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Improvements in Frailty Contribute to Substantial Improvements in Quality of Life after Lung Transplantation in Patients with Cystic Fibrosis

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Abstract

Background: While lung transplantation (LTx) improves health related quality of life (HRQL) in cystic fibrosis (CF), the determinants of this improvement are unknown. In other populations, frailty—a syndrome of vulnerability to physiologic stressors—is associated with disability and poor HRQL. We hypothesized that improvements in frailty would be associated with improved disability and HRQL in adults with CF undergoing LTx.

Methods: In a single-center prospective cohort study from 2010–2017, assessments of frailty, disability, and HRQL were performed before and at 3- and 6-months after LTx. We assessed frailty by the Short Physical Performance Battery (SPPB). We assessed disability with the Lung Transplant Valued Life Activities Scale (LT-VLA) and HRQL by the Medical Outcomes Study Short Form Physical and Mental Component Summary scales (SF12-PCS, -MCS), the Airway Questionnaire 20-Revised (AQ20R), and the Euroqol 5D (EQ5D). We tested the association of concurrent changes in frailty and lung function on disability and HRQL by linear mixed effects models adjusted for sex and body mass index.

Results: Among 23 participants with CF, improvements in frailty and lung function were independently associated with improved disability and some HRQL measures. For example, each 1-point improvement in SPPB or 200mL improvement in FEV_1 was associated with improved LT-VLA disability by 0.14 (95%CI: 0.08 to 0.20) and 0.07 (95%CI: 0.05 to 0.09) points and improved EQ5D by 0.05 (95%CI: 0.03 to 0.07) and 0.02 (95%CI: 0.01 to 0.03) points, respectively.

Conclusion: Improvement in frailty is a novel determinant of improved disability and HRQL in adults with CF undergoing LTx.

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Introduction

Survival in patients with cystic fibrosis (CF) is improving. For many, however, the natural history of the disease is the development of advanced lung disease and progressive respiratory failure[1,2]. For those patients, lung transplantation remains a key therapeutic option[3]. Lung transplantation aims to extend survival, reduce disability, and improve health related quality of life (HRQL). CF remains the third most common indication for lung transplantation, accounting for 16% of lung transplants performed in the United States[4].

Studies demonstrate that patients with CF derive the largest survival and HRQL benefit from lung transplantation when compared to other disease indications[5–11]. For some, however, this benefit is not realized[5]. We recently found that between 20 and 40% of all transplant recipients failed to derive a large improvement in HRQL by one-year after transplant, including those with CF[5]. This lack of improvement was not explained by baseline demographics or routinely collected clinical factors. A lack of understanding of why some patients fail to derive a HRQL benefit hinders the development of practices or interventions to ensure that lung transplantation provides maximum benefit. Although it is assumed that improved lung function from lung transplantation is the primary cause of improved HRQL, few studies have confirmed this[5,8]. Even less well studied are extra-pulmonary determinants of HRQL.

We recently identified that physical frailty is prevalent in candidates for lung transplantation, including patients with CF. Originally a geriatric construct, frailty is a systemic condition resulting from an accumulation of physiologic deficits across multiple interrelated systems[12,13]. In community-dwelling older populations, frailty is associated with poor HRQL[12]. In lung transplantation, frailty is associated with disability and death before and after transplant[13,14]. Further, frailty has been associated with worse HRQL before lung transplant[15]. Given this emerging literature, we hypothesized that changes in frailty may be a novel determinant of the changes in disability and HRQL observed after transplant. Preliminary results have been reported in abstract form[16].

Materials and Methods

Study design, participants, and setting:

We evaluated lung transplant candidates with CF enrolled in the University of California San Francisco (UCSF) “Breathe Again” study. Breathe Again is a prospective cohort study focused on evaluating the impact of lung transplantation on patient centered outcomes as well as potential pulmonary and extra-pulmonary determinants of this impact. As previously described, candidates for first-time lung transplantation at UCSF aged ≥18 years were enrolled between February 2010 and January 2017[5]. At enrollment, assessments of frailty were performed and a multi-instrument HRQL battery was administered. While on the waitlist for lung transplant, assessments were repeated every three months. Assessments were also repeated at the time of a major clinical changes including terminal hospitalization leading up to transplant. After transplant, the same frailty and HRQL battery was performed at 3- and 6-months after transplantation. Our program does not have strict requirements for rehabilitation before or after transplant. Pulmonary rehabilitation is frequently recommended

in the pre-lung transplant evaluation process in order to improve frailty and conditioning ahead of transplant. Following transplant, rehabilitation is tailored to patient specific needs ranging from home physical therapy at a minimum, outpatient pulmonary rehabilitation, to acute inpatient rehabilitation for a small subset of patients.

Conceptual Model: We utilized a conceptual model of disablement developed by Nagi and later adopted by the Institute of Medicine to test the relationship between CF, frailty, disability, and HRQL in patients with CF[17]. In this model, disease results in impaired organ functioning. This impairment leads to functional limitations, which can be measured in a lab-based setting (e.g., pulmonary function testing, distance walked in six minutes, or measures of frailty). Functional limitations, in turn, result in disability, defined as limitations in performing activities in daily life. In this model, functional limitations and disability are "upstream" precursors to HRQL. Applied to CF, we hypothesized that the systemic nature of the disease results in both decreased lung function (low forced expiratory volume in one second, FEV_1) as well as frailty (Figure 1). Our work has previously shown that the association between frailty and disability and mortality is independent of body mass index (BMI) when all diagnostic indications for lung transplantation are considered together[18]. Low BMI has been shown to portend shortened survival in CF patients with low lung function[3]. Given the clinical importance of BMI in CF care, we recognized that low BMI could be considered as a surrogate measure for aspects of frailty such as sarcopenia[19]. Thus, in our conceptual model, we considered an alternative relationship in which BMI could itself be a contributor to frailty, disability, and HRQL (Figure 1).

