

# Underweight Patients With Cystic Fibrosis Have Acceptable Survival Following Lung Transplantation

A United Network for Organ Sharing Registry Study

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## **e-Appendix 1.**

### **Methods**

#### *Population*

Using United Network for Organ Sharing (UNOS) registry data provided by the Organ Procurement and Transplantation Network (OPTN) as of December 13, 2016, patients with a first lung transplantation (LTx) at a United States (US) center between June 1, 2005 and November 30, 2015 were included. The start date of the study period was chosen to follow the initiation of the lung allocation score (LAS) in the US. Subjects had at least one year of potential follow-up time between November 30, 2015 and the end of the dataset. Subjects were included if they were age  $\geq 12$  years at first LTx with a diagnosis of cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) (without notation of alpha-1 antitrypsin disease), or idiopathic pulmonary fibrosis (IPF). Age  $\geq 12$  years was chosen because that age group receives organs using the US LAS, but a sensitivity analysis evaluating subjects  $\geq 18$  years was also performed. Exclusion criteria included: repeat LTx (first LTx before June 1, 2005; indications of graft failure or prior LTx at the time of first documented LTx in the dataset), multi-organ transplantation, and living donor LTx.

#### *Data*

Body mass index (BMI) is calculated as weight divided by height<sup>2</sup> (kg/m<sup>2</sup>), but our analyses utilized the BMI variable in the OPTN dataset. For CF, BMI strata were determined based on World Health Organization classification, comparing subjects with moderate-to-severe thinness (<17.00 kg/m<sup>2</sup>) to healthy or mildly underweight ( $\geq 17.00$  kg/m<sup>2</sup>). BMI <17 kg/m<sup>2</sup> was also determined to be representative of a usual exclusion criterion threshold at many centers based on experience and descriptive statistics. Based on clinical experience, we explored BMI <18 and BMI <17, allowing for rounding to the nearest 0.1 kg/m<sup>2</sup>. Among LTx Centers with at least one CF LTx in a given year, more than half of centers had zero CF recipients with BMI  $\leq 16.9$  and more than one third had zero recipients with BMI  $\leq 17.9$  (Table e1). These findings are consistent with BMI <17 as a possible threshold for relative contraindication to LTx at a majority of US LTx Centers, while BMI <18 kg/m<sup>2</sup> may be the threshold at fewer centers. Conversely, the low proportion of LTx Centers with CF recipients who have BMI <16.9 may be a reflection of the prevalence of the issue of malnutrition.

**e-Table 1: Proportion of LTx Centers with at least one CF LTx but zero individuals with CF below specific BMI thresholds**

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
# Centers with $\geq 1$ CF LTx	41	46	50	48	46	50	51	51	56	49	54
# Centers with zero CF recipients with BMI $< 17.9$ kg/m <sup>2</sup> – N (%)	18 (44%)	18 (39%)	20 (40%)	22 (46%)	17 (37%)	15 (30%)	19 (37%)	21 (41%)	24 (43%)	24 (49%)	25 (46%)
# Centers with zero CF recipients with BMI $< 16.9$ kg/m <sup>2</sup> – N (%)	27 (66%)	27 (59%)	30 (60%)	32 (67%)	27 (59%)	27 (54%)	31 (61%)	29 (57%)	30 (54%)	34 (69%)	39 (72%)

