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# Dynapenia and Sarcopenia as Risk Factors for Mortality in Interstitial Lung Disease

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## ABSTRACT

**Background and Objective:** Fibrotic interstitial lung disease (ILD) is associated with high morbidity and mortality. Patients often exhibit impaired nutritional status and alterations in body composition, such as dynapenia and sarcopenia, which correlate with poor pulmonary function, reduced exercise tolerance and diminished quality of life. However, the impact of dynapenia and sarcopenia on prognosis has not been examined extensively in ILD patients.

We assessed the impact of dynapenia and sarcopenia as risk factors for mortality and their prevalence in ILD.

**Methods:** Prospective cohort study. ILD was classified into idiopathic pulmonary fibrosis (IPF), connective tissue disease-related ILD (CTD-ILD) and chronic hypersensitivity pneumonitis (CHP). Patients over 18 years old with a confirmed diagnosis of ILD were included, while those with diagnoses of cancer, human immunodeficiency virus and neurological disease were excluded. Dynapenia and sarcopenia were determined according to EWGSOP2 criteria.

**Results:** Ninety-eight ILD patients were included; 33.66% had IPF, 47.96% had CTD-ILD, and 18.37% had CHP. The mean age was 63.89 ± 12.02 years; 37.76% were male.

The risk factors associated with mortality included dynapenia (HR: 2.04, 95% CI: 1.10–3.77, $p = 0.022$), sarcopenia (HR: 1.88, 95% CI; 1.00–3.33, $p = 0.049$) and exercise tolerance (HR: 0.99, 95% CI; 0.99–0.99, $p = 0.023$), adjusted for confounding variables.

The prevalence of dynapenia was 45% in ILD; 51% in IPF, 35% in CTD-ILD and 61% in CHP. The prevalence of sarcopenia was 29%; both IPF (39%) and CHP (50%) had a higher prevalence of sarcopenia than CTD-ILD (14%).

**Conclusion:** Sarcopenia and dynapenia are independent risk factors for mortality in ILD.

**Abbreviations:** 6MWD, 6-min walk distance; ASMMI, appendicular skeletal muscle mass index; BIA, bioelectrical impedance analysis; CHP, chronic hypersensitivity pneumonitis; CTD-ILD, connective tissue disease-related interstitial lung disease; DLCO, diffusing capacity for carbon monoxide; EWGSOP2, European Working Group on Sarcopenia in Older People 2; $FEV_1$, forced expiratory volume in the first second; FVC, forced vital capacity; HGS, handgrip strength; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PhA, phase angle; R, resistance; Xc, reactance.

**Summary**

- ILD patients had a higher prevalence of body composition alterations, among them dynapenia and sarcopenia; these are independent risks for mortality.
- Pulmonary rehabilitation, including nutritional treatment, should be part of the routine management of this population to improve nutritional status and delay the skeletal muscle disorder.

## 1 | Introduction

Fibrotic Interstitial lung disease (ILD) encompasses a heterogeneous group of non-neoplastic disorders resulting from damage to the lung parenchyma through various patterns of inflammation and fibrosis [1]. Most individuals with end-stage respiratory failure due to ILD experience severe shortness of breath, limited exercise capacity and a reduced health-related quality of life. ILD is associated with high morbidity and mortality [2].

Patients with this condition often experience poor nutritional status associated with the disease, characterised by a subacute or chronic state involving a combination of inflammation and negative energy balance. This compromised nutritional status is frequently reflected in a low body mass index (BMI), reduced muscle strength and mass and a decreased phase angle [PhA] [3, 4]. Numerous mechanisms have been proposed to explain the poor nutritional status and changes in body composition observed in patients, including aging, smoking-induced vitamin D deficiency, gastrointestinal symptoms, weight loss, acute exacerbations, increased respiratory muscle load, anorexia caused by antifibrotic medications such as nintedanib and pirfenidone [5–7]; reduced physical activity due to the general clinical condition of patients; systemic inflammation, oxidative stress, hypercatabolism, low protein intake, decreased forced vital capacity (FVC) and complicated diabetes mellitus, among others [4–6, 8].

Low skeletal muscle mass, dynapenia and sarcopenia are among the primary alterations in body composition. Body weight and skeletal muscle mass have been linked to lower FVC %, reduced diffusing capacity for carbon monoxide (DLCO) and worse prognosis [9–11]. Dynapenia, characterised by low muscle strength, is associated with muscle function [12] and is a powerful predictor of worse adverse events, including prolonged hospital stays, increased functional limitations, reduced health-related quality of life and death in diverse populations [13, 14]. Low handgrip strength (HGS) in ILD has been negatively associated with DLCO % and dyspnoea [10].

Sarcopenia, a progressive and generalised skeletal muscle disorder, is associated with low muscle strength and mass [12]. In various respiratory diseases, dynapenia and sarcopenia have been shown to increase the risk of falls, fractures and hospitalisation, impair the ability to perform daily activities, and have a poor prognosis [15–18]. The prevalence of sarcopenia in ILD was reported to be 32% according to the Asian Working Group for Sarcopenia 2019 criteria [19], 22.5% in systemic sclerosis patients [20] and 26% in idiopathic pulmonary fibrosis (IPF) [21]. The prevalence of dynapenia in IPF was reported to be 23.5% [22].

