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# Frailty in Chronic Obstructive Pulmonary Disease and Risk of Exacerbations and Hospitalizations

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**Background:** Frailty is a complex clinical syndrome associated with vulnerability to adverse health outcomes. While frailty is thought to be common in chronic obstructive pulmonary disease (COPD), the relationship between frailty and COPD-related outcomes such as risk of acute exacerbations of COPD (AE-COPD) and hospitalizations is unclear.

**Purpose:** To examine the association between physical frailty and risk of acute exacerbations, hospitalizations, and mortality in patients with COPD.

**Methods:** A longitudinal analysis of data from a cohort of 280 participants was performed. Baseline frailty measures included exhaustion, weakness, low activity, slowness, and under-nutrition. Outcome measures included AE-COPD, hospitalizations, and mortality over 2 years. Negative binomial regression and Cox proportional hazard modeling were used.

**Results:** Sixty-two percent of the study population met criteria for pre-frail and 23% were frail. In adjusted analyses, the frailty syndrome was not associated with COPD exacerbations. However, among the individual components of the frailty syndrome, weakness measured by handgrip strength was associated with increased risk of COPD exacerbations (IRR 1.46, 95% CI 1.09–1.97). The frailty phenotype was not associated with all-cause hospitalizations but was associated with increased risk of non-COPD-related hospitalizations.

**Conclusion:** This longitudinal cohort study shows that a high proportion of patients with COPD are pre-frail or frail. The frailty phenotype was associated with an increased risk of non-COPD hospitalizations but not with all-cause hospitalizations or COPD exacerbations. Among the individual frailty components, low handgrip strength was associated with increased risk of COPD exacerbations over a 2-year period. Measuring handgrip strength may identify COPD patients who could benefit from programs to reduce COPD exacerbations.

**Keywords:** chronic obstructive pulmonary disease, frailty, weakness, handgrip strength

## Introduction

Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and remains the third leading cause of death in the United States.<sup>1</sup> Acute exacerbations of COPD (AE-COPD) frequently occur and place a significant utilization and cost burden on the US healthcare system.<sup>2,3</sup> Additionally, AE-COPD have been shown to accelerate declines in lung function, health-related quality of life, and increase hospitalizations and mortality.<sup>4–7</sup> Identifying patients at high risk may help target interventions to reduce AE-COPD.<sup>8–10</sup> Risk factors for AE-COPD include age, sex, forced expiratory volume (FEV<sub>1</sub>), and frequent prior exacerbations.<sup>7–9,11,12</sup>

Frailty has been described as a state of decreased physiologic reserve causing vulnerability to adverse events,<sup>13,14</sup> and identifies individuals who are at risk for

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disability, adverse health outcomes, and increased all-cause mortality.<sup>14–17</sup> The frailty phenotype proposed by Fried et al is widely accepted and is defined as the presence of three or more of the following measures: exhaustion, weakness, slowness, low activity, and/or weight loss,<sup>14,18</sup> with pre-frailty defined as having 1–2 frailty measures.<sup>19</sup>

COPD patients are twice as likely to be frail than those without COPD, and a review of 27 studies found that an estimated 19% were frail, with 56% meeting criteria for pre-frailty.<sup>19,20</sup> The prevalence of frailty varies by setting, ranging from 9% to 28% in the majority of studies, whereas pre-frailty prevalence varies from 48% to 64%.<sup>19</sup> Few longitudinal studies have examined the association of frailty with COPD outcomes such as exacerbations,<sup>20</sup> and have used heterogeneous definitions of frailty.<sup>19</sup> Most studies have used questionnaires to assess frailty, with few using objectively measured muscle strength or gait speed to assess frailty in people with COPD. A longitudinal study using the Fried criteria found that mortality among frail COPD patients was four times higher than non-frail patients.<sup>20</sup> Longitudinal studies using questionnaires to measure frailty have found an increased risk of re-admissions and mortality in COPD.<sup>13,21</sup> Also, among participants in the National Emphysema Treatment Trial, frail COPD participants had an increased risk of all-cause hospitalization and worse quality of life.<sup>22</sup>