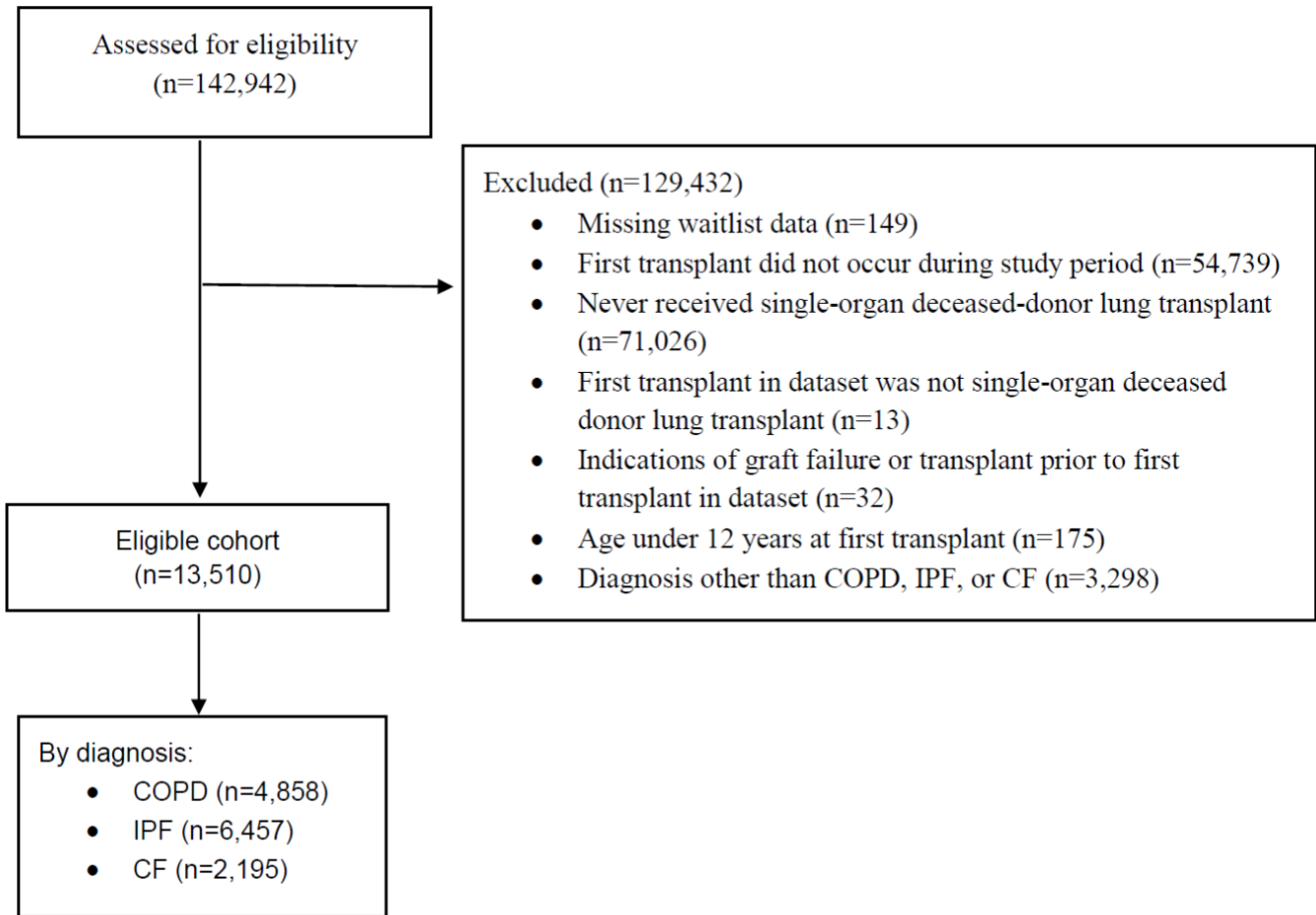
LTx: lung transplant; CF: cystic fibrosis; BMI: body mass index

**Statistical Analyses:**

The proportional hazard assumption was formally tested using Schoenfeld residuals and by evaluating the significance of interactions between the predictor of interest and time in exploratory Cox regression models since we thought a priori that hazard ratios might vary between early and late post-transplant periods. We evaluated 30 days, 3 months, 6 months, 1 year and 2 years post-transplant as possible transition points. Time interactions for transition points up to one year were statistically significant for models comparing CF and IPF to COPD as the reference group. Results from models with and without time interactions were similar. Transition points were 3 months post-LTx for the CF with BMI  $< 17$  vs. COPD model (including time interaction: HR at 0-3 months 0.46 [95% CI 0.24, 0.90] and HR at  $> 3$  months 1.12 [0.95, 1.31]) and 6 months for the model comparing all CF subjects to COPD (including time interaction: HR at 0-6 months 0.73 [0.60, 0.88] and HR at  $> 6$  months 0.87 [0.80, 0.95]). In both cases, the early (0-3 months or 0-6 months) HR was more favorable to CF, but we interpret that skeptically given that it represents a very small part of our overall follow-up period. As our question of interest addressed overall post-transplant survival, and the HR were not qualitatively different when the time interaction was included, we omitted time interactions from the final Cox models.