Previous studies have indicated that body composition alterations such as body weight loss > 5%, low fat-free mass index and reduced muscle cross-sectional area are independent factors associated with mortality [6, 9, 23]. However, the impact of dynapenia and sarcopenia on prognosis in ILD patients has not been extensively studied. Our primary objective was to assess the impact of dynapenia and sarcopenia as risk factors for mortality, while the secondary objective was to determine the prevalence of dynapenia and sarcopenia in ILD.

## 2 | Methods

A prospective cohort study was conducted at the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas in Mexico City, Mexico, from August 1, 2017, to January 31, 2024. ILD was classified into three categories: idiopathic pulmonary fibrosis (IPF), chronic hypersensitivity pneumonitis (CHP) and connective tissue disease-related ILD (CTD-ILD), including lupus, systemic sclerosis, rheumatoid arthritis, Sjögren's syndrome, idiopathic inflammatory myopathies and antisynthetase syndrome. Outpatient subjects over 18 years old with a confirmed diagnosis of ILD according to ATS/ERS/JRS guidelines [1] and ILD experts (both male and female) were included. Patients with cancer, human immunodeficiency virus, neurological disease, or a history of hospitalisation within the previous 3 months were excluded.

### 2.1 | Outcome Measures

Demographic, clinical, anthropometry, body composition, pulmonary function and exercise tolerance variables were evaluated at the beginning of the study cohort as part of the clinical management of outpatients at our institute.

### 2.2 | Anthropometry

Weight and height were measured according to the manual reference for anthropometric standardisation [24]. All subjects wore light clothing and were barefoot.

### 2.3 | Handgrip Strength (HGS)

HGS was measured using a mechanical Smedley Hand Dynamometer (Stoelting, Wood Dale, UK) according to the technique described by Rodriguez et al. Subjects stood with their arms parallel to the trunk, picked up the dynamometer and applied maximum force with the dominant hand. To avoid fatigue, the measurement was repeated three times, 1 min apart. The maximum value was recorded in kilograms [25].

### 2.4 | Dynapenia

Dynapenia was defined according to EWGSOP2 [12] as the presence of low muscle strength (HGS < 27 kg for men and HGS < 16 kg for women).

**TABLE 1** | Demographic and clinical characteristics according to survival in interstitial lung disease subjects.

| | All, $n=98$ | Non-survival, $n=49$ | Survivors, $n=49$ | $p$ |
|---|---|---|---|---|
| Men, *n* (%) | 37 (37.76) | 22 (44.90) | 15 (30.61) | 0.211 |
| Age, years | 63.89 ± 12.02 | 64.93 ± 13.01 | 62.85 ± 10.99 | 0.247 |
| Comorbidities | | | | |
| Hypertension, *n* (%) | 30 (30.61) | 15 (30.61) | 15 (30.61) | 1.000 |
| COPD, *n* (%) | 6 (6.12) | 1 (2.04) | 5 (10.20) | 0.204 |
| Diabetes, *n* (%) | 19 (19.59) | 11 (22.92) | 8 (16.33) | 0.453 |
| Asthma, *n* (%) | 6 (6.12) | 2 (4.08) | 4 (8.16) | 0.678 |
| Heart failure, *n* (%) | 17 (17.35) | 10 (20.41) | 7 (14.29) | 0.595 |
| ILD type | | | | |
| IPF | 33 (33.67) | 21 (42.86) | 12 (24.49) | 0.144 |
| CTD-ILD | 47 (47.96) | 21 (42.86) | 26 (53.06) | |
| CHP | 18 (18.37) | 7 (14.29) | 11 (22.45) | |
| Pulmonary function | | | | |
| $FEV_1$, L | 1.68 ± 0.74 | 1.60 ± 0.71 | 1.74 ± 0.76 | 0.382 |
| $FEV_1$, % | 71.76 ± 26.16 | 69.94 ± 27.39 | 73.35 ± 25.23 | 0.544 |
| FVC, L | 2.05 ± 0.96 | 1.93 ± 0.87 | 2.16 ± 1.02 | 0.272 |
| FVC, % | 66.91 ± 25.39 | 63.35 ± 25.48 | 68.15 ± 25.36 | 0.379 |
| DLCO, % predicted | 48.78 ± 22.09 | 42.65 ± 20.2 | 54.22 ± 22.46 | 0.016 |
| Composite physiologic index | 49.70 ± 16.50 | 54.74 ± 14.83 | 44.67 ± 16.69 | 0.002 |
| Treatment | | | | |
| Corticosteroid | 57 (58.76) | 29 (59.18) | 28 (58.33) | 0.932 |
| Antifibrotic | 27 (27.55) | 12 (24.49) | 15 (30.61) | 0.498 |
| Body composition | | | | |
| Weight, kg | 64.12 ± 14.64 | 63.58 ± 14.54 | 64.65 ± 14.87 | 0.722 |
| Height, cm | 155.67 ± 9.37 | 155.25 ± 8.51 | 156.09 ± 10.08 | 0.659 |
| BMI, $kg/m^2$ | 26.32 ± 4.94 | 26.27 ± 5.18 | 26.37 ± 4.75 | 0.921 |
| Underweight, *n* % | 3 (3.09) | 1 (2.08) | 2 (4.08) | 0.944 |
| Normal weight, *n* % | 35 (36.08) | 18 (37.50) | 17 (34.69) | |
| Overweight, *n* % | 33 (34.02) | 16 (33.33) | 17 (34.69) | |
| Obese, *n* % | 26 (26.80) | 13 (27.08) | 13 (26.53) | |
| Waist, cm | 91.12 ± 12.81 | 92.72 ± 13.81 | 89.55 ± 11.69 | 0.250 |
| Total body water, L | 52.33 ± 8.94 | 52.25 ± 9.12 | 52.40 ± 8.87 | 0.938 |
| Intracellular water, L | 28.23 ± 4.08 | 28.38 ± 4.44 | 28.08 ± 3.72 | 0.747 |
| Third space, L | 0.26 ± 0.96 | 0.13 ± 0.99 | 0.39 ± 0.92 | 0.223 |
| Impedance index, 200/5 kHz | 0.82 ± 0.05 | 0.82 ± 0.05 | 0.81 ± 0.05 | 0.280 |
| Handgrip strength, kg | 20.81 ± 7.37 | 19.93 ± 7.30 | 21.70 ± 7.41 | 0.237 |
| Phase angle, ° | 5.43 ± 1.22 | 5.12 ± 1.24 | 5.74 ± 1.12 | 0.011 |
| ASMMI, *n* % | 6.57 ± 0.97 | 6.52 ± 1.04 | 6.62 ± 0.91 | 0.594 |

