knapp EA, Fink AK, Goss CH, Sewall A, Ostrenga J, Dowd C, Elbert A, Petren KM, Marshall BC. The Cystic Fibrosis Foundation Patient Registry. Design and methods of a national observational disease registry. Annals of the American Thoracic Society. 2016 Jul;13(7):1173-9.

2 This study used data from the Organ Procurement and Transplantation Network (OPTN). The OPTN data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN contractor.

3 An Overview of Record Linkage Methods – NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

listed and then removed from the waitlist with no transplant, and then listed again. In these cases, we removed any records where the removal code indicated 1) the patient was medically unsuitable for transplant (removal code 5), 2) the patient refused (removal code 6), 3) the candidate was listed in error (removal code 10 or 16) or 4) the patient's condition improved (removal code 12). Once those records were removed, for any additional duplicates records where the patient transferred transplant centers (removal codes 14, 3, 7, 15), the waitlist date from the first record was used and a cumulative time on the waitlist over the records until the final record of the transplant was calculated.

e-Figure 1: Match scores across cohorts in the Cystic Fibrosis Foundation Patient Registry (CFFPR) and the United Network for Organ Sharing (UNOS) registry. Patients could be labeled in UNOS as having "CF" or "No CF" to designate the indication for lung transplant was cystic fibrosis or not, respectively. Patients could be labeled in the CFFPR as "Tx" or "no Tx" to designate whether they are recorded as having a lung transplant in the CFFPR or not, respectively. Patients labeled in UNOS as "No CF" and in CFFPR as "no Tx" had the lowest match scores.



Definition of key variables

Values for covariates that change over time (e.g. age, body mass index (BMI), non-invasive ventilation) were obtained from the year prior to entry to the cohort. FEV_1 in Table 1 (describing the cohort) was obtained from the annual data of the year prior to cohort entry.

BMI was classified as 1) underweight if BMI percentile was less than 12% for pediatrics (defined as age <19 years) or BMI under 18.5 kg/m^2 for adults, 2) normal weight if their BMI percentile was 12-84% for pediatrics or BMI 18.5-24.9 kg/m^2 for adults, or 3) overweight if their BMI percentile was over 84% for pediatrics or BMI over 24.9 kg/m^2 for adults.

Pulmonary exacerbations were determined by adding number of hospitalizations to the number of home IV courses; this approach may lead to misclassification for some people who were hospitalized for indications other than pulmonary exacerbations or for people who had a course of IV antibiotics that spanned both home and hospital encounters (and could be counted twice). CF-related diabetes (CFRD) was considered ever/never present prior to first low FEV_1; the presence of CFRD was determined by the reporting CF clinic based on published consensus guidelines and not limited to those prescribed insulin. Pancreatic insufficiency (defined by pancreatic enzyme use) and *Burkholderia cepacia* complex sputum culture status were considered ever/never present. Non-invasive ventilation with bilevel support was only available in the Canadian CF Registry beginning in 2011 and data in the US for this variable was limited to the same timeframe (2011-2016).

Medicaid and Medicare eligibility

Medicaid and Medicare are the public insurance options in the US and have specific requirements for eligibility. Medicaid and Medicare are frequently considered together as "public health insurance" in the US. Medicaid is a benefits program for individuals with low income and low assets, jointly funded by the state and federal governments4. Medicaid can be reliably used to confirm that an individual has low income in the US, though state to state variation exists to define the low income and low asset thresholds for qualification. Medicare is available to senior citizens in the US (age 65 years and older) and for certain younger individuals with long-term disability or specific medical conditions (e.g. end-stage renal disease, Amyotrophic Lateral Sclerosis (ALS), terminal illnesses)5. Individuals under the age of 65 can qualify for Medicare after spending two years with disability benefits (under the Social Security Disability Insurance (SSDI) program6 or Supplemental Security Income (SSI) program7). A disabled person cannot earn more than $1,260/month (as of 2020)[4] when applying for SSDI but the there are no restrictions on assets to qualify. For SSI, an individual cannot have more than $2,000 in assets and must earn less than $1,627/month in wages. These rules generally lead to younger Medicare recipients (under

4 https://www.healthcare.gov/medicaid-chip/
5 https://www.medicare.gov/Pubs/pdf/10050-Medicare-and-You.pdf
6 https://www.ssa.gov/benefits/disability/qualify.html
7 https://www.ssa.gov/ssi/text-eligibility-ussi.htm#top

the age of 65) having lower income in order to qualify for Medicare in the setting of receiving long-term disability benefits.