Frailty is defined as a syndrome; however, one of the individual frailty components is muscle weakness measured by handgrip strength (HGS), which has been associated with increased risk of acute COPD exacerbations in a cross-sectional study.<sup>23</sup> Limb muscle dysfunction is common in COPD and contributes to poor clinical outcomes including exercise tolerance and mortality.<sup>24,25</sup> Importantly, limb muscle strength can be improved with exercise training and is a modifiable risk factor for adverse outcomes.

This study's primary aim is to examine the relationship between the frailty syndrome with the risk of COPD exacerbations in a longitudinal outpatient cohort of patients with COPD utilizing objectively measured muscle strength and physical activity. We examined the impact of grip strength and other individual components of frailty on risk of adverse COPD outcomes. Additional aims are to evaluate the associations between frailty and all-cause hospitalizations, non-COPD hospitalizations, and mortality.

## Methods

### Study Design

This study analyzed data collected as part of the COPD Activity: Serotonin Transporter, Cytokine, and Depression (CASCADE) study.<sup>26</sup> Approvals were obtained by institutional review boards, in compliance with the Declaration of Helsinki, at the three clinical sites: University of Washington, VA Puget Sound Health Care System, and University of Texas Health Science Center-San Antonio. All participants provided written informed consent.

Inclusion criteria included a diagnosis of COPD, post-bronchodilator FEV<sub>1</sub>/FVC <0.70% and FEV<sub>1</sub>% predicted <80%, age ≥40 years, current or past cigarette use (>10 pack-years), and stable disease in the past 4 weeks. Exclusion criteria were: non-COPD lung disease (eg, asthma, diffuse parenchymal lung disease), chronic inflammatory diseases, lung cancer or metastatic cancer, severe chronic kidney disease, uncompensated heart failure, advanced liver disease, HIV/AIDS, chronic antibiotic or oral prednisone use, bipolar disease, psychotic disorders, or dementia.

### Measures

#### Disease Severity

Measures of disease severity included: forced expiratory volume in 1 second, body mass index (BMI), home oxygen use, Charlson co-morbidity index,<sup>27,28</sup> COPD hospitalizations in the prior year, and dyspnea with Modified Medical Research Council scale (mMRC).<sup>29</sup> Individual comorbidities were also examined including myocardial infarction, angina, heart failure, peripheral vascular disease, stroke, hemiplegia, neurologic disease (multiple sclerosis or Parkinson's disease), pneumonia, ARDS, drug abuse, peptic ulcer disease (history of endoscopy), visual impairment, hearing impairment, degenerative disc disease, diabetes, diabetes treatment (diet, oral hypoglycemics or insulin), diabetes complications (eye, kidney), post-traumatic stress disorder, chronic kidney disease, rheumatoid arthritis, osteoarthritis, osteoporosis, cirrhosis, leukemia, lymphoma, and non-metastatic cancer.

#### Frailty

Using baseline data, we adapted the 5 components of the frailty phenotype model defined by Fried using the following established measures:<sup>14</sup> 1) Exhaustion was defined as a score of ≤55 on the vitality scale of the SF-36 quality of life measure, an approach used in other studies of frailty;<sup>30,31</sup> 2) Weakness was assessed using a Jamar