(Continues)

**TABLE 1** | (Continued)

| | All, $n=98$ | Non-survival, $n=49$ | Survivors, $n=49$ | $p$ |
|---|---|---|---|---|
| Muscle wasting, *n* % | 42 (43.30) | 23 (47.92) | 19 (38.78) | 0.416 |
| Dynapenia, *n* % | 45 (45.92) | 30 (61.22) | 15 (30.61) | 0.004 |
| Sarcopenia, *n* % | 29 (29.59) | 21 (42.86) | 8 (16.33) | 0.007 |
| Sarcopenic obesity, *n* % | 0 (0) | 0 (0) | 0 (0) | 1 |
| 6MWD test, m | 330.95 ± 127.21 | 284.96 ± 139.96 | 365.45 ± 105.92 | 0.011 |

Abbreviations: 6MWD, 6 min walk distance; ASMMI, appendicular skeletal muscle mass index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CTD-ILD, connective tissue disease-related ILD; DLCO, carbon monoxide diffusing capacity; $FEV_1$, forced expiratory volume in the first second; FVC, forced vital capacity; HP, chronic hypersensitivity pneumonitis; ILD, interstitial lung diseases; IPF, idiopathic pulmonary fibrosis.

### 2.5 | Bioelectrical Impedance Analysis (BIA)

Total body composition was measured using whole-body BIA with four-pole multifrequency equipment (BodyStat QuadScan 4000, BodyStat, Isle of Man, UK) by standard technique [26]. The BIA method injects an alternating electric current of minimal intensity below the sensing thresholds. The impedance (Z) represents the opposition biological materials show to the passage of an alternating electric current. The electrical impedance Z comprises resistance (R) and reactance (Xc). The current passage determines R through the intracellular and extracellular electrolyte solutions, and Xc is the delay in current flow measured as a phase shift, reflecting the dielectric properties of the cell mass and the integrity of cell membranes [27]. The same operator conducted the measurements in the morning in a comfortable area free of drafts, with portable electric heaters. The area was cleaned before the study. Subjects were fasting and had not exercised 8 h before or consumed alcohol 12 h before the study. During the study, the person was supine, with arms separated from the trunk by about 30° and legs by about 45°. Electrodes were placed on the hand and ipsilateral foot.

Phase angle (PhA) was calculated using the following equation: PhA (degrees) = arctan (Xc/R)·(180/π) [28]. In our population, PhA below the 25th percentile value was < 4.5 for both men and women.

### 2.6 | Appendicular Skeletal Muscle Mass Index

Appendicular skeletal muscle mass index (ASMMI) was assessed using Sergi's equation [29]: ASMMI ($kg/m^2$) = [(2 −3.964 + 0.227 * (Height ($cm^2$)/R) + 0.095 * Weight + 1.384 * Sex + 0.064 * Xc)/ Height ($m^2$)].

### 2.7 | Muscle Wasting

Muscle wasting was defined according to the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) [12] as ASMMI < 7.0 $kg/m^2$ for men and < 6.0 $kg/m^2$ for women.

### 2.8 | Sarcopenia

Sarcopenia was defined according to EWGSOP2 [12] as the presence of low muscle strength (HGS < 27 kg for men and < 16 kg for women) and low muscle mass (ASMMI < 7.0 $kg/m^2$ for men and < 6.0 $kg/m^2$ for women).

### 2.9 | Sarcopenic Obesity

Sarcopenic obesity was defined as low muscle mass (ASMMI < 7.0 $kg/m^2$ in men and ASMMI < 6.0 $kg/m^2$ in women), low muscle strength (HGS < 27 kg in men and HGS < 16 kg in women) and excess adiposity (body mass index > 30) [30].

### 2.10 | Exercise Tolerance

Exercise tolerance was assessed by a 6-min walk distance (6MWD), performed according to American Thoracic Society standards [31].