Multiple imputation of missing data

Missing variables were imputed using multiple imputation with chained equations (MICE) using the mice package in R version 3.6.2. Cystic fibrosis (CF)-related diabetes prior to first low lung function (defined as forced expiratory volume in 1 second, FEV_1, <40% predicted), BiPAP, infection with pseudomonas aeruginosa, and White race were all imputed using a logistic regression model with all other covariates as possible predictors. Body mass index (BMI) percentile, BMI, and percent predicted FEV_1 were imputed using a predictive mean matching. Outcome variables were not used as predictors in any of the missing variable equations. Ten different imputed datasets were run and the results were combined using the techniques in Rubin, D.B.: Multiple imputation for nonresponse in surveys. Wiley, New York 1987.

Results:

e-Table 1: Time between first (low) and confirmatory (second low) FEV_1 measurements for patients with two FEV_1 < 40% predicted within 5 years, 2005-2016

	Canada		US	
Time between first 2 low FEV_1, Median (range), years	1	(1-5)	1	(1-5)
Time between first 2 low FEV_1, Median [IQR], years	1	[1-2]	1	[1-2]
# patients in the cohort after the first low FEV_1% predicted				
	Canada N=905	%	US N=5899	%
2 low FEV_1 within the first 2 annual measurements (1 year)	665	73.5	4386	74.4
2 low FEV_1 within the first 3 annual measurements (2 years)	796	88	5235	88.7
2 low FEV_1 within the first 4 annual measurements (3 years)	856	94.6	5592	94.8
2 low FEV_1 within the first 5 annual measurements (4 years)	885	97.8	5782	98
2 low FEV_1 within the first 6 annual measurements (5 years)	905	100	5899	100