Exposure variables:

Frailty—Frailty was assessed by the Short Physical Performance Physical Battery (SPPB)[20,21]. The SPPB has three timed components: chair stands, balance, and gait speed. Each component of the SPPB has a score range of 0–4 with an aggregate range of 0–12[21]. Lower scores denote worse frailty. Frailty can be evaluated as a binary (frail, ≤ 7) or ordinal scale (0–12)[21]. Our prior work has demonstrated a change in SPPB score by one point is clinically significant[13,14].

FEV1: Lung function was measured by spirometry routinely performed in our clinical pulmonary function lab at clinic visits after transplantation. Spirometry was performed according to ATS guidelines[22]. These data were abstracted from the medical records at the same time points as HRQL measures (i.e., before and at 3- and 6-months after transplantation).

Outcome Variables:

Disability—Disability was assessed using the Lung Transplant Valued Life Activities Scale (LT-VLA)[23]. The LT-VLA is a 15-item self-rated measure of physical disability specific for advanced lung disease and lung transplantation[23]. The LT-VLA measures patient-reported ability to complete daily life activities across a hierarchy of three domains. These domains include activities required for survival such as activities of daily living (ADLs); activities associated with one's principal productive social roles such as being able to work for pay; and activities that provide enjoyment and life satisfaction such as traveling or visiting friends

and family[23]. The LT-VLA provides a more comprehensive understanding of how lung disease affects a person's ability to perform a broad range of life activities than measures of (instrumental) ADLs.

For the 15 items, participants rate the level of difficulty in performing a given activity on a 4-point scale (0=no difficulty, 1=some, 2=a great deal, 3=unable to perform). Participants can also respond "does not apply". Thus, participants only report disability in life activities that are personally meaningful[23]. Scored items are summed and divided by total rated items yielding a summary score with a range from 0–3. Higher scores denote worse disability and a change of 0.3 is considered clinically significant[23].

HRQL—HRQL is, by definition, multi-dimensional[24]. In order to capture the broad array of dimensions relevant to lung transplant recipients, a battery of generic and respiratory disease-specific instruments was used. To assess generic HRQL, the Medical Outcomes Study Short Form Physical and Mental Component Summary Scales (SF12-PCS and -MCS) were used[25,26]. The SF12-PCS and -MCS have a range of 0 to 100 points. The normative population mean is 50 points with a standard deviation of 10. Higher scores denote better HRQL and a change of five points is considered clinically significant[25,26]. We assessed health utility with the Euroqol 5D (EQ5D)[27]. The EQ5D has a range of −0.11 to 1 points. Higher scores denote better HRQL and a change of 0.06 points is considered clinically significant[27]. We assessed respiratory specific HRQL with the Airway Questionnaire 20-Revised (AQ20-R). The AQ20-R has a range of 0 to 20 points. Lower scores denote better HRQL and a change of 1.75 points is considered clinically significant[28,29]. The AQ20-R was used in lieu of the Cystic Fibrosis Questionnaire Revised (CFQ-R) because the Breathe Again study evaluated HRQL outcomes in all lung transplant recipients[30].

Other Variables

Baseline demographic and clinical variables were collected from the electronic medical record (Epic ®). Data collected included participant age at transplant, sex, preoperative FEV_1, preoperative forced vital capacity (FVC), BMI, and Lung Allocation Score (LAS). Pre-transplant baseline assessments were defined as those collected most proximal to the date of transplant.

Analytic Approach

The differences in frailty, BMI, lung function, disability, and HRQL between baseline and 6-months after transplantation were estimated using linear mixed effects models with study wave as a categorical variable and a subject-specific random effect to account for correlation among serial outcome measures of the same individual. Next, we utilized linear mixed effects models to evaluate the impact of changes in frailty and FEV_1 on changes in disability and HRQL from before through 6-months after transplantation. We included both frailty and FEV_1 in our models to test their independent associations with our outcomes of interest. Since our sample size limited the number of covariates we could include, we limited our models to adjust for sex and BMI. Sex and BMI were selected based upon their hypothesized relationship between our exposures and outcomes of interest.

Low BMI is thought to be associated with frailty based on its role as a putative surrogate measure of sarcopenia, defined as low muscle mass and peripheral muscle strength or function[19,31]. Although we hypothesized that the association between frailty and disability and mortality is independent of BMI based on our prior work, we recognized the potential for alternative associations in CF[32]. In CF, we considered the possibility that frailty lies on the causal pathway between BMI and disability and HRQL (Figure 1)[33,34]. To evaluate this possibility, we tested the association of change in BMI on disability and HRQL in unadjusted linear mixed effects models and with models including SPPB and FEV_1.

While uncommon, some participants did not complete all assessments. Missing data was not imputed because the maximum likelihood methods used to fit mixed effects models provide valid estimates for missing values[5,35,36].

Analyses were conducted using Stata 15 (StataCorp, College Station, Texas) and SAS 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

Over the study period, three hundred ninety-two lung transplant candidates were enrolled in “Breathe Again.” Of these, 259 underwent lung transplantation, including 23 participants with CF (Figure 2).