### 2.11 | Pulmonary Function

Forced spirometry was performed using a portable spirometer (EasyOne Pro Lab, Ndd Medical Technologies Inc., Zürich, Switzerland) by an experienced respiratory medicine technician according to American Thoracic Society/European Respiratory Society standards [32]. The analysed spirometric variables included forced expiratory volume in the first second ($FEV_1$) and forced vital capacity (FVC). Following a 15-min rest, participants performed a maximal forced inspiration and a forceful expiration using a nose clip. Spirometry reference values were derived from Mexican-American individuals [33].

### 2.12 | Carbon Monoxide Diffusing Capacity (DLCO)

A trained respiratory technician conducted tests for DLCO using EasyOne pro equipment (Ndd Medical Technologies Inc., Zürich, Switzerland). The assessment accounted for altitude and haemoglobin levels, employing predicted values for the Latino population [34].

### 2.13 | Composite Physiologic Index (CPI)

The CPI was assessed using Wells's equation [35]: CPI = 91.0 − (0.65 * % predicted DLCO) − (0.53 * % predicted FVC) + (0.34 * % predicted $FEV_1$).

**TABLE 2** | Risk factors associated with mortality in interstitial lung disease subjects.

| | Crude model | | | Adjusted model | | |
|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | ***p*** | **HR** | **95% CI** | ***p*** |
| Men | 1.39 | 0.79–2.45 | 0.244 | | | |
| Age, years | 1.01 | 0.98–1.03 | 0.351 | | | |
| Comorbidities | | | | | | |
| Hypertension | 1.00 | 0.54–1.85 | 0.981 | | | |
| COPD | 0.22 | 0.03–1.60 | 0.136 | | | |
| Diabetes | 1.20 | 0.61–1.36 | 0.593 | | | |
| Asthma | 0.57 | 0.13–2.35 | 0.440 | | | |
| Heart failure | 1.28 | 0.64–2.59 | 0.477 | | | |
| ILD type | | | | | | |
| IPF | 1 | Reference | | | | |
| CTD-ILD | 0.76 | 0.41–1.40 | 0.385 | | | |
| CHP | 0.54 | 0.23–1.29 | 0.171 | | | |
| Pulmonary function | | | | | | |
| $FEV_1$, L | 0.79 | 0.53–1.18 | 0.256 | | | |
| $FEV_1$, % predicted | 0.99 | 0.98–1.00 | 0.538 | | | |
| FVC, L | 0.76 | 0.56–1.04 | 0.096 | | | |
| FVC, % predicted | 0.99 | 0.98–1.00 | 0.166 | | | |
| DLCO, % predicted | 0.97 | 0.96–0.99 | 0.002 | | | |
| Composite physiologic index | 1.03 | 1.01–1.04 | 0.001 | | | |
| Treatment | | | | | | |
| Corticosteroid | 1.03 | 0.58–1.82 | 0.916 | | | |
| Antifibrotic | 0.62 | 0.32–1.19 | 0.156 | | | |
| Body composition | | | | | | |
| Weight, kg | 0.99 | 0.97–1.01 | 0.598 | | | |
| Height, cm | 0.99 | 0.98–1.02 | 0.626 | | | |
| BMI, $kg/m^2$ | 0.99 | 0.93–1.05 | 0.771 | | | |
| Normal weight, *n* % | 1 | Reference | | | | |
| Underweight, *n* % | 1.30 | 0.17–9.82 | 0.794 | | | |
| Overweight, *n* % | 0.89 | 0.45–1.75 | 0.743 | | | |
| Obese, *n* % | 1.01 | 0.49–2.07 | 0.972 | | | |
| Waist, cm | 1.01 | 0.99–1.04 | 0.176 | 1.02 | 1.00–1.05 | 0.047 |
| Total body water, L | 1.00 | 0.96–1.04 | 0.785 | | | |
| Intracellular water, L | 1.01 | 0.93–1.10 | 0.717 | | | |
| Third space, L | 0.84 | 0.60–1.18 | 0.321 | | | |
| Impedance index > 0.81 | 2.41 | 1.20–4.83 | 0.013 | 1.65 | 0.77–3.56 | 0.195 |
| Handgrip strength, kg | 0.97 | 0.93–1.01 | 0.272 | | | |
| Phase angle < 4.5° | 2.23 | 1.25–3.97 | 0.006 | 1.74 | 0.95–3.19 | 0.073 |

(Continues)

**TABLE 2** | (Continued)

| | Crude model | | | Adjusted model | | |
|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | ***p*** | **HR** | **95% CI** | ***p*** |
| ASMMI, kg/m$^2$ | 0.89 | 1.33–4.20 | 0.003 | 0.95 | 0.66–1.38 | 0.824 |
| Muscle wasting | 1.38 | 0.78–2.44 | 0.259 | | | |
| Dynapenia | 2.36 | 0.95–3.33 | 0.069 | 2.04 | 1.10–3.77 | 0.022 |
| Sarcopenia | 2.30 | 1.30–4.06 | 0.004 | 1.88 | 1.00–3.33 | 0.049 |
| 6MWD, m | 0.99 | 0.99–0.99 | 0.002 | 0.99 | 0.99–0.99 | 0.023 |
| 6MWD < 300 m | 2.44 | 1.18–5.01 | 0.015 | 2.12 | 0.98–4.56 | 0.053 |

*Note:* Adjusted model by age, sex, heart failure, diabetes, ILD type and composite physiologic index.
Abbreviations: 6MWD, 6 min walk distance; ASMMI, appendicular skeletal muscle mass index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CTD-ILD, connective tissue disease-related ILD; DLCO, carbon monoxide diffusing capacity; $FEV_1$, forced expiratory volume in the first second; FVC, forced vital capacity; HP, chronic hypersensitivity pneumonitis; ILD, interstitial lung diseases; IPF, idiopathic pulmonary fibrosis.