dynamometer (Fabrication Enterprises, White Plains, NY).<sup>32</sup> While standing, participants were instructed to squeeze the grip handle as hard as they were able using their dominant hand with a 90-degree flexion at the elbow. The measurement was repeated 3 times and the best results used. Low HGS was defined using cutoffs by Fried which is commonly used and based on one cohort of older participants.<sup>14</sup> Because our cohort included younger participants than in the Fried study, we also performed a sensitivity analysis using a statistically based cutoff of 2 standard deviations below the gender-specific peak mean from 12 large population studies by Dodd et al which included participants <65 years;<sup>33</sup> 3) Participants wore a StepWatch 3 Activity Monitor (OrthoCare Innovations, Washington, DC)<sup>34,35</sup> during waking hours for 7 consecutive days. Low activity was defined as total daily step count <2500,<sup>36</sup> 4) Slowness was defined as a cadence <30 steps/minute,<sup>37</sup> obtained using the StepWatch 3 Activity Monitor reflecting the average steps/minute during the top 30 one-minute periods each day; and, 5) Chronic undernutrition defined using the BMI cutoff of  $\leq 21$  as described in the BODE index.<sup>29</sup>

### Other Covariates

Baseline demographic characteristics and smoking status were obtained by questionnaire. Peak performance, a measure of physical activity, was measured using the StepWatch Activity Monitor and defined as the highest number of steps per minute during the top 30 one-minute periods each day.

### Outcomes

Moderate-to-severe acute COPD exacerbations during the 2-year follow-up were defined as exacerbations treated with prednisone and/or antibiotics, treated in the emergency department or requiring hospitalization. AE-COPDs were identified through standardized phone surveys every 3 to 4 months. All-cause mortality was reported to research coordinators throughout the study duration.

### Statistical Analysis

We compared unadjusted participant characteristics by the frailty phenotype defined by Fried's study: Non-frail (0 frailty measures), Pre-frail (1–2 frailty measures), and Frail ( $\geq 3$  frailty measures) using Wald test with robust standard errors of linear regression models for continuous variables, and Wald chi-square test for categorical variables. For significant comparisons, we calculated p-values for each

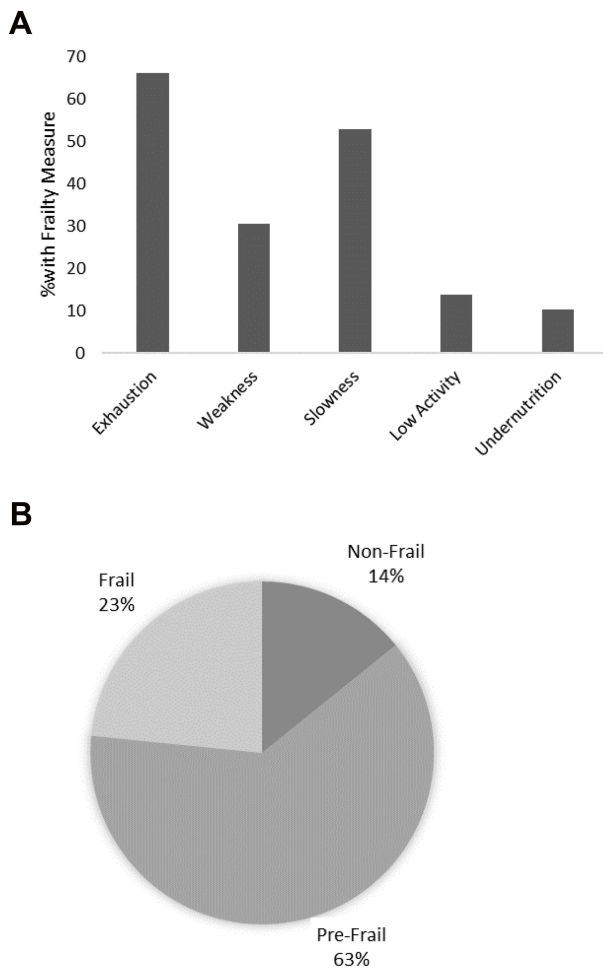
pairwise comparison of baseline characteristic by frailty status with adjustment for multiple testing with Bonferroni correction. Next, we modeled the risk of moderate-to-severe exacerbations, hospitalizations, and mortality over 2 years for each frailty measure. Regression models were adjusted for the following baseline covariates: age, sex, Charlson comorbidity index  $\geq 1$ , supplemental home oxygen use, COPD hospitalizations in the prior year, FEV<sub>1</sub>% predicted, and mMRC score. The logarithm of the total number of days of follow-up was included in the model with the coefficient constrained to 1 to measure time at risk. Due to over-dispersion of AE-COPD and hospitalization data, negative binomial modeling was used producing incidence rates ratios. Cox proportional hazards modeling was used for survival analysis. To examine whether individual comorbidities might confound the relationship between frailty and COPD exacerbations, we examined the association between comorbid conditions and both frailty and COPD exacerbations. A sensitivity analysis was performed with variables associated with frailty and COPD exacerbations at  $p < 0.10$  level to assess whether the coefficient for frailty changed by  $>10\%$ . Analyses were conducted using Stata 15.0 (StataCorp LP, College Station, TX).