**Results**

**e-Figure 1: CONSORT Flow Diagram**



**e-Table 2. Lung transplant recipient characteristics**

	All CF N=2195	BMI ≥17.0 N=1831	BMI < 17 N=352
Recipient Age in years, median (IQR)	28 (23-37)	29 (24-38)	23 (18-29)
Male, n (%)	1129 (51)	972 (53)	151 (43)
Race/ethnicity, n (%)			
White	2076 (95)	1737 (95)	328 (93)
Black	29 (1)	24 (1)	5 (1)
Hispanic	83 (4)	68 (4)	14 (4)
Asian	0 (0)	0 (0)	0 (0)
American Indian/Alaska Native	4 (0)	2 (0)	2 (1)
Native Hawaiian/other Pacific Islander	0 (0)	0 (0)	0 (0)
Multiracial	3 (0)	0 (0)	3 (1)
Transplant year 2010-2015 (reference: 2005-2009), n (%)	1288 (59)	1088 (59)	192 (55)
Private insurance, n (%)	1288 (59)	1058 (58)	224 (64)
Height in centimeters at transplant, mean (SD)	165 (159-173)	166 (160-173)	163 (155-170)
Weight in kilograms at transplant, mean (SD)	53 (47-60)	54 (49-62)	42 (38-47)
BMI at transplant, mean (SD)	19 (18-21)	20 (18-21)	16 (16-17)
Diabetes present, n (%)	1034 (47)	887 (48)	143 (41)
O2 requirement at rest at transplant in L/min, median (IQR)	4 (2-6)	4 (2-6)	3 (2-6)
FEV1 % at transplant, median (IQR)	22 (18-27)	22 (18-27)	21 (17-27)
FVC % at transplant, median (IQR)	37 (30-46)	38 (30-46)	37 (29-45)
Lung Allocation Score at transplant, median (IQR)	41 (37-50)	41 (37-49)	42 (38-57)
On ventilator at transplant, n (%)	250 (11)	197 (11)	50 (14)
ECMO at transplant, n (%)	101 (5)	79 (4)	20 (6)
Repeat transplant, n (%)	157 (7)	124 (7)	33 (9)

**e-Table 3 Distribution of BMI at time of transplant, by diagnosis**

	<b>CF</b>	<b>COPD</b>	<b>IPF</b>
	<b>BMI (kg/m<sup>2</sup>)</b>	<b>BMI (kg/m<sup>2</sup>)</b>	<b>BMI (kg/m<sup>2</sup>)</b>
1 <sup>st</sup> Percentile	14.9	16.6	17.9
5 <sup>th</sup> Percentile	15.7	18.2	20.3
10 <sup>th</sup> Percentile	16.4	19.3	22.0
25 <sup>th</sup> Percentile	17.6	21.4	24.7
<b>Median</b>	<b>19.1</b>	<b>24.4</b>	<b>27.6</b>
75 <sup>th</sup> Percentile	20.9	27.6	30.0
95 <sup>th</sup> Percentile	24.7	31.3	33.1
99 <sup>th</sup> Percentile	28.3	33.7	35.6
Mean (SD)	19.5 (2.8)	24.6 (4.1)	27.3 (3.9)

Sensitivity analysis: survival time censored at re-transplant, limited to patients who underwent **bilateral lung transplantation**