The 23 participants were 52% female with a mean age of 31.0 (standard deviation (±) 7.9 years). Mean lung allocation score (LAS) was 49.9 (±18.3); median LAS was 43 (Interquartile range [IQR]: 38–53). The mean SPPB score was 9.8 (± 2.5); median SPPB score was 11 (IQR: 9–12) and 22% were frail by an SPPB cutoff of ≤ 7 (Table 1). No participants died during the study period.

Participants experienced improvements in frailty, lung function, disability, and HRQL after lung transplantation (Table 2). Overall, SPPB improved by 1.1 point (95% CI −0.2, 2.4) which is 1.1-fold what is considered to be clinically significant. Of the five subjects who were frail before lung transplant, four subjects were not frail six months after lung transplant with a change in SPPB of 3.8 (95% CI 0.3, 7.3) (Figure 3). FEV_1 improved by 2.4L (95% CI 2.2, 2.7) which is 12.0-fold what is considered to be clinically significant. Participants reported marked improvements in disability and HRQL. HRQL improvements were greatest in generic physical and respiratory-specific HRQL. The SF12-PCS improved by 33.0 (95% CI 28.9, 37.1), 6.6-fold what is considered to be clinically significant. The AQ20-R improved by 12.41 (95% CI 11.19, 13.64), 7.1-fold what is considered to be clinically significant. Overall, improvements ranged from 1.5 – 7.1-fold the clinically significant difference by instrument.

Improvements in frailty were associated with improvements in LT-VLA disability, SF12-MCS, and EQ5D, independent of changes in lung function (Table 3). For example, each one-point improvement in SPPB was associated with a 0.14-point improvement in LT-VLA disability (95%CI: 0.08 to 0.20) and 1.4-point improvement in generical mental health HRQL (95%CI: 0.7 to 2.0) (Table 3). We also found that improvements in lung function were associated with improvements in all measures of disability and HRQL, independent of

changes in frailty. For example, each 200mL improvement in FEV_1 was associated with a 2.1-point improvement in generic physical HRQL SF12-PCS (95%CI: 1.7 to 2.5) and 0.78-point improvement in respiratory HRQL AQ20-R (95%CI: 0.64 to 0.92) (Table 3).

Finally, as hypothesized, changes in BMI were not associated with improvements in any measure of disability or HRQL (Table 3). For example, each 1-point increase in BMI was associated with a 0.03-point change in LT-VLA disability (95%CI: −0.01 to 0.08), a −0.9-point change in generic physical HRQL SF12-PCS (95%CI: −2.0 to 0.1), and 0.01-point change in respiratory HRQL AQ20-R (95%CI: −0.39 to 0.42) (Table 3).

Discussion

In this single-center prospective cohort study, we found that lung transplantation results in marked improvements in disability and HRQL for patients with cystic fibrosis. We found that frailty is a reversible process after lung transplant; four of five patients who were frail before lung transplant were no longer frail six months after lung transplant. Further, we found that improvements in frailty as well as in lung function were independently associated with improvements in disability and HRQL. Finally, we found that changes in BMI were not associated with changes in disability or HRQL suggesting that the impact of frailty on HRQL after lung transplantation cannot be explained by improvements in BMI. Taken as a whole, our findings support frailty as a novel determinant of disability and HRQL in patients with CF undergoing lung transplantation.

Our findings suggest that frailty may be an important determinant in disability and HRQL both before and after lung transplantation. CF is a well-described systemic inflammatory disease[37]. CF patients are vulnerable to putative causes of frailty. Abnormal fluid transport results in the accumulation of thick mucus in the airways, pancreas, and intestines[38]. The result is chronic lung infection, airway inflammation, exocrine pancreas dysfunction, malabsorption, and malnutrition[37,38]. Over time, increased energy expenditure due to work of breathing, malnutrition, and anorexia due to chronic inflammation result in weight loss, muscle loss, and the development of sarcopenia[19,37,38]. Frailty measures may capture the summative negative impact of these extra-pulmonary CF manifestations on disability and HRQL in a distinct manner from lung function. After lung transplantation, weight gain is expected with improvement of some of these disease manifestations[32]. We did not find that changes in BMI were associated with improvements in disability or HRQL. Prior work has demonstrated that BMI is a poor measure of muscle mass and surrogate marker for sarcopenia[18]. Prior work has also demonstrated that low BMI does not portend worse outcomes after lung transplant[39]. Thus, it is possible that frailty is a more accurate assessment of sarcopenia than is BMI.

Notably, it has been found that pre-transplant frailty increases mortality both before and after lung transplantation[13,14]. Importantly, emerging literature suggests that lung disease related frailty reverses after lung transplantation[40]. Thus, while pre-transplant frailty is a risk factor for death after transplant, current measures of frailty do not distinguish between lung related and other causes of frailty. For this reason, frailty should not be viewed as a contraindication to lung transplantation[40,41].

Compared to other diffuse lung diseases, patients with CF experience the greatest improvements in HRQL after lung transplantation[5–11]. This consistent finding across studies offers opportunity for future research efforts. Careful evaluation of patients with CF undergoing lung transplantation could identify reasons why other patient groups fail to achieve improved HRQL after lung transplantation. The observed relationship between frailty and HRQL in this study also suggests that frailty may be a latent factor after lung transplantation and a potential target for intervention. Interventions to improve frailty are largely speculative and rehabilitation based in advanced lung disease including cystic fibrosis. These include home based exercised regimens, pulmonary rehabilitation, and physical therapy as well as nutritional[42–47]. Interventions designed to improve frailty may be useful to maximize HRQL outcomes after lung transplantation.