## Results

### Participant Characteristics and Frailty Measures

This analysis included 280 participants with complete measures of HGS, physical activity data, and longitudinal follow-up out of 302 enrolled in the CASCADE study. Overall, there was a high prevalence of frailty measures (Figure 1).

Exhaustion (SF 36-vitality scale score  $< 55$ ) was present in 65.6% of participants, slowness (cadence  $< 30$  steps/min) in 52.8%, weakness (low HGS) in 30.1%. Nearly two-thirds of participants fell into the pre-frail category with 1–2 frailty measures (62.4%). Approximately a quarter had 3 or more frailty measures (23.4%) consistent with the frailty phenotype. When using the criteria by Dodd et al to define weakness (low handgrip strength), there was a slightly larger proportion of patients classified as having weakness (37.2% vs 30.1%). The proportion of patients who were pre-frail and frail were similar using the Dodd HGS criteria (non-frail 13.1%, pre-frail 62.1%, frail 24.8%). The study cohort was mainly white non-Hispanic (88%), male (80%) with mean age of 68 years. Non-white participants



**Figure 1** Prevalence of frailty measures at baseline. **(A)** Prevalence of individual frailty measures: Exhaustion (Short Form Health Survey 36 scale score <50); Weakness (low handgrip strength); Slowness (Cadence <30 steps per minute); Low activity (total daily steps <2500); Undernutrition (body mass index  $\leq 21$ ). **(B)** Prevalence of frailty phenotypes: non-frail (0 frailty measures); pre-frail (1–2 frailty measures); Frail ( $\geq 3$  frailty measures).

were more likely to be pre-frail or frail ( $p = 0.04$ ). Comparison of the baseline characteristics found that frail participants were more likely to use home supplemental oxygen ( $p < 0.001$ ; Table 1).

## Frailty and Acute Exacerbations of COPD

The unadjusted rates of moderate-to-severe exacerbations did not differ significantly by frailty phenotype class (Table 2).

Results from adjusted negative binomial regression models examining the association between frailty and acute exacerbations are summarized in Table 3.

There was no association between the frailty phenotype ( $\geq 3$  criteria) and increased risk of moderate-to-severe AE-COPD. Among the individual frailty components,

exhaustion was associated with higher risk of moderate-to-severe AE-COPD (IRR 1.47, 95% CI 1.07–2.01) in unadjusted models but not after adjustment for covariates (IRR 1.25, 95% CI 0.93–1.69). Only weakness, measured by low HGS defined using Fried criteria, was associated with increased risk of AE-COPD (IRR 1.46, 95% CI 1.09–1.97) in adjusted models. Sensitivity analysis using low HGS as defined by Dodd also showed an association with increased risk of AE-COPD (IRR 1.40, 95% CI 1.05–1.85). The frailty measures of slowness and undernutrition were not associated with increased risk of AE-COPD in unadjusted or adjusted models. Low physical activity was associated with a decreased risk of AE-COPD in adjusted models.

In sensitivity analyses, we examined whether individual comorbidities were associated with frailty and COPD exacerbations, and found that only neurologic disease (multiple sclerosis and Parkinson's disease) were associated with both frailty and COPD exacerbations at a  $p < 0.10$ . Adding neurologic disease to the final model did not change the results (data not shown).