**e-Table 4: Kaplan-Meier estimates of median post-transplant survival time, censored at re-transplantation in patients who received BILATERAL lung transplantation**

	n	Median post-transplant survival time in years	95% CI
CF (entire cohort)*	2193	7.9	7.2, 8.6
CF (BMI ≥ 17)	1830	8.2	7.3, 9.0
CF (BMI < 17)	351	7.0	4.5, 7.9
COPD (bilateral)	3082	6.6	6.2, 7.0
IPF (bilateral)	3430	6.5	6.1, 7.1

\*12 CF subjects had missing BMI data

**e-Table 5: Adjusted hazard ratio for post-transplant death, censored at re-transplantation (adjusted for transplant year, stratified by center) in patients who received BILATERAL lung transplantation**

	HR (95% CI)	P-value
COPD (bilateral) as reference group:		
CF BMI <17 kg/m <sup>2</sup>	1.07 (0.87, 1.30)	0.53
IPF (bilateral)	1.05 (0.97, 1.14)	0.24

Sensitivity analysis: survival time censored at re-transplant, limited to patients who were **age ≥18 years** at the time of transplantation

**e-Table 6: Kaplan-Meier estimates of median post-transplant survival time, censored at re-transplantation in patients who were AGE ≥18 years at the time of lung transplantation**

	n	Median post-transplant survival time in years	95% CI
CF (entire cohort)*	1989	8.1	7.4, 8.9
CF (BMI ≥ 17)	1713	8.4	7.5, 9.5
CF (BMI < 17)	264	5.7	3.9, 7.9
COPD	4857	5.9	5.6, 6.2
IPF	6446	5.5	5.2, 5.8

\*12 CF subjects had missing BMI data

**e-Table 7: Adjusted hazard ratio for post-transplant death, censored at re-transplantation (adjusted for transplant year, stratified by center) in patients who were AGE ≥18 years at the time of lung transplantation**

	HR (95% CI)	P-value
COPD as reference group:		
CF (age ≥18 years) BMI <17 kg/m <sup>2</sup>	1.04 (0.85, 1.27)	0.68
IPF	1.11 (1.05, 1.17)	<0.01

CF Patients who were **age <18 years** at the time of transplantation had an estimated median survival time of 5.2 years (95% CI 3.8, 7.7).

**e-Table 8: Adjusted hazard ratio for post-transplant death, censored at re-transplantation (adjusted for transplant year, stratified by center), among transplant recipients with cystic fibrosis; BMI change calculated from listing to time of LTx**

	HR (95% CI)	P-value
<b>BMI at LTx &lt;17 kg/m<sup>2</sup></b>		
BMI decline (1 kg/m <sup>2</sup> increments)	0.98 (0.86, 1.11)	0.74
BMI categorical change (reference: < 1 kg/m <sup>2</sup> change)		
"Decreased BMI" (≥1 kg/m <sup>2</sup> decrease)	1.28 (0.32, 5.09)	0.73
"Increased BMI" (≥1 kg/m <sup>2</sup> increase)	1.08 (0.63, 1.84)	0.78
<b>BMI at listing &lt;17 kg/m<sup>2</sup></b>		
BMI decline (1 kg/m <sup>2</sup> increments)	0.96 (0.81, 1.14)	0.64
BMI categorical change (reference: < 1 kg/m <sup>2</sup> change)		
"Decreased BMI" (≥1 kg/m <sup>2</sup> decrease)	1.25 (0.75, 2.09)	0.38
"Increased BMI" (≥1 kg/m <sup>2</sup> increase)	0.79 (0.28, 2.26)	0.66
<b>BMI at listing &lt;18.5 kg/m<sup>2</sup></b>		
BMI decline (1 kg/m <sup>2</sup> increments)	1.01 (0.92, 1.12)	0.78
BMI categorical change (reference: < 1 kg/m <sup>2</sup> change)		
"Decreased BMI" (≥1 kg/m <sup>2</sup> decrease)	1.05 (0.76, 1.46)	0.76
"Increased BMI" (≥1 kg/m <sup>2</sup> increase)	0.81 (0.45, 1.48)	0.48