Our study is not without limitations. Although prospective, this is a single center study. Additionally, while the overall number of participants in the “Breathe Again” study is large for studies of HRQL in lung transplantation, the number of participants with CF was modest. Further, while a battery of well-validated instruments was used to assess HRQL across multiple domains, the CF specific Cystic Fibrosis Questionnaire Revised (CFQ-R) instrument was not used[30,48]. This was because “Breathe Again” was a study of all lung transplant recipients.

Despite these limitations, our study had several notable strengths. This was a multi-year prospective study that followed a cohort of participants longitudinally over time. We had minimal missing data and no loss to follow up. Further, this was the first study since 2004 to focus in-depth on patient-centered outcomes in patients with CF undergoing lung transplantation[10]. Since then, the system for lung allocation was overhauled in the U.S., with sicker patients now being prioritized for transplant[49]. This study provides contemporary CF-specific estimates of the impact of lung transplantation on disability and HRQL. Additionally, by comprehensively measuring multiple potential predictors at the same time, we were able to identify the novel effect of frailty on patient-centered outcomes independent of lung function.

In conclusion, patients with CF experience robust improvements in disability and HRQL after lung transplantation. The role of frailty in determining HRQL outcomes after lung transplantation in patients with cystic fibrosis is a potential area for future interventions to optimize HRQL after transplant.

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References:

1. Morrell MR, Kiel SC, Pilewski JM. Organ Transplantation for Cystic Fibrosis. Semin Respir Crit Care Med. 2019;40(6):842–856. [PubMed: 31887769]
2. Stephenson AL, Sykes J, Berthiaume Y, et al. Clinical and demographic factors associated with post-lung transplantation survival in individuals with cystic fibrosis. J Hear Lung Transplant. 2015;34(9):1139–1145.

3. Ramos KJ, Quon BS, Heltshe SL, et al. Heterogeneity in Survival in Adult Patients With Cystic Fibrosis With FEV1 < 30% of Predicted in the United States. Chest. 2017;151(6):1320–1328. [PubMed: 28115168]
4. Chambers DC, Cherikh WS, Goldfarb SB, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth adult lung and heart-lung transplant report—2018; Focus theme: Multiorgan Transplantation. J Hear Lung Transplant. 2018;37(10):1169–1183.
5. Singer JP, Katz PP, Soong A, et al. Effect of Lung Transplantation on Health-Related Quality of Life in the Era of the Lung Allocation Score: A U.S. Prospective Cohort Study. Am J Transplant. 2017;17(5):1334–1345. [PubMed: 27743488]
6. Singer LG, Chowdhury NA, Faughnan ME, et al. Effects of recipient age and diagnosis on health-related quality-of-life benefit of lung transplantation. Am J Respir Crit Care Med. 2015;192(8):965–973. [PubMed: 26131729]
7. Ramsey SD, Patrick DL, Lewis S, Albert RK, Raghu G. Improvement in quality of life after lung transplantation: a preliminary study. The University of Washington Medical Center Lung Transplant Study Group. J Heart Lung Transplant. 1995;14(5):870–877. [PubMed: 8800722]
8. Vasiliadis H-M, Collet J-P, Poirier C. Health-related quality-of-life determinants in lung transplantation. J Heart Lung Transplant. 2006;25(2):226–233. [PubMed: 16446225]
9. Smeritschnig B, Jaksch P, Kocher A, et al. Quality of life after lung transplantation: a cross-sectional study. J Heart Lung Transplant. 2005;24(4):474–480. [PubMed: 15797751]
10. Vermeulen KM, Van Der Bij W, Erasmus ME, Duiverman EJ, Koëter GH, TenVergert EM. Improved Quality of Life after Lung Transplantation in Individuals with Cystic Fibrosis. Pediatr Pulmonol. 2004;37(5):419–426. [PubMed: 15095325]
11. Finlen Copeland CA, Vock DM, Pieper K, Mark DB, Palmer SM. Impact of lung transplantation on recipient quality of life: a serial, prospective, multicenter analysis through the first posttransplant year. Chest. 2013;143(3):744–750. [PubMed: 23188377]
12. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M157.
13. Singer JP, Diamond JM, Gries CJ, et al. Frailty phenotypes, disability, and outcomes in adult candidates for lung transplantation. Am J Respir Crit Care Med. 2015;192(11):1325–1334. [PubMed: 26258797]
14. Singer JP, Diamond JM, Anderson MR, et al. Frailty phenotypes and mortality after lung transplantation: A prospective cohort study. Am J Transplant. 2018;18(8):1995–2004. [PubMed: 29667786]
15. Rozenberg D, Mathur S, Wickerson L, Chowdhury NA, Singer LG. Frailty and clinical benefits with lung transplantation. J Hear Lung Transplant. 2018;37(10):1245–1253.
16. Perez AA, Kleinhenz ME, Gao Y, et al. Improvements in lung function and frailty are associated with improved HRQL and less disability in patients with CF undergoing lung transplantation. In: North American Cystic Fibrosis Conference. Denver, Colorado.
17. Nagi S. Disability Concepts Revisited: Implications for Prevention. Washington, DC: National Academy Press; 1991.
18. Singer JP, Peterson ER, Snyder ME, et al. Body composition and mortality after adult lung transplantation in the United States. Am J Respir Crit Care Med. 2014;190(9):1012–1021. [PubMed: 25233138]
19. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis. Age Ageing. 2010;39(4):412. [PubMed: 20392703]
20. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-Extremity Function in Persons over the Age of 70 Years as a Predictor of Subsequent Disability. N Engl J Med. 1995;332(9):556–562. [PubMed: 7838189]
21. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49(2):M94.

