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## Frailty and Geriatric Conditions in Older Patients with Idiopathic Pulmonary Fibrosis

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### Abstract

**BACKGROUND:** Functional status, an important predictor of health outcomes in older patients, has not been studied in an IPF population. This study aimed to determine the prevalence of frailty and geriatric conditions in older patients with IPF.

**METHODS:** IPF patients age ≥ 65 years were identified prospectively at the University of Michigan. Frailty was assessed using the Fried frailty phenotype. Questionnaires addressing functional status, geriatric conditions and symptoms were administered. Quantitative measurement of pectoralis muscle area was performed. Patient variables were compared among different frailty groups.

**RESULTS:** Of the 50 participants, 48% were found to be frail and 40% had ≥ 2 geriatric conditions. Frailty was associated with increased age, lower lung function, shorter 6-minute walk distance, higher symptom scores and a greater number of comorbidities, geriatric conditions and functional limitations ( $p < 0.05$ ). Pectoralis muscle area was nearly significant ( $p = 0.08$ ). Self-reported fatigue score (odds ratio [OR]=2.13, confidence interval [CI] 95% 1.23–3.70,  $p = 0.0068$ ) and diffusion capacity (OR=0.54 CI 95% 0.35–0.85,  $p = 0.0071$ ) were independent predictors of frailty.

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**CONCLUSIONS:** Frailty and geriatric conditions are common in older patients with IPF. The presence of frailty was associated with objective (diffusion capacity) and subjective (self-reported fatigue score) data. Longitudinal evaluation is necessary to determine impact of frailty on disease-related outcomes in IPF.

### Keywords

idiopathic pulmonary fibrosis; frailty; geriatric conditions; body composition

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## INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial pneumonia of unknown etiology that occurs primarily in older adults and is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (1). The incidence and prevalence of IPF increase almost exponentially with each decade of life and two thirds of patients are >60 at time of presentation (2). Furthermore, IPF has been shown to share common pathophysiologic mechanisms with the aging process itself (3). While the pathologic process in IPF is thought to be limited to the lungs, IPF may have extra-pulmonary impact and comorbidities are common at diagnosis and as disease progresses.

Frailty is characterized as a generalized vulnerability to stressors, resulting from cumulative declines across multiple physiologic systems, causing susceptibility to adverse outcomes (4). Frailty is highly prevalent with increasing age and confers higher risk for adverse health outcomes. Markers of frailty include age-associated declines in lean body mass, strength, endurance, balance, walking performance and low activity (4). Frailty and deconditioning have been suggested as important comorbidities associated with IPF in elderly patients (age 65) specifically (5). Geriatric conditions are a collection of symptoms and signs common in older adults not necessarily related to a specific disease that are precipitated by a variety of acute insults (often episodic) and are often followed by functional decline (6, 7). Functional status is one of the most important predictors of health outcomes in older patients and becomes more predictive than specific diagnoses as people age (8). Clinical frailty has been associated with decreased survival in chronic obstructive pulmonary disease (COPD) (9); however, this outcome has not been studied in an IPF population and the prevalence in IPF is unknown.

Our goal was to determine the prevalence of clinical frailty and geriatric conditions in older patients with IPF. We hypothesized that geriatric conditions and frailty, as manifestations of aging, are frequent in persons with IPF, with higher prevalence than published controls, elderly patients in the general population (4, 7, 9). To explore the association between frailty and body composition we also performed quantitative assessment of thoracic muscles in persons with IPF.

## MATERIAL & METHODS

### Patient Selection & Data Collection

Patients age  $\geq 65$  years with IPF based on the American Thoracic Society international consensus definition were identified prospectively through the University of Michigan pulmonary clinics for inclusion (1). All disease severities were included with no limitations based on treatment. Non-ambulatory patients were excluded. The study was organized as a pilot study to address the utility of assessing frailty in a new population, IPF patients  $\geq 65$ , therefore a target of 50 patients was selected. Patients were recruited from March 14, 2016, to July 22, 2016. Participants provided written informed consent for participation. Very few subjects approached regarding the study ultimately declined to participate due to time constraints (i.e. subsequent appointments, travel). The institutional review board at the University of Michigan approved this study (HUM00110674).