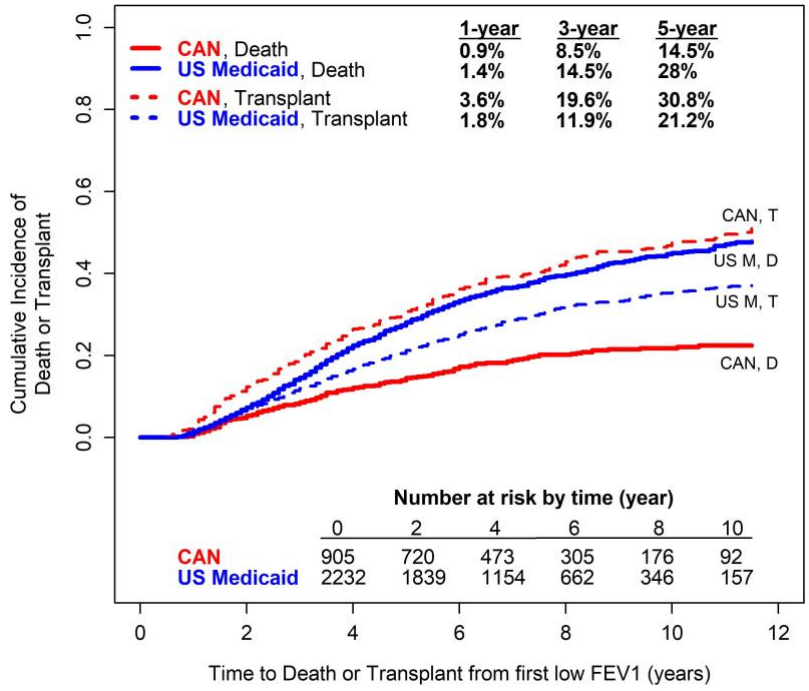
Death on the waitlist

Of patients with FEV_1 <40% predicted who were listed on or after January 1, 2005, 307 (14.4%) in the US and 19 (5.2%) in Canada died without lung transplant. For people who died on the waiting list, in Canada they waited a median of 0.3 years (range 0.1-2.3 years) and in the US they waited a median of 0.4 years (range 0-8.5 years). Ascertainment of listing status was confirmed by a CF physician (Dr. Anne Stephenson) in Canada for nearly all deaths among patients with FEV_1 <40% predicted in Canada, but this was not captured by the CF Canada registry and there may be incomplete ascertainment of listing status for Canadian patients.

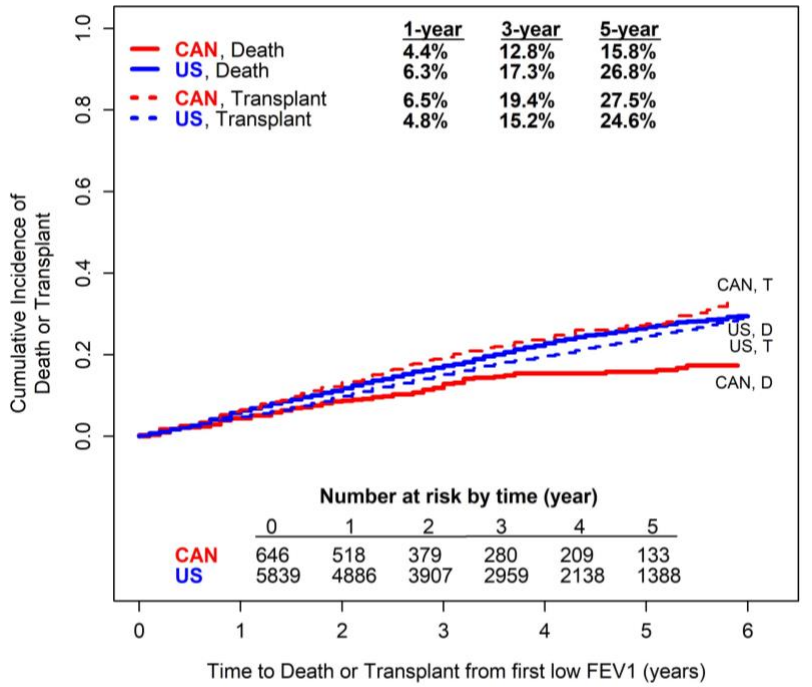
Sensitivity analyses

Rates of LTx and death without LTx for individuals with Medicaid insurance were similar to results for the cohort with Medicaid/Medicare insurance (eFigure2). In both countries, rates of LTx and death without LTx were increased for individuals with two FEV_1 < 40% predicted measurements within one year (compared to two annual measurements within 5 years) (eFigure 3), two FEV_1 < 40% predicted measurements within three years (eFigure 4), and for individuals with FEV_1 <30% predicted (eFigures 5 and 6). A difference in the LTx to death ratio between the countries was present at 1 year in these sensitivity analyses and continued to widen as time from cohort entry increased (eFigures 3-6). Results were similar when limited to patients age 18 years and older (eFigure 7).