22. Culver BH, Graham BL, Coates AL, et al. Recommendations for a Standardized Pulmonary Function Report. An Official American Thoracic Society Technical Statement. Am J Respir Crit Care Med. 2017;196(11):1463–1472. [PubMed: 29192835]
23. Singer JP, Blanc PD, Dean YM, et al. Development and validation of a lung transplant-specific disability questionnaire. Thorax. 2014;69(5):437–442. [PubMed: 24355825]
24. Singer JP, Yusen RD. Defining patient-reported outcomes in chronic obstructive pulmonary disease: the patient-centered experience. Med Clin North Am. 2012;96(4):767. [PubMed: 22793944]
25. Beaton D, Boers M, Wells G. Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. Curr Opin Rheumatol. 2002;14(2):109–114. [PubMed: 11845014]
26. Ware JE, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. Med Care. 1996;34(3):220–233. [PubMed: 8628042]
27. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy (New York). 1990;16(3):199–208.
28. Norman GR, Sloan JA, Wyrwich KW. Interpretation of Changes in Health-related Quality of Life. Med Care. 2003;41(5):582–592. [PubMed: 12719681]
29. Chen H, Eisner MD, Katz PP, Yelin EH, Blanc PD. Measuring disease-specific quality of life in obstructive airway disease: validation of a modified version of the airways questionnaire 20. Chest. 2006;129(6):1644. [PubMed: 16778287]
30. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. Chest. 2005;128(4):2347–2354. [PubMed: 16236893]
31. Rozenberg D, Wickerson L, Singer LG, Mathur S. Sarcopenia in lung transplantation: a systematic review. J Heart Lung Transplant. 2014;33(12):1203–1212. [PubMed: 25044057]
32. Hollander FM, van Pierre DD, de Roos NM, van de Graaf EA, Iestra JA. Effects of nutritional status and dietetic interventions on survival in Cystic Fibrosis patients before and after lung transplantation. J Cyst Fibros. 2014;13(2):212–218. [PubMed: 24041590]
33. Abbott J, Hurley MA, Morton AM, Conway SP. Longitudinal association between lung function and health-related quality of life in cystic fibrosis. Thorax. 2013;68(2):149–154. [PubMed: 23143792]
34. Sawicki GS, Sellers DE, Robinson WM. Self-Reported Physical and Psychological Symptom Burden in Adults with Cystic Fibrosis. J Pain Symptom Manage. 2008;35(4):372–380. [PubMed: 18215497]
35. Kolaitis NA, Soong A, Shrestha P, et al. Improvement in patient-reported outcomes after lung transplantation is not impacted by the use of extracorporeal membrane oxygenation as a bridge to transplantation. J Thorac Cardiovasc Surg. 2018;156(1):440–448.e2. [PubMed: 29550072]
36. Laird NM. Missing data in longitudinal studies. Stat Med. 1988;7(1–2):305–315. [PubMed: 3353609]
37. Cohen-Cymberknoh M, Shoseyov D, Kerem E. Managing Cystic Fibrosis. Am J Respir Crit Care Med. 2011;183(11):1463–1471. [PubMed: 21330455]
38. Calella P, Valerio G, Brodlie M, Donini LM, Siervo M. Cystic fibrosis, body composition, and health outcomes: a systematic review. Nutrition. 2018;55–56:131–139.
39. Ramos KJ, Kapnadak SG, Bradford MC, et al. Underweight Patients With Cystic Fibrosis Have Acceptable Survival Following Lung Transplantation: A United Network for Organ Sharing Registry Study. Chest. 1 2020.
40. Venado A, McCulloch C, Greenland JR, et al. Frailty trajectories in adult lung transplantation: A cohort study. J Heart Lung Transplant. 3 2019.
41. Kobashigawa J, Dadhania D, Bhorade S, et al. Report from the American Society of Transplantation on frailty in solid organ transplantation. Am J Transplant. 2019;19(4):984–994. [PubMed: 30506632]
42. Candemir I, Ergun P, Kaymaz D, et al. The Efficacy of Outpatient Pulmonary Rehabilitation After Bilateral Lung Transplantation. J Cardiopulm Rehabil Prev. 2019;39(4):E7–E12. [PubMed: 31241521]

43. Kidd T, Mold F, Jones C, et al. What are the most effective interventions to improve physical performance in pre-frail and frail adults? A systematic review of randomised control trials. BMC Geriatr. 2019;19(1):184. [PubMed: 31291884]
44. Singer JP, Soong A, Bruun A, et al. A mobile health technology enabled home-based intervention to treat frailty in adult lung transplant candidates: A pilot study. Clin Transplant. 2018;32(6):e13274. [PubMed: 29742287]
45. Marcucci M, Damanti S, Germini F, et al. Interventions to prevent, delay or reverse frailty in older people: a journey towards clinical guidelines. BMC Med. 2019;17(1):193. [PubMed: 31660959]
46. Abizanda P, López MD, García VP, et al. Effects of an oral nutritional supplementation plus physical exercise intervention on the physical function, nutritional status, and quality of life in frail institutionalized older adults: The ACTIVNES study. J Am Med Dir Assoc. 2015;16(5):439.e9–439.e16.
47. Latham NK, Harris BA, Bean JF, et al. Effect of a home-based exercise program on functional recovery following rehabilitation after hip fracture: A randomized clinical trial. JAMA - J Am Med Assoc. 2014;311(7):700–708.
48. Schmidt A, Wenninger K, Niemann N, Wahn U, Staab D. Health-related quality of life in children with cystic fibrosis: validation of the German CFQ-R. Health Qual Life Outcomes. 2009;7:97. [PubMed: 19954541]
49. Egan TM, Murray S, Bustami RT, et al. Development of the new lung allocation system in the United States. Am J Transplant. 2006;6(5 Pt 2):1212–1227. [PubMed: 16613597]