### Frailty Assessment

Several validated measures of frailty have been described in the literature, which have been derived from distinct theoretical views on how frailty develops and manifests in older adults (10). Models address frailty as deficiencies in functional domains, an index of cumulative health burden, a biological syndrome, and a battery of lower extremity performance measures (4, 11–14). The Fried Biologic Syndrome model is commonly used (4, 13, 15–18), and was chosen for this evaluation based on its emphasis on physical functioning with both objective and subjective measures that can be rapidly assessed in the clinical setting. The Fried Frailty Phenotype (FFP) is an aggregate score of five components: shrinking, weakness, exhaustion, slowness and low physical activity (4). A categorical scoring system identifies participants with FFP score  $\geq 3$  as frail, 1–2 as pre-frail, and 0 as not frail (4). Self-reported performance measures have been used in place of physical performance measures with replicable results (10, 13, 19). These self-reported measures were chosen to simplify frailty assessment for ease of implementation in the clinical setting and to decrease patient burden. Use of hand-grip strength testing was maintained. Details on frailty measures and scoring are provided in Table E1 in the online supplement.

### Geriatric Conditions, Functional Limitations and Measures of Disability & Dependence

The instruments and measures of geriatric conditions, functional limitations, activities of daily living (ADL) and instrumental-ADL (IADL) utilized in our evaluation were based on those used in the Health and Retirement Study, which are available in public domain and have been extensively validated (7, 20–23). Geriatric conditions assessed include incontinence, dizziness, vision impairment, hearing impairment and falls. The specific ADL, IADL and functional limitations assessed are outlined in Table E2 of the online supplement.

### Quantitative Pectoralis Muscle Mass Determination

Computerized tomography (CT) based assessments of muscle area have been increasingly performed in COPD populations to assess disease-related outcomes (24–26), but have not been evaluated in IPF. Quantitative assessment of pectoralis muscle area (PMA) was performed on a single axial slice of the CT scan above the aortic arch using Slicer body

composition software ([www.slicer.org](http://www.slicer.org)), a slice chosen due to ease of identification and replicability (Figure 1) (26, 27). Muscles were manually shaded, using a predefined attenuation range of  $-50$  to  $90$  Hounsfield units (26, 27). PMA was presented as the aggregate area (in  $\text{mm}^2$ ) of the right and left pectoralis major and minor assessed in this axial plane. The last available CT for each patient was used for analysis. Chest CTs completed within 6 months of study inclusion were prioritized for evaluation if available ( $n=22$ ).

### Other Measures

Clinical and physiologic data obtained as part of routine evaluation were recorded. Comorbidities were based on documented history and active medications. The University of California San Diego Shortness of Breath questionnaire (UCSD-SOBQ) was used to assess the level of dyspnea or breathlessness (28, 29). The Fatigue Severity Scale (FSS) was administered to assess fatigue (30).

### Statistical Analysis

Binary and ordinal comparisons were performed among different frailty groups (frail, pre-frail or not frail). Descriptive statistics were used to describe patient variables. For associations of frailty with other factors, the Cochran-Armitage trend test p-value was used. A p-value of 0.05 was used as the threshold for statistical significance. Univariate analysis was performed using binary logistic regression to identify odds ratio for frailty for each individual variable. Best-fit multivariable logistic regression models that were age-adjusted were utilized to identify factors that were independent predictors of frailty.

## RESULTS

Of the 50 participants enrolled, age ranged from 65 to 86 years. Complete demographic data are presented in Table 1. Frailty was more common in our elderly IPF cohort, occurring in 48% ( $n=24$ ), compared to 6.9% in the general population over age 65 in the Cardiovascular Health Study (4). The prevalence of individual components of the FFP is shown in Table E3 in the online supplement. Unintentional weight loss was the most common frailty criteria met in pre-frail participants and the only category without a statistically significant difference among frailty group comparisons.

Geriatric conditions were also more prevalent in our cohort with 40% reporting  $\geq 2$  geriatric conditions, compared to 19.5% with  $\geq 2$  geriatric conditions in the 2000 wave of the Health and Retirement (7). Of the 20 participants with  $\geq 2$  geriatric conditions, 45% were found to be frail. Of the 30 participants with  $<2$  geriatric conditions, 50% were found to be frail.