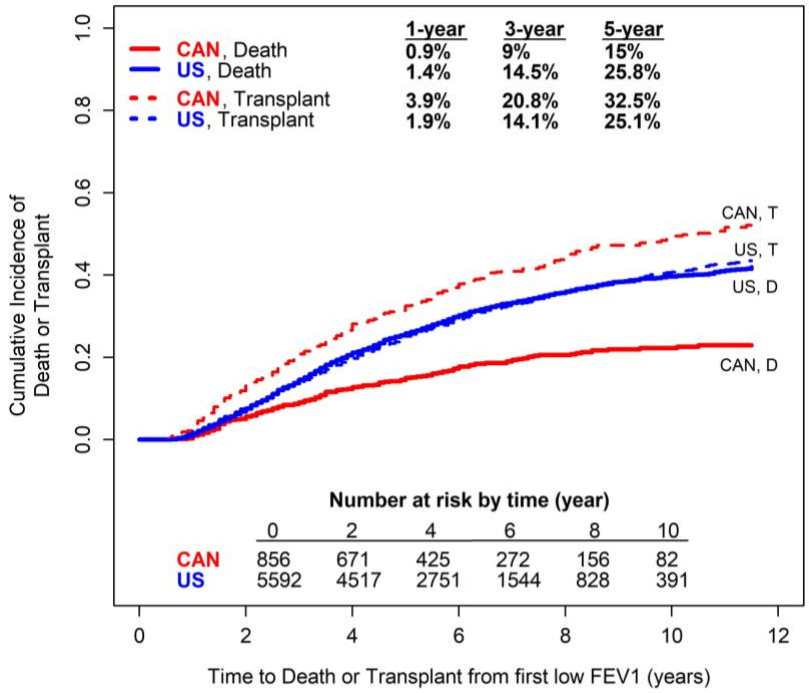
e-Figure 2: Cumulative incidence curves with 1-, 3- and 5-year rates of death without LTx and lung transplant among individuals with **two FEV_1 <40% predicted in a 5-year period, with "Medicaid only" insurance** in the United States (US) vs Canada (CAN), 2005-2016



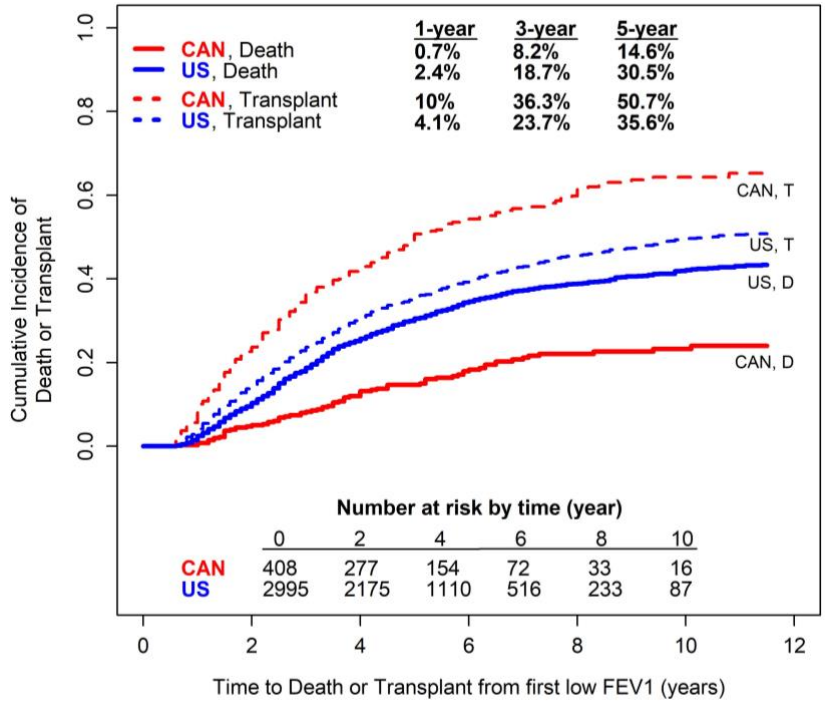
e-Figure 3: Cumulative incidence curves with 1-, 3- and 5-year rates of death without LTx and lung transplant among individuals with **two FEV_1 <40% predicted within one year, in the United States (US) vs Canada (CAN), 2011-2016**