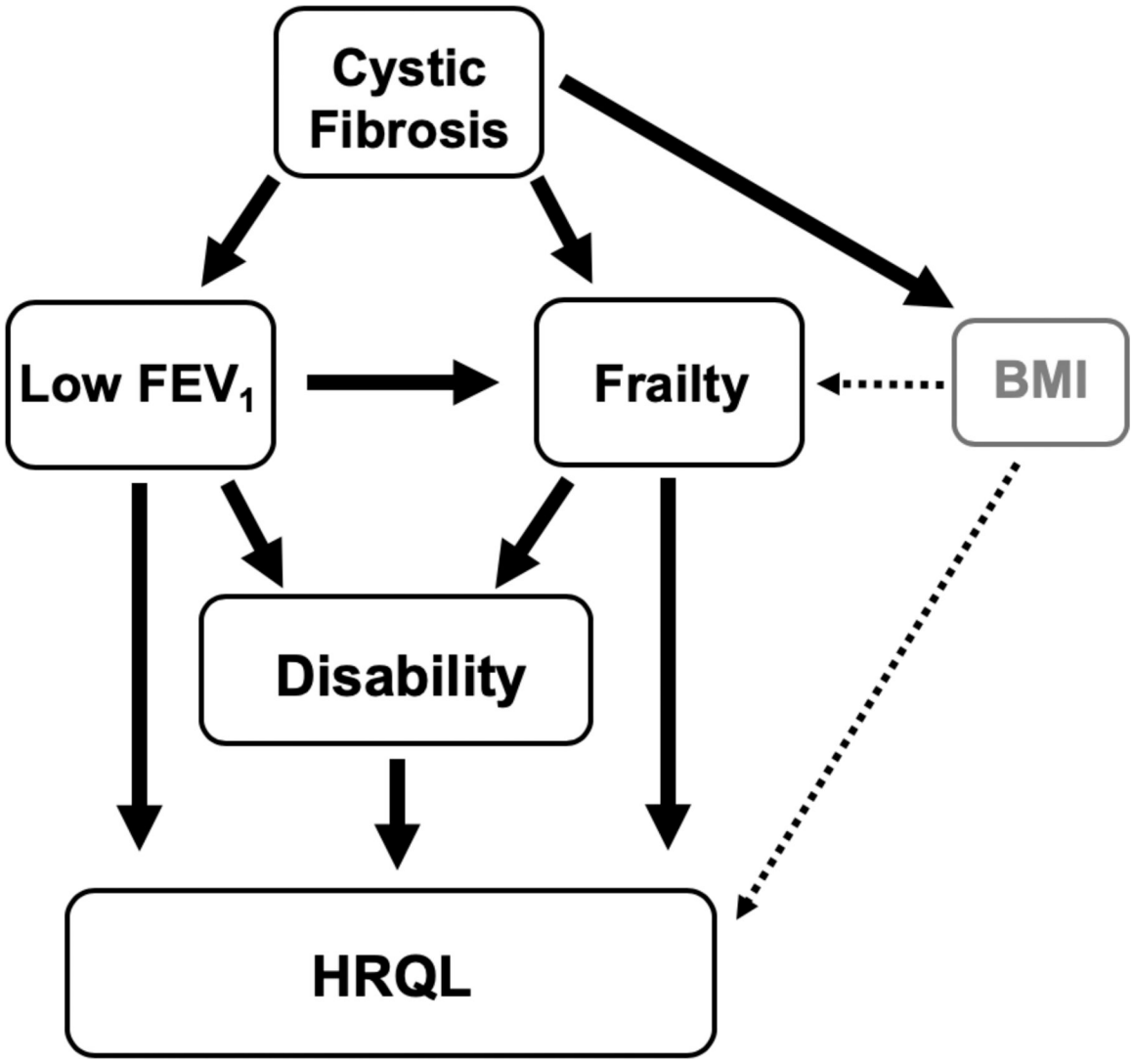


Figure 1:
Conceptual model of the relationship between cystic fibrosis, frailty, disability, and HRQL. FEV_1, Forced expiratory volume in 1 second; BMI, body mass index; HRQL, health related quality of life.