We explored the frequency of frailty based on the severity of other individual variables, including FVC, DLCO and the number of functional limitations and comorbidities (Table 2). Severity cut-offs for FVC and DLCO were based on median values as well as phase III clinical trial inclusion criteria identifying mild-to-moderate disease (FVC  $\geq 50\%$  predicted, DLCO  $\geq 35\%$  predicted) (31–33). The median value was used for functional limitations. For comorbidities,  $\geq 4$  comorbid conditions were chosen based on previously published data (34).

Overall, there was a high burden of comorbid conditions, with a mean of 6.0 (SD 2.2) amongst all participants, with 86% having 4 comorbid conditions. Comorbidities identified in our cohort were similar to those reported in publications investigating impact of comorbidities in IPF (34), including cardiovascular diseases, gastroesophageal reflux disease, COPD, psychiatric conditions, diabetes, obstructive sleep apnea, hyperlipidemia, cancer, thromboembolic disease and obesity. No participants were undergoing active therapy for malignancy at time of study inclusion. Gastroesophageal reflux, hyperlipidemia and arterial hypertension were most frequently observed, documented in 68–76% of participants. Obesity, defined as BMI  $\geq 30$ , was found in 46%. Please refer to online supplement Table E4 for full breakdown of comorbid conditions as well as comorbidity-associated therapies.

The presence of frailty was associated with statistically significant ( $p < 0.05$ ) differences in age, FVC, forced expiratory volume, DLCO, 6-minute walk distance (6MWD), dyspnea/fatigue scores and the number of comorbidities, geriatric conditions and functional limitations (Table 1). There was no difference in sex, smoking status, BMI or the use of antifibrotic agents. While there was a trend towards a difference in PMA between frailty groups (frail participants with lower PMA), this did not reach statistical significance ( $p = 0.08$ ). Four participants (3 pre-frail, 1 frail) were excluded from PMA analysis due to inadequate CT. The average time between CT and frailty assessment was 12 months (median 9 months prior, range 7.5 years prior to 6 months post inclusion). There was a significant difference in self-reported difficulty with ADLs and IADLs, but not dependency. The minimal clinically important difference for the UCSD-SOBQ in IPF has been estimated as 5–11 points (28, 29, 35). For the FSS, a score of  $>36$  is indicative of severe fatigue or need for further evaluation (30). Therefore, the difference in symptom scores across frailty groups also met clinical significance (Table 1).

Univariate analysis using binary logistic regression (frail versus not frail/pre-frail) determined odds ratio for the presence of frailty using each individual parameter listed in table 1 (Table 3). Best-fit multivariable logistic regression models, adjusted for age, identified both self-reported fatigue score (OR=2.13, CI 95% 1.23–3.70,  $p = 0.0068$ ) and DLCO (OR=0.54 CI 95% 0.35–0.85,  $p = 0.0071$ ) as independent predictors of frailty (AUC=0.82 and 0.81, respectively) (Figure 2). DLCO & self-reported fatigue score were negatively correlated,  $r = -0.73$   $p < 0.0001$ , with clustering of frail patients in area of low DLCO and high fatigue score (Figure 3). This strong correlation, limited the ability of these two factors to be utilized in the same model. When PMA was incorporated into multivariable models with age and self-reported fatigue score, we found a statistically significant association between PMA and frailty status with higher overall AUC (0.83) (Figure 2).

## DISCUSSION

In our pilot study of fifty patients aged 65 or older with IPF, we found that frailty as defined by the Fried Frailty Phenotype and geriatric conditions (incontinence, dizziness, vision impairment, hearing impairment and/or falls) are common comorbidities. The presence of frailty is associated with both objective & subjective disease measures, including low DLCO and high self-reported fatigue scores, with possible association with PMA, a novel measure

in patients with IPF. Although frailty appears to be associated with patient characteristics indicative of more severe disease or a higher number of comorbid conditions, it is also a recognizable parameter in patients with more preserved pulmonary function and less comorbidity.