### 2.14 | Endpoint

The endpoint was defined as mortality from all causes. Death records were obtained through referrals from relatives or registration in the hospital medical record.

### 2.15 | Statistical Analysis

Analyses were conducted using STATA version 14 (Stata Corp., College Station, TX, USA). Categorical variables were expressed as frequencies and percentages. The Shapiro–Wilk test assessed the normality of continuous variables; normal variables were expressed as mean and standard deviation, while non-normal variables were reported as median and percentiles 25–75. Comparisons between study groups (survival vs. non-survival) were analysed using the chi-square test for categorical variables and the t-student test or Mann–Whitney *U* test for continuous variables.

Comparisons between IPF, CTD-ILD and CHP were analysed using the chi-square test for categorical variables and the one-way ANOVA test for continuous variables.

Kaplan–Meier survival curves and a Cox proportional-hazards regression model were used to evaluate the association between body composition alterations and mortality. The multivariate model was adjusted by bivariate analysis for variables with a *p*-value < 0.10 and clinical variables such as sex, age, heart failure, diabetes and ILD type. Potential interactions and multicollinearity between variables were tested. Results were reported as hazard ratios (HR) with 95% confidence intervals (CI). A *p*-value < 0.05 was considered statistically significant.

## 3 | Results

Ninety-eight subjects with an ILD diagnosis were included; 33.67% had IPF, 47.96% had CTD-ILD and 18.37% had CHP. The mean age was 63.89 ± 12.02 years, and 37.76% were male. The median follow-up period was 4.2 years (range, 1.11–4.8), and 50% of subjects died during the follow-up.

Non-surviving subjects had lower DLCO %, PhA and 6MWD test, a higher composite physiologic index and more prevalence of dynapenia and sarcopenia than surviving subjects (Table 1).

Risk factors associated with mortality in the crude model were DLCO %, CPI, impedance index > 0.81, PhA < 4.5°, ASMMI, sarcopenia, 6MWD test and 6MWD < 300 m.

In the multivariate model shown in Table 2, the body composition factors associated with mortality were dynapenia (HR: 2.04, 95% CI; 1.10–3.77, $p = 0.022$) and sarcopenia (HR: 1.88, 95% CI; 1.00–3.33, $p = 0.049$) after adjusted by age, sex, heart failure, diabetes, ILD type and CPI (Figure 1). The impact of dynapenia over mortality according to ILD type was HR: 2.05, 95% CI; 0.85–4.97, $p = 0.109$ in IPF, HR: 2.47, 95% CI; 1.04–5.83, $p = 0.039$ in CHP and HR: 5.56, 95% CI; 0.66–46.62, $p = 0.114$ in CTD-ILD. Concerning the impact of sarcopenia on mortality according to ILD type was HR: 2.42, 95% CI; 1.01–5.75, $p = 0.045$ in IPF; 2.28, 95% CI; 0.83–6.24, $p = 0.108$ in CHP and HR: 3.82, 95% CI; 0.73–19.99, $p = 0.111$ in CTD-ILD.

Regarding body composition among ILD types, there were no differences in HGS, ASMMI, PhA, 6MWD and dynapenia. In ILD types, the prevalence of sarcopenic obesity was 0%. The prevalence of dynapenia was 45% in the ILD population. Although both IPF (51%, $p = 0.149$) and CHP (61%, $p = 0.060$) had a higher prevalence of dynapenia than CTD-ILD (35%), however, no-showed differences between the groups. The prevalence of sarcopenia was 29%; both IPF (39%, $p = 0.011$) and CHP (50%, $p = 0.003$) had a higher prevalence of sarcopenia than CTD-ILD (14%) subjects (Figure 2).

When analysed by age groups, subjects aged 60 and older had a higher prevalence of dynapenia (47.60% vs. 41.18%, $p = 0.536$) and sarcopenia (32.32% vs. 23.53%, $p = 0.363$) compared to those under 60 years of age; however, this difference was not statistically significant (Figure 3).

## 4 | Discussion

The primary finding of our research highlights the impact of dynapenia and sarcopenia on prognosis in ILD patients.

