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Severity and features of frailty in systemic sclerosis-associated interstitial lung disease

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ABSTRACT

Background: Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is characterized by multiple symptoms and comorbidities. The cumulative impact of these deficits can be summarized using the concept of frailty; however, frailty has not been characterized in patients with SSc-ILD.
Methods: Patients with SSc-ILD and non-CTD fibrotic ILD were recruited from specialized clinics. Frailty was assessed using a 42-item patient-reported Frailty Index, calculated as the proportion of reported deficits divided by the total number of surveyed items. Frailty was defined as a Frailty Index >0.21. Unadjusted and multivariate analyses were used to identify correlates of frailty.
Results: The study cohort included 86 patients with SSc-ILD and 167 patients with non-CTD fibrotic ILD. The mean age in SSc-ILD was 60.5 years, 80% were women, and on average patients had mild to moderate restrictive lung function impairment (mean FVC 78%-predicted, DLCO 51%-predicted). The mean Frailty Index was 0.23 ± 0.15, with 55% of the SSc-ILD population meeting criteria for frailty. Dyspnea had the strongest association with the Frailty Index ($r = 0.62$, $p < 0.001$) and was the only variable independently associated with frailty on multivariate analysis. Frailty severity was similar in SSc-ILD and non-CTD fibrotic ILD, including with adjustment for differences in baseline cohort characteristics.
Conclusion: Frailty is highly prevalent in patients with SSc-ILD, indicating that chronological age significantly underestimates biological age in this population. Dyspnea is the variable with the strongest association with frailty in SSc-ILD; however, future studies are needed to identify additional modifiable determinants of frailty and the ability of frailty to predict outcomes in SSc-ILD.

1. Introduction

Systemic Sclerosis (SSc) is a multi-organ connective tissue disease (CTD) with frequent pulmonary complications. Interstitial lung disease (ILD) is the most common cause of mortality in SSc [1], occurring in more than half of patients with diffuse cutaneous SSc and more than one third of patients with limited cutaneous SSc [2]. Patients with SSc have other common manifestations, including dermatological, musculoskeletal, renal, gastrointestinal, and cardiac disease. The prevalence of SSc increases with age, resulting in frequent association with additional age-related comorbidities. The cumulative impact of the manifestations of SSc-ILD and comorbid diseases can be represented by the concept of frailty, which has been defined as the accumulation of multiple deficits that increase vulnerability to biological stress [3]. Frailty predicts mortality in SSc and multiple other chronic diseases [4], and may similarly be important in SSc-ILD.

We previously reported a high prevalence of frailty in non-CTD fibrotic ILD with a strong and independent association of frailty with dyspnea severity [5]; however, there are no studies describing the features of frailty in SSc-ILD. The objectives of the present study were to describe the prevalence and characteristics of frailty in SSc-ILD, and to compare the severity and features of frailty to patients with non-systemic ILD subtypes.

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Abbreviations

6MWD	6-minute walk distance
6MWT	6-minute walk test
ACR	American College of Rheumatology
CTD	connective tissue disease
DLCO	diffusion capacity of the lung for carbon monoxide
FEV1	forced expiratory volume in 1 s
FI	Frailty Index
FVC	forced vital capacity
HRCT	high-resolution computed tomography
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
NSIP	nonspecific interstitial pneumonia
PASP	pulmonary artery systolic pressure
PFT	pulmonary function test
SSc	systemic sclerosis
SSc-ILD	systemic sclerosis-associated interstitial lung disease
TLC	total lung capacity
UCSD-SOBQ	University of California San Diego Shortness of Breath Questionnaire

2. Methods

2.1. Study population

Outpatients with SSc-ILD and non-CTD fibrotic ILD were recruited from regional SSc-ILD and general ILD referral centres between July 2014 and August 2016. All patients provided informed written consent (UBC ethics board approval H10-03099). Patients were included if they were able to complete study questionnaires in English and had ILD either secondary to SSc or a non-CTD fibrotic ILD. SSc-ILD and IPF were diagnosed according to the 2013 American College of Rheumatology (ACR) Classification Criteria and the 2011 IPF Clinical Practice Guidelines [6,7]. Suspected IPF was defined as a multidisciplinary diagnosis of IPF but without satisfying all guideline criteria. Other diagnoses were based on a face-to-face multidisciplinary discussion that incorporated all available clinical, radiological, and pathological data. Some patients with non-CTD fibrotic ILD were reported in a previous publication [5].