When compared to published controls, frailty and geriatric conditions are more prevalent in patients with IPF over age 65 than the general population. Frailty as defined by multiple different models has been found to be predictive of falls, hospitalization, disability, institutionalization, death and reduced health-related quality of life (HRQOL) in geriatric populations (4, 9, 36). Frailty and respiratory impairment have been shown to have a strong association with increased risk of death in the elderly when both are present (37). In a lung transplant population, frailty was common and independently associated with patient-reported disability and subsequent delisting or death before transplant (18). Furthermore, among patients with IPF awaiting lung transplant, the 6MWD has been shown to be more predictive of survival at 6 months than lung function (38), suggesting that walk distance is capturing more than just lung function. Distinguishing frail from fit elderly in an aging population with chronic lung disease such as IPF may enhance risk assessment of a vulnerable population.

Frailty correlates with both objective and subjective variables including low DLCO and high self-reported fatigue scores. While there was a statistically significant difference in FVC across different frailty groups and on univariate analysis, the association was lost when this variable was incorporated in multivariate models adjusted for age, DLCO and fatigue score. Adverse symptoms commonly reported with antifibrotic therapy, such as nausea, diarrhea and fatigue (31–33, 39), could also impact frailty; however, there was no difference in antifibrotic use among frailty groups. While the presence of frailty correlates with objective markers of disease severity, such as reduced lung function and supplemental oxygen use, patients were identified that met frailty criteria but had relatively preserved pulmonary function. Conversely, patients with severe lung disease were not uniformly frail. These data suggest that while patients with more severe disease may be at increased risk of being frail, frailty may also be an independent marker with the potential to be modifiable at all disease stages.

Unintentional weight loss, an important component of the Fried frailty model, may be missed in overweight or obese patients. BMI does not address low muscle mass and sarcopenia, which still can be present in obese patients. Quantitative assessment of thoracic muscles represents a new potential target for evaluation in patients with IPF. Our investigation of PMA demonstrated a possible association with frailty status, with increased significance when incorporated into multivariable models. As our evaluation was limited by small sample size and timing of CT scans (completed an average of one year prior to frailty assessment), further analyses were not performed. CT is critical in the diagnostic algorithm of ILD, particularly IPF (1). Furthermore, there has been recent interest in using quantitative and semi-quantitative measures of CT features to predict outcomes in IPF. PMA represents a new measure, outside of usual parenchymal evaluation and spirometric measures, that could be applied to existing clinically acquired CT scans of the chest and may provide additional clinically relevant insight into patients with IPF.



The impact of multiple comorbidities on mortality represents an evolving area of interest in IPF. A patient's total number of comorbidities has been significantly associated with survival in IPF (34). Although valuable, geriatric conditions and frailty specifically were not addressed. Geriatric conditions have been shown to have similar prevalence to chronic diseases in older adults and in some cases are as strongly associated with disability (7). These conditions are clinically relevant as they can be prevented or delayed (7), and are not current targets of IPF management. Frailty is conventionally considered secondary to age-related decline, however, chronic disease(s) can accelerate the rate of decline and precipitate a frail state (40). The modified FFP as applied here has the potential for easy applicability in a clinical setting to rapidly identify frail patients that may benefit from further evaluation and intervention.

In a disease where treatment options are limited, establishing interventions that improve symptoms and function can have a positive impact on HRQOL. Prior investigations have highlighted the ability to improve frailty status with a multifactorial interdisciplinary approach utilizing targeted exercise and nutrient based interventions in both general geriatrics and COPD (40–42). However, the impact of these interventions on long-term outcomes is unknown and their impact in IPF has not been addressed. Pulmonary rehabilitation (PR) may represent a specific modality within chronic lung disease to address clinical frailty. Two controlled trials of PR in IPF have demonstrated improvement in 6MWD and symptoms or quality of life (43, 44), with benefits more pronounced in patients with worse baseline functional status (45). Frailty measures may identify more patients who are likely to benefit from PR. However, the ability to improve frailty status with PR is unknown.