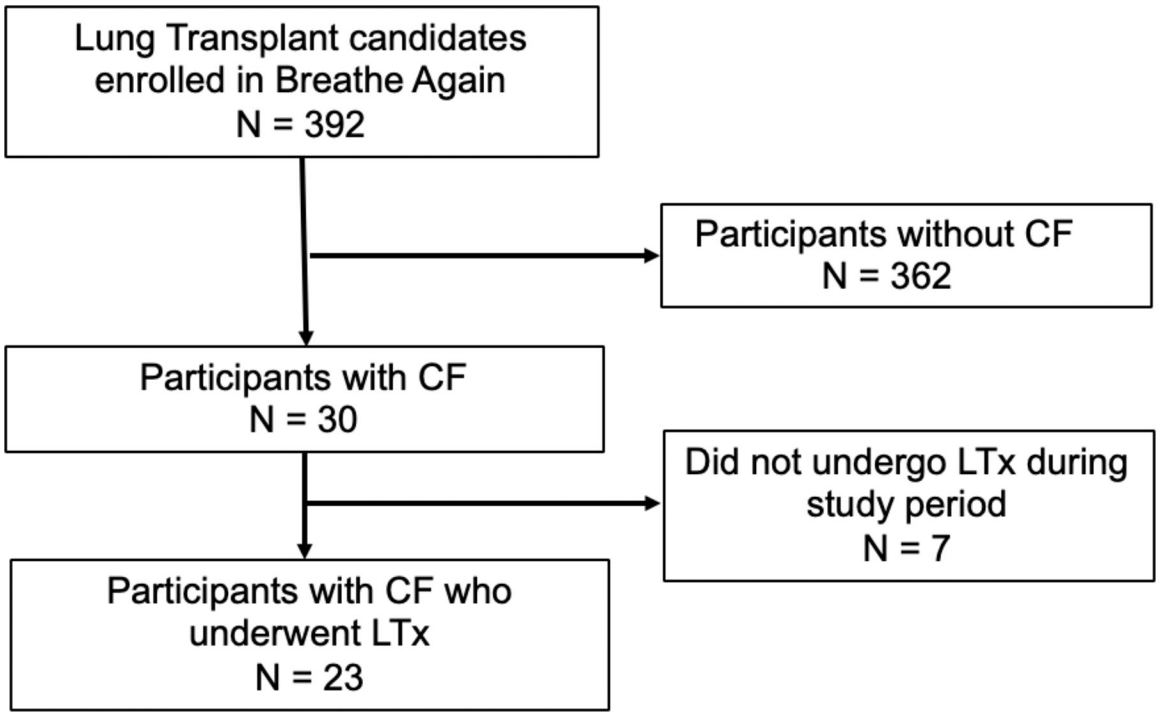
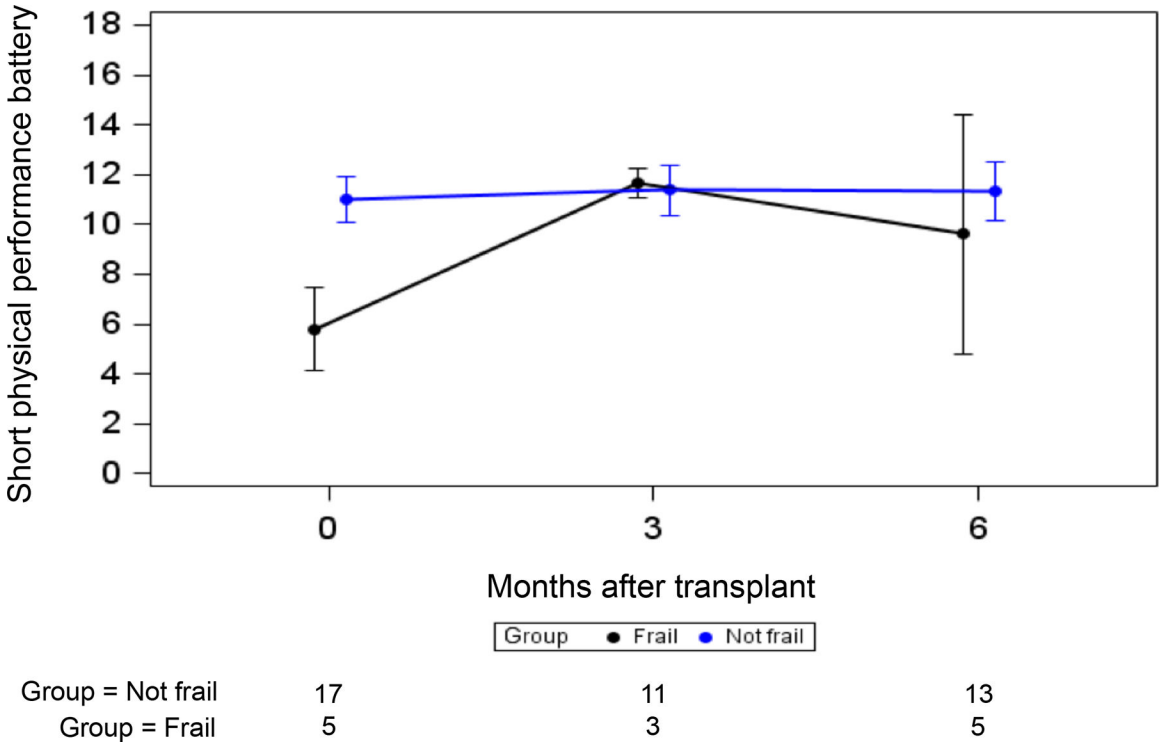


Figure 2:
Flow chart of Breathe Again study participants



Group = Not frail	17	11	13
Group = Frail	5	3	5

Figure 3:
Frailty trajectory after lung transplant. CF, cystic fibrosis; LTx, lung transplantation.

Table 1:
Baseline Demographic and Clinical Variables of Cystic Fibrosis Cohort

Data presented as mean ± SD or n (%)	
Age, years	31.0 ± 7.9
Female	12 (52%)
White	21 (91%)
Black/African American	1 (4.4%)
Other	1 (4.4%)
LAS	49.9 ±18.3 (range 34.0–94.0)
FEV_1 liters	0.9 ± 0.5
FVC, liters	1.7 ± 0.6
BMI kg/m^2	20.4 ± 2.7 (range 15.9–27.0)
6MWD, meters	331.2 ± 154.7 (range 69.5–701.0)
Frail pre-transplant	5 (21.7%)
Inpatient pre-transplant	6 (26.1%)
Mechanical ventilation pre-transplant	4 (17.4%)
ECMO pre-transplant	2 (8.7 %)

LAS = lung allocation score (range 0–100); FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; BMI = body mass index; 6MWD = 6-minute walk distance; SPPB = short physical performance battery. Frail defined as SPPB ≤ 7; ECMO = extracorporeal membrane oxygenation.