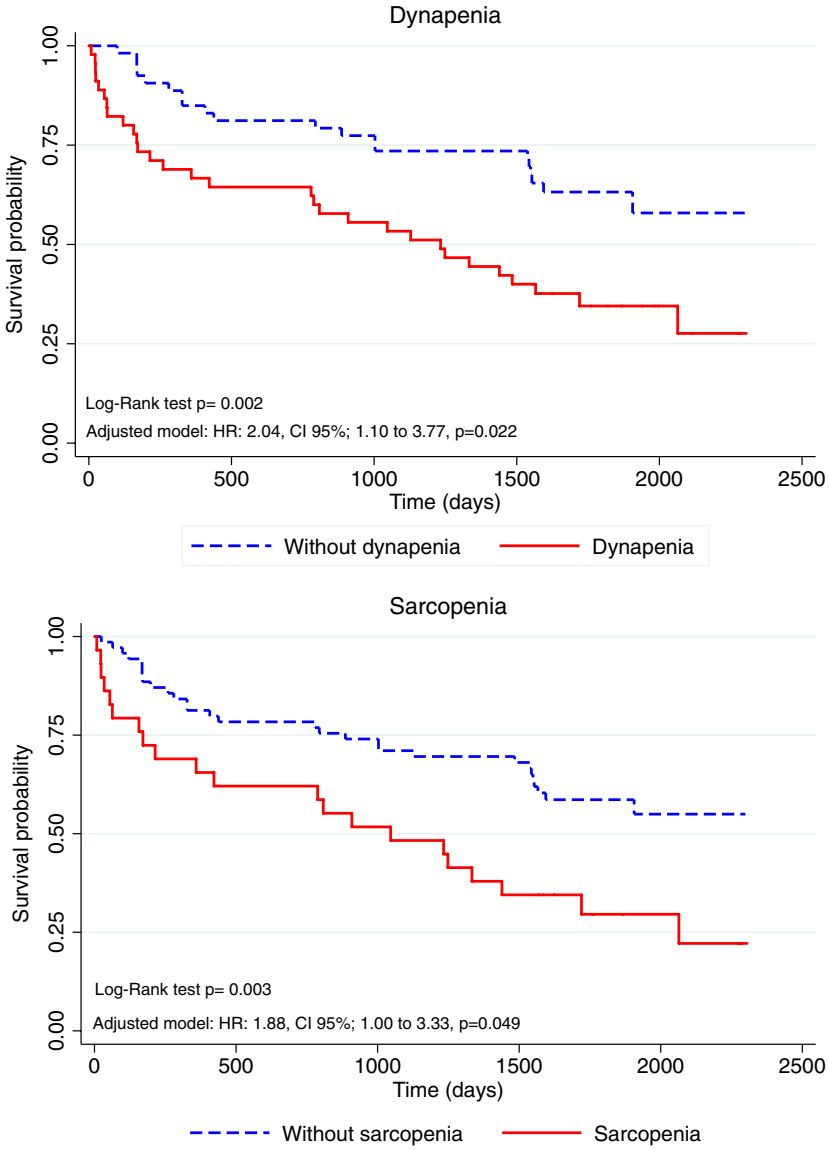


**FIGURE 1** | Kaplan–Meier curves for all causes of death.

Additionally, we report the prevalence of dynapenia and sarcopenia across different ILD types.

Muscle strength is a marker of muscle quality and physical functionality, which is crucial for maintaining mobility and vitality. In our study, the prevalence of dynapenia was 45% in the ILD population. For IPF subjects, Bocchino et al. reported a prevalence of 23.5% in the general IPF population, which increased dramatically to 46.4% in subjects over 75 years of age [22]. However, in our IPF population, the prevalence was 51%. This study reported a prevalence of 35% of dynapenia in CTD-ILD and 61% in CHP. Furthermore, dynapenia was a predictor of mortality in ILD patients (HR: 2.04, 95% CI; 1.10–3.77) independently of sex, age, heart failure, diabetes, ILD type and CPI. Previous studies have demonstrated that muscle strength declines more rapidly than muscle mass [36] and is a better predictor of adverse outcomes than muscle mass [13]. A possible explanation is that muscle mass is estimated by predictive equations, while directly measured raw variables, such as HGS or PhA assessment by BIA, are not susceptible to inherent equation errors.

In ILD patients, the presence of comorbidities, disease severity, antifibrotic agents and acute exacerbations are the most studied factors that determine disease progression and prognosis. However, in recent years, nutritional status and body composition alterations have gained importance. IPF is the most common form of ILDs; therefore, more information on nutritional status and body composition alterations is available. Low muscle mass has been associated with an increased risk of death in IPF [9, 11, 37]. Subjects with low muscle mass or sarcopenia have shown lower FVC, DLCO and exercise tolerance, as well as a higher prevalence of frailty, depression, dyspnoea and worse quality of life [18, 38, 39]. Nonetheless, Sridhar and Cols, in a study cohort of IPF patients, the sarcopenia prevalence was 12.8% and found no association between sarcopenia and mortality risk (HR: 2.1, 95% CI 0.8–5.3), which is possibly due to the small sample size and follow-up duration [39]. In our cohort study, we observed similar results when performing the subanalysis according to the type of ILD's; we found that subjects with IPF with sarcopenia, as well as subjects with CHP with dynapenia, had a higher risk of death. However, no association