Our study is the first prospective evaluation of the prevalence of frailty and geriatric conditions in an IPF-specific population. However, there were some notable limitations to our evaluation. First, this was a pilot study with a small sample size, at a single center. With the cross-sectional study design, we cannot infer causal mechanisms between IPF and frailty. Symptom scores were utilized as a surrogate for HRQOL, though direct HRQOL measures would likely add to assessment. Our frailty model depended on patient report for 4 out of 5 frailty measures. While similar methods were used in prior evaluations, there is opportunity for further validation of our adapted frailty model. Patients were also identified at various time points in disease course for inclusion; some shortly after diagnosis, others having survived several years following diagnosis with minimal change in pulmonary function. Older patients with long standing disease may represent a “survivor” population, less apt to have functional limitation and disability. Given the social and psychological issues IPF patients may have, it is possible that an even greater percentage would be found to be frail if we were to look further outside of physical characteristics. It has been argued that some frailty components, such as low activity or exhaustion in the FFP may be confounded by lung disease itself. However, lung disease could promote frailty, thus placing this population at increased risk.

Age-related factors are infrequently assessed in pulmonary medicine, though may have significant impact, especially in diseases such as IPF, which are strongly associated with advanced age. While the exact physiologic effects of frailty in IPF are unknown, frailty and

geriatric conditions are common in elderly patients with IPF. Results of our evaluation suggest utility of further study of frailty and geriatric conditions in a larger cohort to validate conclusions and to evaluate the contribution of frailty and geriatric conditions to markers of disease progression in IPF, including symptoms, pulmonary function, disability and ultimately mortality. If longitudinally validated, functional measures could enhance traditional measures in predicting outcomes and response to interventions among patients with IPF.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## ABBREVIATIONS LIST

|                  |  |
|------------------|--|
| <b>6MWD</b>      | 6-minute walk distance   |
| <b>ADL</b>       | Activities of daily living   |
| <b>BMI</b>       | Body mass index  |
| <b>CI</b>        | Confidence interval  |
| <b>COPD</b>      | Chronic obstructive pulmonary disease                                |
| <b>CT</b>        | Computed tomography  |
| <b>DLCO</b>      | Diffusion capacity   |
| <b>FEV1</b>      | Forced expiratory volume   |
| <b>FFP</b>       | Fried frailty phenotype  |
| <b>FSS</b>       | Fatigue severity scale   |
| <b>FVC</b>       | Forced vital capacity  |
| <b>HRQOL</b>     | Health-related quality of life                                       |
| <b>IADL</b>      | instrumental activities of daily living                              |
| <b>IPF</b>       | Idiopathic pulmonary fibrosis  |
| <b>OR</b>        | Odds ratio   |
| <b>PMA</b>       | Pectoralis muscle area   |
| <b>PR</b>        | Pulmonary rehabilitation   |
| <b>UCSD SOBQ</b> | University of California San Diego shortness of breath questionnaire |