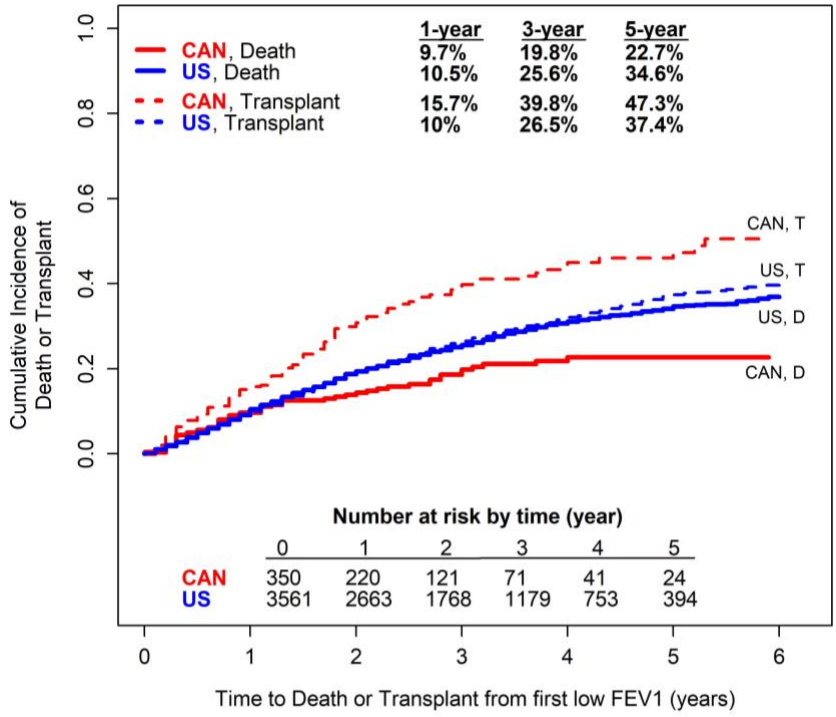
e-Figure 4: Cumulative incidence curves with 1-, 3- and 5-year rates of death without LTx and lung transplant among individuals with **two FEV_1 <40% predicted within three years, in the United States (US) vs Canada (CAN), 2005-2016**



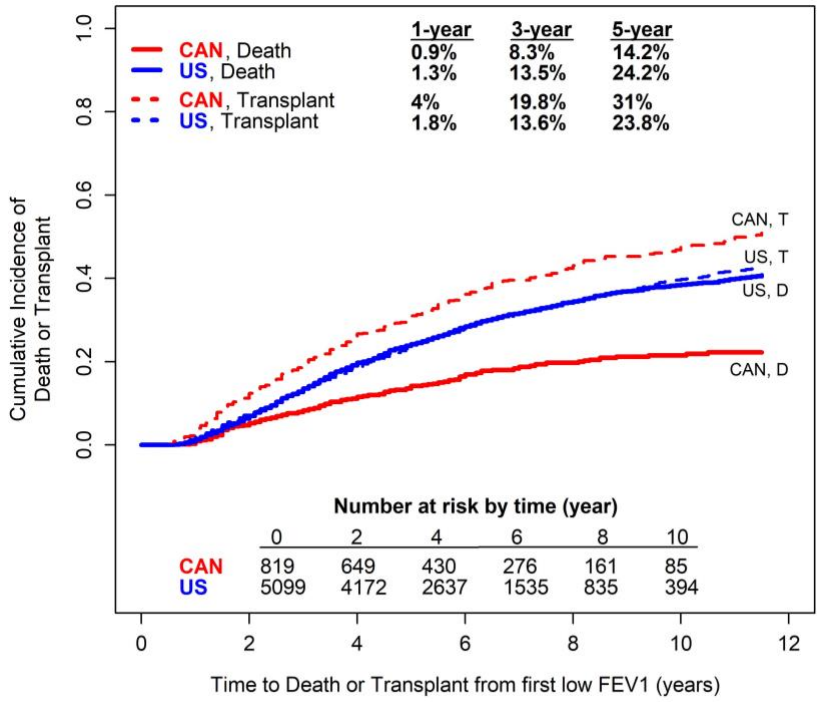
e-Figure 5: Cumulative incidence curves with 1-, 3- and 5-year rates of death without LTx and lung transplant among individuals with **two FEV_1 <30% predicted in a 5-year period, in the United States (US) vs Canada (CAN), 2005-2016**