2.2. Frailty index

Frailty was measured using a 42-item Frailty Index (FI) that is based on the presence or absence of specific deficits listed in Fig. 1 [8]. The FI is calculated as a proportion of reported deficits divided by the total number of surveyed items, expressed as a value between 0 and 1. The Frailty Index combines multiple deficits (disabilities) into a single tool that in our case purposefully represents the cumulative deficits that are caused by SSc, ILD, aging, and other comorbidities. Using this definition, frailty is an overarching concept that supersedes individual diseases or disabilities, and it is therefore not possible to distinguish between different contributors to frailty [9]. Surveyed deficits without a patient response were treated as missing data and removed from the patient's FI calculation. The presence of frailty is defined as an index >0.21, and an index between 0.1 and 0.21 denotes a pre-frail state [10]. The FI can be grouped into items related to comorbidities and items related to independence and self-care. Community dwelling Canadian adults have a mean FI of 0.064 (SD 0.068), with an increase of approximately 3% per year [8]. A FI of 0.67 is considered a submaximal limit as it is exceeded by only 1% of the population [11].

2.3. Measurements

Demographics and baseline characteristics were obtained from the clinical record and self-reported questionnaires. Dyspnea was assessed by the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ), with patients rating their dyspnea from 0 (not at all) to 5 (maximally) in 24 common activities [12]. Pulmonary function tests (PFTs) and six-minute-walk-tests (6MWTs) were performed using established protocols [13–17]. The ILD-GAP (Gender, Age, Physiology) Index is a multidimensional mortality risk prediction model that was calculated as previously described based on the ILD diagnosis, sex, age, forced vital capacity (FVC), and diffusion capacity of the lung for carbon monoxide (DLCO) [18,19]. The Composite Physiologic Index (CPI) was developed to predict radiological severity of fibrosis using FVC, forced expiratory volume in 1 s (FEV_1) and DLCO [20], and also predicts mortality in both IPF and SSc-ILD [21]. The favored radiological pattern in patients with SSc-ILD was determined by a chest radiologist based on review of high-resolution computed tomography (HRCT). The echocardiographic estimate of the right ventricular systolic pressure was determined based on the velocity of the tricuspid regurgitant jet [22]. Questionnaires were completed on the same day as the frailty assessment, and all other clinical measurements were completed within six months.

2.4. Statistical analysis

Data are reported as mean (standard deviation, SD) or median (interquartile range, IQR). The association of the FI with categorical and continuous variables was calculated using a Wilcoxon rank sum test or Spearman's rank correlation coefficient (r value) as applicable. The internal consistency of the items in the FI was determined using Cronbach's-α. Independent correlates of the FI were identified using stepwise multivariate regression with backward elimination, incorporating variables that were associated with the FI on unadjusted analysis with a $p < 0.10$. A second multivariate analysis was performed that forced age, sex, and smoked pack-years into the multivariate model. The FI in SSc-ILD and non-CTD ILD was compared using a Wilcoxon rank sum test for unadjusted analysis, followed by a multivariate analysis that adjusted for potential confounders. We did not correct for multiple comparisons since our analysis focused on a limited number of prespecified variables that we believed may be associated with frailty, as well as specific demographic variables that were included for face validity in multivariate models. A two-sided $p < 0.05$ was used to indicate statistical significance for all comparisons. All data was analyzed using STATA 11.2 (StataCorp, Texas, USA).

3. Results

3.1. Study population

The study cohort included 86 patients with SSc-ILD and 167 patients with non-CTD fibrotic ILD (Table 1). The non-CTD fibrotic ILD cohort included 71 cases of unclassifiable ILD, 55 cases of confirmed and 6 cases of suspected IPF, 34 cases of hypersensitivity pneumonitis, and one patient with idiopathic NSIP. Patients with SSc-ILD were younger, more frequently female, and had a lower body mass index compared to patients with non-CTD fibrotic ILD. The prevalence of ever-smokers was similar in the two cohorts, but with a lower pack-year history in SSc-ILD. SSc-ILD patients had a longer time since ILD diagnosis and a higher baseline FVC