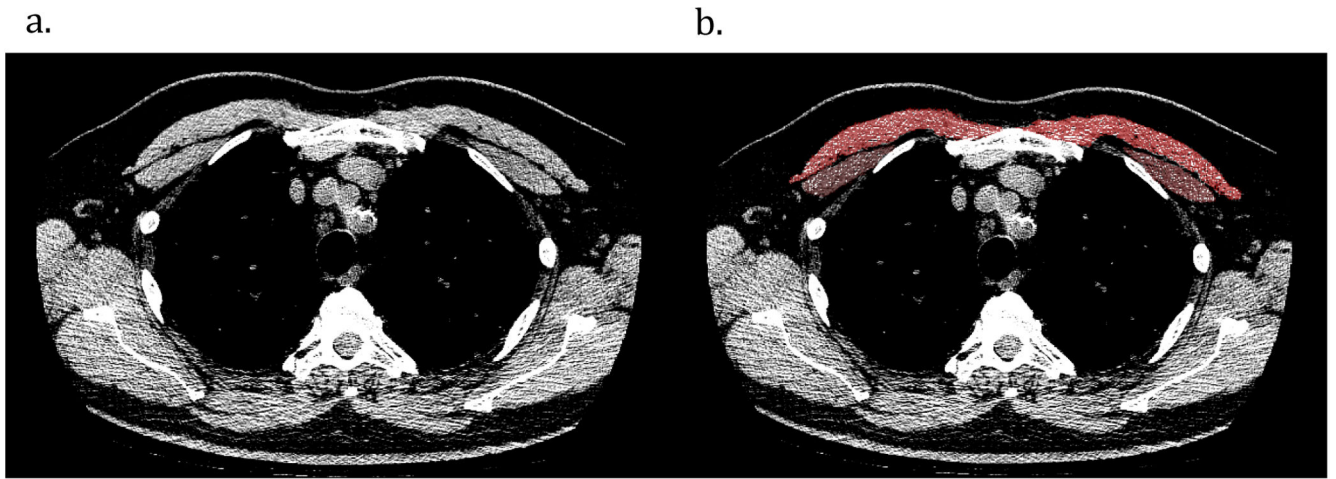
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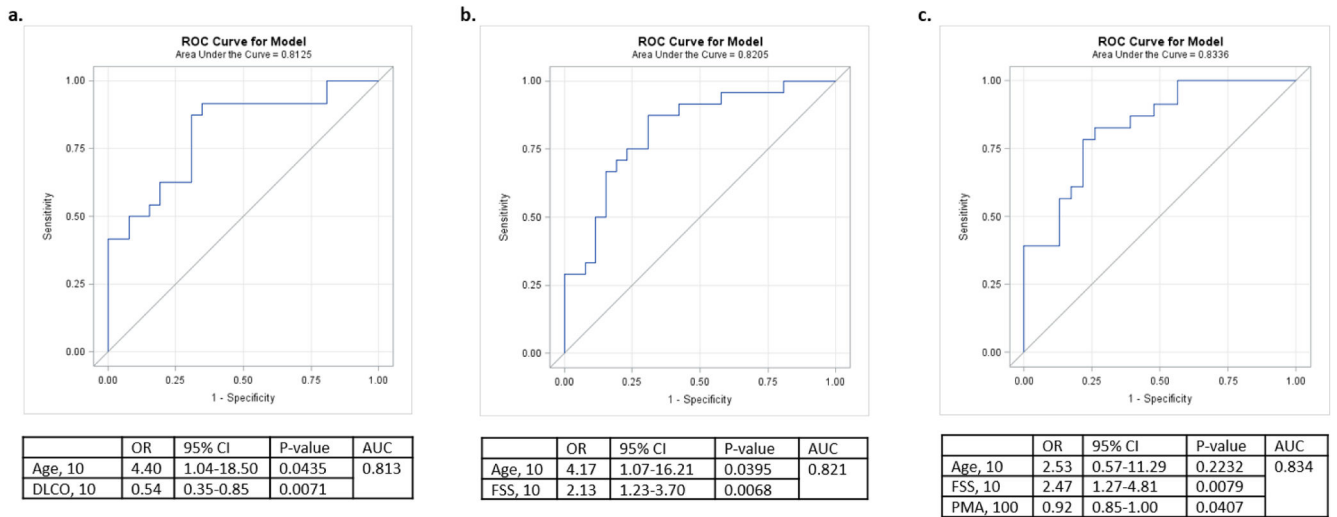
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**Figure 1.** Sample computed tomography (CT) scans used to determine muscle area in idiopathic pulmonary fibrosis patients. (a) CT image used for pectoralis muscle imaging. (b) Pectoralis muscles shaded in *red* and *brown*.



**Figure 2.** Multivariate models of frailty (yes versus no/pre). DLCO: diffusion capacity; FSS: fatigue severity scale; OR: odds ratio; PMA: pectoralis muscle area.