Table 2:
Changes in Frailty, BMI, Lung Function, Disability, and HRQL

	Baseline	Three months after LTx	Six months after LTx	Difference*, 95% confidence interval	MCID*
SPPB (MCID=1)	9.8 (± 2.5)	11.4 (± 0.9)	10.8 (± 2.7)	1.1 (−0.2, 2.4)	1.1-fold
BMI$^{\lambda}$ (m/kg^2)	20.4 (± 2.7)	20.9 (± 2.9)	21.7 (± 3.0)	1.5 (1.0, 2.1)	N/A
FEV$_1$$^{\circ}$(L) (MCID=200cc)	0.9 (± 0.5)	3.1 (± 0.7)	3.3 (± 0.7)	2.4 (2.2, 2.7)	12.0-fold
LT-VLA (MCID=0.3)	1.6 (± 0.6)	0.3 (± 0.2)	0.3 (± 0.6)	−1.3 (−1.6, −1.1)	4.3-fold
SF12-PCS (MCID=5)	21.0 (± 7.2)	51.1 (± 8.8)	54.5 (± 8.4)	33.0 (28.9, 37.1)	6.6-fold
SF12-MCS (MCID=5)	46.3 (± 7.5)	56.7 (± 8.3)	53.5 (± 9.4)	7.6 (3.7, 11.5)	1.5-fold
AQ20-R (MCID=1.75)	15.00 (± 1.98)	3.37 (± 2.43)	2.58 (± 2.01)	−12.41 (−13.64, −11.19)	7.1-fold
EQ5D (MCID=0.06)	0.56 (± 0.29)	0.90 (± 0.09)	0.90 (± 0.16)	0.34 (0.23, 0.46)	5.7-fold

Baseline, three months after LTX, and six months after LTX data presented as mean (± SD).

Differences were estimated by linear mixed effects models.

*Difference and MCID between baseline and 6-months after LTx

$^{\lambda}$Range for BMI m/kg^2: before LTx: 15.9–27.0; 6-months after LTx:16.1–28.6

$^{\circ}$Range for FEV$_1$ L: before LTx: 0.4–2.8; 6-months after LTx: 2.1–5.0.

LTx = lung transplant; MCID = minimally clinically important difference. SPPB = short physical performance battery; range 0–12; lower score denotes worse frailty. BMI = body mass index, m/kg^2. FEV$_1$ = forced expiratory volume in 1 second. LT-VLA = Lung Transplant Valued Life Activies; range 0–3; higher score denotes more disability. SF12-PCS = Medical Outcomes Study Short Form 12 Physical Component Summary scale; range 0–100; higher scores denote better HRQL. SF12-MCS = Medical Outcomes Study Short Form 12 Mental Component Summary scale; range 0–100, higher scores denote better HRQL. AQ20-R = Airway Questionnaire 20-Revised; range 0–20; lower score denotes better HRQL. EQ5D = Euroqol 5D; range −0.11–1; higher scores denote better HRQL.

Table 3:
Effects of Changes in Frailty, Lung Function, and BMI on Disability and HRQL

	LT-VLA MCID=0.3	SF12-PCS MCID=5	SF12-MCS MCID=5	AQ20-R MCID=1.75	EQ5D MCID=0.06
Frailty$^{\gamma}$ (SPPB)	−0.14* (−0.2, −0.08)	0.4 (−0.7, 1.5)	1.4* (0.7, 2.0)	−0.36 (−0.76, 0.04)	0.05* (0.03, 0.07)
Lung Function$^{\gamma}$ (FEV_1)	−0.07* (−0.09, −0.05)	2.1* (1.7, 2.5)	0.5* (0.2, 0.7)	−0.78* (−0.92, −0.64)	0.02* (0.01, 0.03)
BMI$^{\theta}$	0.03 (−0.01, 0.08)	−0.9 (−2.0, 0.1)	−0.2 (−1.1, 0.7)	0.01 (−0.39, 0.42)	0.01 (−0.01, 0.03)

Effect estimates (95% confidence intervals) reflect the change in disability or HRQL instrument per 1 point improvement in in SPPB, 200 mL improvement in FEV_1, and 1 point improvement in BMI by linear mixed effect models.

$^{\gamma}$adjusted for FEV_1 or SPPB; sex, and BMI.

$^{\theta}$adjusted for FEV_1, SPPB, and sex.

*Denotes $p<0.05$.

SPPB = short physical performance battery; FEV_1 = forced expiratory volume in 1 second; BMI = body mass index; MCID = mean clinically important difference; Disability: LT-VLA = Lung Transplant Valued Life Activies, higher score denotes more disability; HRQL: SF12-PCS = Medical Outcomes Study Short Form 12 Physical Component Summary scale, higher score denotes better HRQL; SF12-MCS = Medical Outcomes Study Short Form 12 Mental Component Summary scale, higher score denotes better HRQL; AQ20-R = Airway Questionnaire 20-Revised, lower score denotes better HRQL; EQ5D = Euroqol 5D, higher score denotes better HRQL.