e-Figure 6: Cumulative incidence curves with 1-, 3- and 5-year rates of death without LTx and lung transplant among individuals with **two FEV_1 <30% predicted within one year, in the United States (US) vs Canada (CAN), 2011-2016**



e-Figure 7: Cumulative incidence curves with 1-, 3- and 5-year rates of death without LTx and lung transplant among individuals with **two FEV_1 <40% predicted in a 5-year period, limited to age ≥18 years, in the United States (US) vs Canada (CAN), 2005-2016**



e-Table 2: Multivariable competing risk regression, time to death without LTx (LTx as a competing risk) and time to LTx (death as a competing risk), for **Medicaid/Medicare vs Canada** (and "other" vs Canada), 2005-2016, multiple imputation analysis

	Time to death			Time to lung transplant		
Variable	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Insurance status						
Medicaid/Medicare vs Canada	2.24	1.89-2.63	**<0.001**	0.54	0.47-0.61	**<0.001**
Other Insurance vs Canada	1.25	1.05-1.49	**0.014**	0.84	0.74-0.95	**0.005**
None/Missing Insurance vs Canada	2.56	1.63-4.02	**<0.001**	0.47	0.26-0.84	**0.012**
Age at low lung function	1.01	1.01-1.02	**<0.001**	0.99	0.99-0.99	**<0.001**
Gender (Female vs Male)	1.02	0.94-1.12	0.6	1.04	0.95-1.13	0.41
Age at diagnosis (≥2 yrs vs <2yrs)	1.01	0.91-1.12	0.85	0.85	0.77-0.94	**0.002**
CF-related diabetes	1.23	1.12-1.35	**<0.001**	0.97	0.88-1.07	0.53
Burkholderia cepacia complex	1.17	1-1.37	**0.047**	0.64	0.54-0.77	**<0.001**
Race (Non-White vs White)	1.40	1.19-1.66	**<0.001**	0.51	0.39-0.67	**<0.001**
BMI Categories						
Overweight vs Adequate Weight	1.01	0.85-1.2	0.95	0.69	0.56-0.85	**0.002**
Underweight vs Adequate Weight	1.2	1.08-1.34	**0.003**	0.98	0.88-1.08	0.68
FEV_1 % Predicted	1.00	0.99-1.00	0.72	0.98	0.98-0.99	**<0.001**
# Pulmonary exacerbations						
1-2 vs 0	1.17	1.05-1.31	**0.006**	1.15	1.04-1.27	**0.008**
3+ vs 0	1.5	1.33-1.68	**<0.001**	1.36	1.21-1.52	**<0.001**
Supplemental oxygen	1.24	1.09-1.41	**0.001**	1.31	1.14-1.51	**<0.001**

n=6,804 observations. These observations include 2,014 deaths and 2,195 transplants. All variables are assessed prior to the first low lung function (FEV_1 <40% predicted) measurement. BMI was classified as 1) underweight if BMI percentile was less than 12% for pediatrics (defined as age <19 years) or BMI under 18.5 kg/m^2 for adults, 2) normal weight if their BMI percentile was 12-84% for pediatrics or BMI 18.5-24.9 kg/m^2 for adults, or 3) overweight if their BMI percentile was over 84% for pediatrics or BMI over 24.9 kg/m^2 for adults.