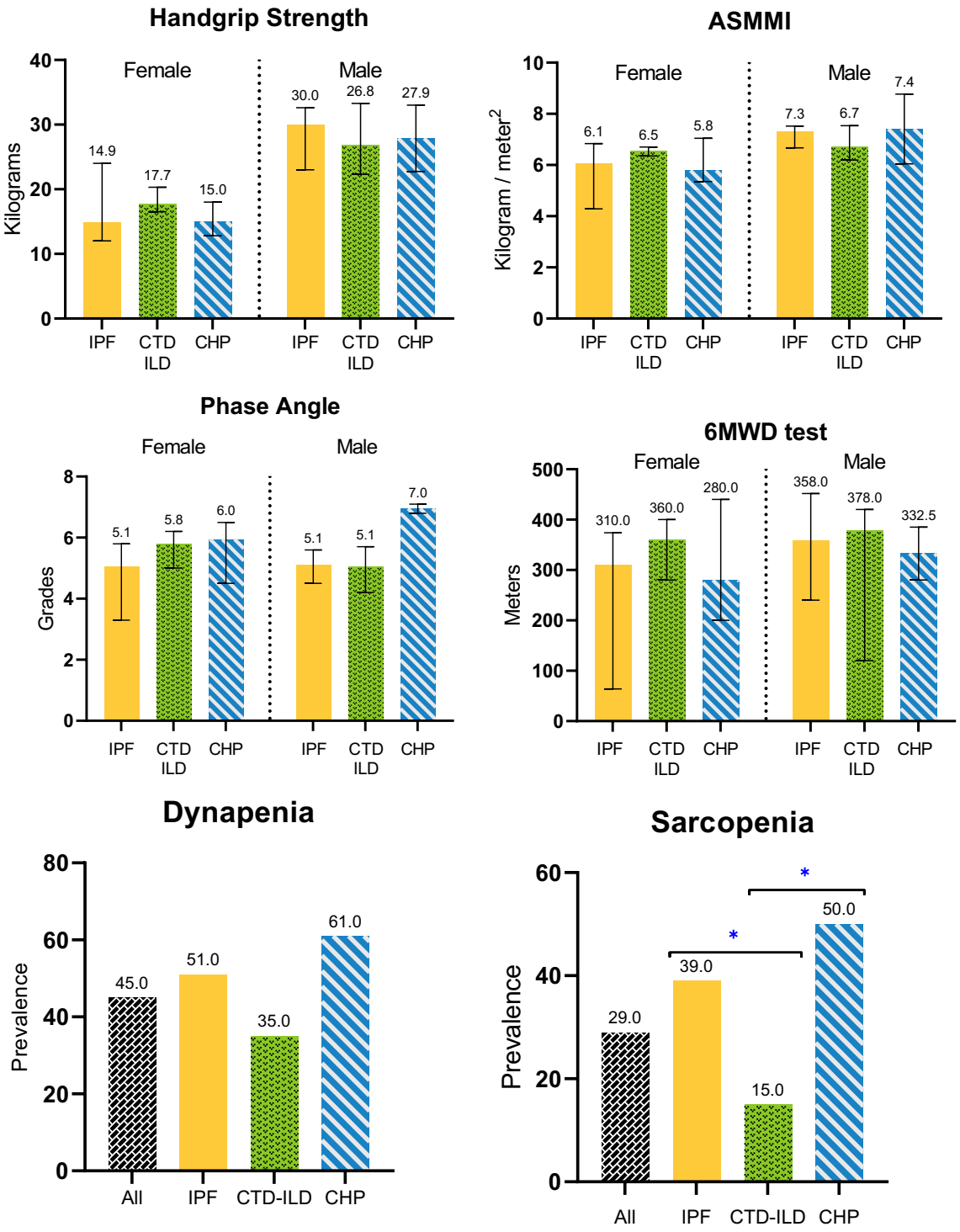


**FIGURE 2** | Body composition according to interstitial lung disease type.

was observed between IPF and CHP with dynapenia, as well as CHP and CTD-ILD with sarcopenia and mortality risk. The ILDs are relatively rare, which results in a small sample size, so it was decided to analyse ILDs together and adjust the model according to ILD's type.

In our study, non-surviving subjects had a greater prevalence of sarcopenia than surviving subjects. Additionally, we demonstrated that sarcopenia was an independent risk factor for death (HR: 1.88, 95% CI; 1.00–3.33) adjusted for confounding variables. Notably, our population observed a higher prevalence of sarcopenia in IPF than that reported in the meta-analysis performance by Li et al., with 26% of sarcopenia [21, 39, 40]. Interstitial lung diseases are relatively rare, which makes diagnosis challenging in primary care centres and often delays referral to specialised tertiary care centre such as ours. Variability in the sarcopenia diagnostic criteria applied also contributes to these challenges [39, 40].

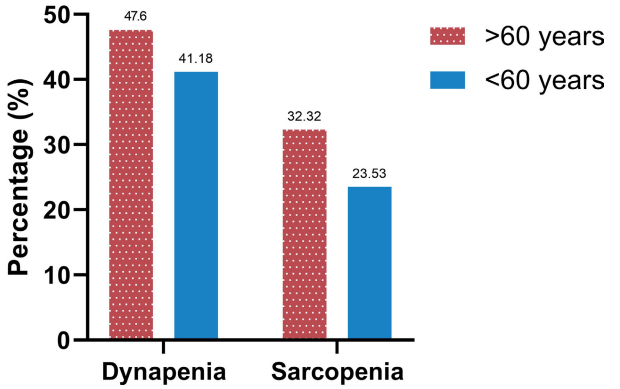


**FIGURE 3** | Prevalence of dynapenia and sarcopenia according to age group.

In our study, no cases of sarcopenic obesity were observed in with IPF, CTD-ILD, or CHP; similar results were found by Faveiro et al., showing a prevalence of 2.3% in IFP subject [40].