**Table1.**

Patient characteristics overall and by the presence of frailty\*

|   | All Patients<br>N=50 | Not Frail<br>N=6 (12%) | Pre-frail<br>N=20 (40%) | Frail<br>N=24 (48%) | Trend<br>P-value |
|---|----------------------|------------------------|-------------------------|---------------------|------------------|
| Age, years                              | 73.8 (5.4)           | 70.2 (4.4)             | 72.2 (5.6)              | 76.0 (4.5)          | 0.0032           |
| Male                                    | 33 (66.0%)           | 5 (83.3%)              | 14 (70.0%)              | 14 (58.3%)          | 0.2100           |
| Smoking                                 |                      |                        |                         |                     | 0.4366           |
| Never                                   | 16 (32.0%)           | 3 (50.0%)              | 6 (30.0%)               | 7 (29.2%)           |                  |
| Former                                  | 33 (66.0%)           | 3 (50.0%)              | 13 (65.0%)              | 17 (70.8%)          |                  |
| Current                                 | 1 (2.0%)             | 0                      | 1 (5.0%)                | 0                   |                  |
| BMI, kg/m <sup>2</sup>                  | 30.2 (4.4)           | 30.7 (3.8)             | 30.0 (4.8)              | 30.2 (4.3)          | 0.9041           |
| FVC, % predicted                        | 67.6 (15.8)          | 77.0 (6.3)             | 71.6 (15.0)             | 61.9 (16.3)         | 0.0102           |
| FVC, L                                  | 2.5 (0.9)            | 3.1 (0.6)              | 2.67 (0.7)              | 2.2 (0.9)           | 0.0045           |
| FEV1, % predicted                       | 81.7 (17.3)          | 95.0 (9.6)             | 85.7 (16.3)             | 75.1 (17.1)         | 0.0035           |
| FEV1, L                                 | 2.0 (0.6)            | 2.6 (0.6)              | 2.1 (0.5)               | 1.7 (0.6)           | 0.0008           |
| Ratio                                   | 82.2 (8.0)           | 83.5 (4.2)             | 81.5 (9.0)              | 82.3 (8.1)          | 0.9200           |
| DLCO, % predicted                       | 51.8 (18.8)          | 73.3 (10.7)            | 56.7 (16.4)             | 42.4 (16.5)         | <0.0001          |
| 6MWD, feet                              | 1117.7 (477.0)       | 1579 (494.3)           | 1150.9 (486.4)          | 989.7 (420.1)       | 0.0299           |
| Oxygen use                              | 12 (24.5%)           | 0                      | 3 (15.0%)               | 9 (39.1%)           | 0.0193           |
| Number of Comorbidities                 | 6.0 (2.2)            | 4.3 (1.5)              | 5.5 (2.0)               | 6.8 (2.2)           | 0.0050           |
| Antifibrotic Agent                      | 30 (60%)             | 3 (50%)                | 11 (55%)                | 16 (66.7%)          | 0.3545           |
| UCSD SOB                                | 37.4 (23.4)          | 6.5 (5.7)              | 33.2 (18.3)             | 48.7 (22.1)         | <0.0001          |
| FSS                                     | 37.5 (15.3)          | 17.5 (7.8)             | 34.2 (13.3)             | 45.2 (12.7)         | <0.0001          |
| Pectoralis muscle area, mm <sup>2</sup> | 2921.8 (1118.3)      | 3194.3 (833.9)         | 3271.7 (1396.8)         | 2592.0 (867.5)      | 0.0836           |
| Functional limitations                  | 4.2 (2.2)            | 1.5 (1.1)              | 3.4 (1.8)               | 5.6 (1.5)           | <0.0001          |
| Geriatric conditions <sup>†</sup>       | 1.3 (1.2)            | 0.2 (0.4)              | 1.1 (1.2)               | 1.8 (1.1)           | 0.0014           |
| ADL dependence                          | 0.1 (0.4)            | 0                      | 0.1 (0.2)               | 0.2 (0.5)           | 0.2164           |
| ADL difficulty                          | 0.5 (0.7)            | 0                      | 0.3 (0.6)               | 0.7 (0.9)           | 0.0128           |
| IADL dependence                         | 0.3 (0.8)            | 0.2 (0.4)              | 0.1 (0.2)               | 0.6 (1.1)           | 0.0592           |
| IADL difficulty                         | 0.5 (0.9)            | 0.2 (0.4)              | 0.1 (0.3)               | 0.9 (1.1)           | 0.0069           |

\* Frailty categories based on number of criteria met: not frail = 0; pre-frail = 1–2; frail = 3 (Fried frailty phenotype). Continuous variables are summarized by mean (standard deviation); categorical variables are summarized by count (percentage).

<sup>†</sup> Geriatric conditions include incontinence, vision impairment, hearing impairment, dizziness, falls.

Abbreviations: 6MWD=6-minute walk distance; ADL=activities of daily living; BMI=body mass index; DLCO=diffusion capacity; FEV1=forced expiratory volume; FSS=fatigue severity scale; FVC=forced vital capacity; IADL=instrumental activities of daily living; UCSD SOB=University of California San Diego shortness of breath questionnaire.