LTx: lung transplantation; HR: hazard ratio; CI: confidence interval; US: United States; CF: cystic fibrosis; BMI: body mass index; FEV_1: forced expiratory volume in 1 second

Bold p-value indicates a value <0.05, a statistically significant result

e-Table 3: Multivariable competing risk regression, time to death without LTx (LTx as a competing risk) and time to LTx (death as a competing risk), for individuals with **two FEV_1 <40% predicted in a 5-year period, limited to age ≥18 years**, 2005-2016, multiple imputation analysis*

	Time to death			Time to lung transplant		
Variable	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Country (US vs Canada)	1.75	1.47-2.08	**<0.001**	0.67	0.59-0.76	**<0.001**
Age	1.02	1.01-1.02	**<0.001**	0.99	0.98-0.99	**<0.001**
Gender (Female vs Male)	1.03	0.94-1.14	0.54	1.03	0.94-1.13	0.54
Age at diagnosis (≥2 yrs vs <2yrs)	0.99	0.89-1.1	0.85	0.87	0.79-0.97	**0.010**
CF-related diabetes	1.28	1.16-1.41	**<0.001**	0.94	0.85-1.04	0.24
Burkholderia cepacia complex	1.14	0.96-1.36	0.13	0.69	0.57-0.83	**<0.001**
Race (Non-White vs White)	1.52	1.26-1.84	**<0.001**	0.49	0.36-0.66	**<0.001**
BMI Categories						
Overweight vs Adequate Weight	1.00	0.84-1.20	0.98	0.69	0.56-0.85	**0.003**
Underweight vs Adequate Weight	1.32	1.17-1.49	**<0.001**	0.91	0.81-1.01	0.093
FEV_1 % Predicted	1.00	0.99-1.00	0.67	0.98	0.98-0.99	**<0.001**
# Pulmonary exacerbations						
1-2 vs 0	1.14	1.01-1.28	**0.031**	1.15	1.03-1.28	**0.015**
3+ vs 0	1.56	1.38-1.77	**<0.001**	1.32	1.17-1.49	**<0.001**
Supplemental oxygen	1.27	1.10-1.46	**0.001**	1.24	1.06-1.44	**0.007**

*87% of patients were over 17 at their first low FEV_1. n=5,918 observations. These observations include 1,714 deaths and 1,921 transplants. All variables are assessed prior to the first low lung function (FEV_1 <40% predicted) measurement. BMI was classified as 1) underweight if BMI percentile was less than 12% for pediatrics (defined as age <19 years) or BMI under 18.5 kg/m^2 for adults, 2) normal weight if their BMI percentile was 12-84% for pediatrics or BMI 18.5-24.9 kg/m^2 for adults, or 3) overweight if their BMI percentile was over 84% for pediatrics or BMI over 24.9 kg/m^2 for adults.
LTx: lung transplantation; HR: hazard ratio; CI: confidence interval; US: United States; CF: cystic fibrosis; BMI: body mass index; FEV_1: forced expiratory volume in 1 second
Bold p-value indicates a value <0.05, a statistically significant result

e-Table 4: Multivariable competing risk regression, time to death without LTx (LTx as a competing risk) and time to LTx (death as a competing risk), for individuals with **two FEV_1 <30% within 1 year**, 2011-2016, multiple imputation analysis

	Time to death			Time to lung transplant		
Variable	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Country (US vs Canada)	1.52	1.15-1.99	**0.003**	0.54	0.44-0.65	**<0.001**
Age	1.02	1.01-1.03	**<0.001**	1	0.99-1	0.29
Gender (Female vs Male)	1.07	0.94-1.21	0.31	1.01	0.9-1.13	0.89
Age at diagnosis (≥2 yrs vs <2yrs)	0.92	0.8-1.07	0.27	0.9	0.78-1.03	0.13
CF-related diabetes	0.82	0.72-0.93	**0.002**	1.84	1.6-2.12	**<0.001**
Burkholderia cepacia complex	1.49	1.24-1.79	**<0.001**	0.67	0.53-0.84	**0.001**
Race (Non-White vs White)	1.47	1.16-1.86	**0.002**	0.51	0.36-0.73	**<0.001**
BMI Categories						
Overweight vs Adequate Weight	1.01	0.8-1.27	0.95	0.81	0.63-1.02	0.081
Underweight vs Adequate Weight	1.34	1.16-1.54	**<0.001**	0.94	0.82-1.08	0.38
FEV_1 % Predicted	1.01	1-1.01	0.064	0.99	0.98-0.99	**0.001**
# Pulmonary exacerbations						
1-2 vs 0	1.1	0.92-1.31	0.28	1.1	0.94-1.29	0.24
3+ vs 0	1.71	1.44-2.04	**<0.001**	1.2	1.02-1.41	**0.029**
Supplemental oxygen	1.4	1.21-1.62	**<0.001**	1.53	1.34-1.75	**<0.001**