Another important parameter of body composition is PhA determined by BIA. This is a useful indicator of health and nutritional status. A low PhA suggests lower cellularity, membrane integrity, cellular function, malnutrition status, inflammatory and stress oxidative markers, impaired quality of life and worse prognosis in diverse populations [41–43]. In IPF, subjects with low PhA had lower FVC %, $FEV_1$ %, total lung capacity %, 6MWD, SF-36 physical score and low fat-free mass index [38, 44]. Additionally, Fernández-Jiménez et al. showed that PhA <4.5° increased the mortality risk by 6.35 times at a 12-month follow-up [37]. Machado et al. showed that subjects with low PhA had lower FVC, $FEV_1$ and quality of life in IPF subjects. Moreover, PhA was independently associated with 6MWD (Difference mean: −76.2 m, 95% CI −119.1 to −33.3 m; $p = 0.001$) [38]. In our study, however, non-surviving subjects had lower PhA than surviving subjects. Nevertheless, the multivariate analysis did not show an association between PhA and mortality (HR: 1.79, 95% CI 0.98–3.2, $p = 0.056$); this could be due to the small sample size.

The decline in nutritional status and body composition alterations in ILD subjects has multifactorial mechanisms such as systemic inflammation, oxidative stress, physical inactivity and medication [7, 8, 45]. Regarding medication, antifibrotic drugs such as nintedanib and pirfenidone have been demonstrated to reduce deterioration in lung function and improve life expectancy [46, 47]. However, both have adverse events; the most common in nintedanib were anorexia (46.7%), diarrhoea (46.7%) and weight loss, whereas anorexia (63.3%) and ≥5% weight loss (56.7%) were common during pirfenidone administration [7]. These adverse events limit energy intake, gastrointestinal absorption and essential nutrients for muscle development. Additionally, corticosteroid treatment has been associated with muscle weakness and reduced exercise capacity [45].

Pulmonary rehabilitation is an effective therapeutic strategy that has been shown to improve FVC, exercise capacity and quality of life, decreasing dyspnoea in ILD patients [48, 49]. Moreover, optimal nutrition treatment must be an effective strategy for preserving muscle mass and the quality of muscle fibres. In chronic obstructive pulmonary disease, nutritional support has improved fat-free mass, 6MWD, pulmonary function and quality of life [50–52]. In IPF subjects, supplementation with a combination of vitamins D, C and E has shown improved respiratory function, as well as reduced inflammation and oxidative stress [53]. Both pulmonary rehabilitation and nutritional therapy represent viable alternatives for maintaining optimal nutritional status and preventing dynapenia or sarcopenia.

A limitation of this study is that it is a single-centre study with a small sample size. Another limitation is the lack of reference values for BIA variables and PhA in the Mexican population; therefore, our study used the population median of 4.5 as the cut-off point. In diverse populations, values below than 4.5° or 5° have been associated with adverse events and worse prognosis [43, 54]. Moreover, we did not perform cognitive impairment scales, which could influence muscle strength measurements. Another limitation is that the cohort study included subjects with dynapenia and sarcopenia prevalent, and the exact time at which they developed dynapenia and sarcopenia is unknown, which influences the median survival of the subjects. However, a recognised strength the study is that the longitudinal nature of the cohort study allows us to evaluate causality and determine the impact of sarcopenia and dynapenia on mortality risk in subjects with ILD. Additionally, the follow-up time of the subjects is long, allowing for a thorough evaluation of their outcomes.

In conclusion, sarcopenia and dynapenia are independent risk factors for mortality in ILD.

### Author Contributions

**Alan Aldair Ibarra-Fernández:** conceptualization (equal), investigation (equal), writing – original draft (equal), writing – review and editing (equal). **Robinson Robles-Hernández:** conceptualization (equal), investigation (equal), writing – original draft (equal), writing – review and editing (equal). **Arturo Orea-Tejeda:** conceptualization (equal), investigation (equal), writing – original draft (equal), writing – review and editing (equal). **Dulce González-Islas:** conceptualization (equal), formal analysis (equal), methodology (equal), writing – original draft (equal), writing – review and editing (equal). **Angelia Jiménez-Valentín:** data curation (equal), investigation (equal), supervision (equal), writing – review and editing (equal). **Rocío Sánchez-Santillán:** data curation (equal), project administration (equal), writing – review and editing (equal). **Laura Patricia Arcos-Pacheco:** data curation (equal), visualization (equal), writing – review and editing (equal). **Emilio Gutiérrez-Luna:** data curation (equal), project administration (equal), writing – review and editing (equal). **Andrea Zurita-Sandoval:** data curation (equal), visualization (equal), writing – review and editing (equal). **Tomas Peña-Espinosa:** investigation (equal), supervision (equal), writing – review and editing (equal). **Rosaura Gutiérrez-Vargas:** formal analysis (equal), methodology (equal), writing – review and editing (equal). **Laura Flores-Cisneros:** formal analysis (equal), methodology (equal), writing – review and editing (equal).

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### Ethics Statement

This research study was approved by the Institutional Ethics and Research Committee for Biomedical Research in Humans at the

Instituto Nacional de Enfermedades Respiratorias 'Ismael Cosío Villegas' (approval number E02-18). All participants provided informed consent.

### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section.