**Table 2.**

Frequency of frailty based on the severity of individual variables

| Variable<br>(n, %)                     |                               | Not Frail<br>n (%) | Frail<br>n (%) |
|--|-------------------------------|--------------------|----------------|
| FVC<br>(median 67.5% predicted)        | FVC ≥67.5% predicted (25, 50) | 17 (68)            | 8 (32)         |
|  | FVC <67.5% predicted (25, 50) | 10 (40)            | 15 (60)        |
|  | FVC ≥50% predicted (43, 86)   | 25 (58.1)          | 18 (41.9)      |
|  | FVC <50% predicted (7, 14)    | 1 (14.3)           | 6 (85.7)       |
| DLCO<br>(median 52% predicted)         | DLCO ≥52% predicted (26, 52)  | 16 (61.5)          | 10 (38.5)      |
|  | DLCO <52% predicted (24, 48)  | 10 (41.7)          | 14 (58.3)      |
|  | DLCO ≥35% predicted (40, 80)  | 25 (62.5)          | 15 (37.5)      |
|  | DLCO <35% predicted (10, 20)  | 1 (10)             | 9 (90)         |
| Functional limitations<br>(median 4.5) | <4.5<br>(25, 50)              | 15 (60)            | 10 (40)        |
|  | 4.5<br>(25, 50)               | 11 (44)            | 14 (56)        |
| Number of Comorbidities<br>(median 6)  | <4<br>(7, 14)                 | 3 (42.9)           | 4 (57.1)       |
|  | 4<br>(43, 86)                 | 23 (53.5)          | 20 (46.5)      |

Abbreviations: DLCO=diffusion capacity; FVC=forced vital capacity

**Table 3.**

Univariate regression analysis predicting the presence of frailty\*

|  | Frail vs. No/Pre-binary logistic |              |         |
|--|----------------------------------|--------------|---------|
|  | OR                               | 95% CI       | P-value |
| Age (per 10-year increase)   | 5.623                            | 1.555–20.328 | 0.0085  |
| Male   | 0.516                            | 0.157–1.691  | 0.2744  |
| Smoking  | 1.286                            | 0.389–4.247  | 0.6801  |
| BMI  | 1.003                            | 0.882–1.141  | 0.9614  |
| FVC, % predicted (per 10% increase)  | 0.610                            | 0.404–0.921  | 0.0187  |
| FVC, L   | 0.381                            | 0.176–0.827  | 0.0147  |
| FEV1, % predicted (per 10% increase)                                       | 0.608                            | 0.409–0.904  | 0.0140  |
| FEV1, L  | 0.226                            | 0.076–0.670  | 0.0073  |
| DLCO, % predicted (per 10% increase)                                       | 0.516                            | 0.338–0.787  | 0.0021  |
| 6MWD, feet (per 100 ft increase)   | 0.870                            | 0.735–1.031  | 0.1074  |
| Oxygen use   | 4.929                            | 1.138–21.347 | 0.0329  |
| Number of comorbidities  | 1.465                            | 1.064–2.016  | 0.0192  |
| UCSD SOB (per 10 point increase)   | 1.644                            | 1.189–2.274  | 0.0027  |
| FSS (per 10 point increase)  | 2.252                            | 1.347–3.763  | 0.0019  |
| Functional limitations   | 2.483                            | 1.522–4.051  | 0.0003  |
| Geriatric conditions <sup>†</sup>  | 2.016                            | 1.157–3.515  | 0.0134  |
| Pectoralis muscle area, mm <sup>2</sup> (per 100 mm <sup>2</sup> increase) | 0.94                             | 0.89–1.00    | 0.0525  |

\* Odds ratio (OR) presented for each variable is per 1-unit increase, unless otherwise listed

<sup>†</sup>Geriatric conditions include incontinence, vision impairment, hearing impairment, dizziness, falls.

Abbreviations: 6MWD=6-minute walk distance; BMI=body mass index; DLCO=diffusion capacity; FEV1=forced expiratory volume; FSS=fatigue severity scale; FVC=forced vital capacity; UCSD SOBQ=University of California San Diego shortness of breath questionnaire.