n=3,911 observations. These observations include 1,039 deaths and 1,156 transplants. All variables are assessed prior to the first low lung function (FEV_1 <30% predicted) measurement. BMI was classified as 1) underweight if BMI percentile was less than 12% for pediatrics (defined as age <19 years) or BMI under 18.5 kg/m^2 for adults, 2) normal weight if their BMI percentile was 12-84% for pediatrics or BMI 18.5-24.9 kg/m^2 for adults, or 3) overweight if their BMI percentile was over 84% for pediatrics or BMI over 24.9 kg/m^2 for adults.

LTx: lung transplantation; HR: hazard ratio; CI: confidence interval; US: United States; CF: cystic fibrosis; BMI: body mass index; FEV_1: forced expiratory volume in 1 second

Bold p-value indicates a value <0.05, a statistically significant result

e-Table 5: Multivariable competing risk regression, time to death without LTx (LTx as a competing risk) and time to LTx (death as a competing risk), for individuals with two FEV_1 <40% predicted in a 5-year period, 2005-2016, **complete case analysis**

	Time to death			Time to lung transplant		
Variable	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Country (US vs Canada)	1.91	1.58-2.3	**<0.001**	0.65	0.57-0.74	**<0.001**
Age	1.01	1-1.02	**0.002**	0.99	0.99-1	**0.001**
Gender (Female vs Male)	1.01	0.91-1.12	0.88	1.05	0.95-1.16	0.31
Age at diagnosis (≥2 yrs vs <2yrs)	0.98	0.88-1.1	0.76	0.91	0.81-1.01	0.084
CF-related diabetes	1.29	1.17-1.44	**<0.001**	0.94	0.85-1.04	0.24
Burkholderia cepacia complex	1.2	1-1.44	0.054	0.67	0.55-0.81	**<0.001**
Race (Non-White vs White)	1.64	1.35-1.99	**<0.001**	0.47	0.34-0.64	**<0.001**
BMI Categories						
Overweight vs Adequate Weight	1.01	0.84-1.22	0.89	0.66	0.53-0.81	**<0.001**
Underweight vs Adequate Weight	1.25	1.1-1.4	**<0.001**	0.95	0.85-1.07	0.39
FEV_1 % Predicted	1	0.99-1	0.56	0.98	0.98-0.99	**<0.001**
# Pulmonary exacerbations						
1-2 vs 0	1.22	1.07-1.39	**0.004**	1.17	1.04-1.32	**0.008**
3+ vs 0	1.65	1.43-1.89	**<0.001**	1.31	1.15-1.49	**<0.001**
Supplemental oxygen	1.29	1.12-1.49	**<0.001**	1.33	1.15-1.55	**<0.001**

n=5,111 observations (1,693 observations deleted due to missing data). These observations include 1,506 deaths and 1,715 transplants. All variables are assessed prior to the first low lung function (FEV_1 <40% predicted) measurement. BMI was classified as 1) underweight if BMI percentile was less than 12% for pediatrics (defined as age <19 years) or BMI under 18.5 kg/m^2 for adults, 2) normal weight if their BMI percentile was 12-84% for pediatrics or BMI 18.5-24.9 kg/m^2 for adults, or 3) overweight if their BMI percentile was over 84% for pediatrics or BMI over 24.9 kg/m^2 for adults.
LTx: lung transplantation; HR: hazard ratio; CI: confidence interval; US: United States; CF: cystic fibrosis; BMI: body mass index; FEV_1: forced expiratory volume in 1 second
Bold p-value indicates a value <0.05, a statistically significant result