## Frailty and Hospitalizations

Those defined as frail ( $\geq 3$  frailty measures) had an increased risk of all-cause hospitalization in the unadjusted analysis using the frailty measure of weakness as defined by Fried et al (IRR 2.26, 95% CI 1.09–4.71), but failed to have a significant association in adjusted analyses (IRR 1.96, 95% CI 0.92–4.19). In both unadjusted and adjusted analyses, individual frailty measures of exhaustion, weakness, slowness, low activity, and undernutrition were not significantly associated with risk of all-cause hospitalizations (Table 3).

In an analysis restricted to non-COPD-related hospitalizations, participants with the frailty phenotype were at increased risk of non-COPD-related hospitalizations (IRR 2.62, 95% CI 1.00–6.84,  $p = 0.05$ ). Among the individual frailty measures, slowness was significantly associated with increased risk of non-COPD hospitalizations whereas there was a non-significant increased risk of non-COPD hospitalizations with exhaustion, weakness and low activity.

In a sensitivity analysis using the Dodd et al criteria for weakness based on low handgrip strength, similar results were seen (Table 4).

## Frailty and Mortality

There was a low number of deaths in our study population with most deaths occurring in those who were frail (Table

**Table 1** Participant Characteristics (N=280)

	Not Frail n=40	Pre-Frail n=176	Frail n=64	P-value*
Age, yr, mean (SD)	69.4 (8.0)	66.9 (8.4)	68.6 (9.2)	0.14
Sex, female (%)	10 (25.0)	34 (19.3)	12 (18.2)	0.67
Race, non-White (%)	0	23 (13.1)	10 (15.2)	0.04 <sup>b</sup>
BMI				
Mean (SD)	28.5 (3.9)	28.0 (5.9)	28.0 (7.9)	0.82
Low BMI ( $\leq 21$ )	0	12 (6.8)	17 (25.8)	<0.001 <sup>a,b,c</sup>
Current smoker (%)	8 (20.0)	47 (26.7)	21 (31.8)	0.41
COPD Disease severity				
FEV <sub>1</sub> % predicted mean (SD)	49.5 (15.1)	46.9 (15.4)	36.9 (14.5)	<0.001 <sup>b,c</sup>
GOLD severity category				0.002 <sup>b,c</sup>
Moderate (50–80%)	20 (50.0)	78 (44.3)	14 (21.2)	
Severe (30–49%)	14 (35.0)	71 (40.3)	30 (45.5)	
Very severe (<30%)	6 (15.0)	27 (15.3)	22 (33.3)	
mMRC, mean (SD)	1.3 (0.8)	1.9 (1.1)	2.6 (1.0)	<0.001 <sup>a,b,c</sup>
Home supplemental oxygen (%)	9 (22.5)	51 (29.0)	36 (54.6)	<0.001 <sup>b,c</sup>
$\geq 1$ COPD hospitalization prior yr (%)	14 (35)	75 (43)	35 (52)	0.23
Comorbidity				
Charlson Comorbidity Index, $\geq 1$ (%)	18 (45.0)	85 (48.3)	35 (53.0)	0.70
Non-metastatic cancer <sup>**</sup>	7 (17.5)	19 (10.8)	9 (13.6)	0.48
Neurologic disease <sup>#</sup>	3(7.5)	3 (1.7)	1 (1.5)	0.09
Physical Function				
6MWT, mean (SD), feet	1301 (277)	1136 (343)	844(377)	<0.001 <sup>a,b,c</sup>
Physical Activity Data				
Total Daily Steps, mean (SD)	7943 (2978)	6675 (3139)	3030 (1981)	<0.001 <sup>b,c</sup>
Low physical activity (<2500 steps/day)	0	3 (1.7)	36 (54.6)	<0.001 <sup>a,b,c</sup>
Slowness (cadence <30 steps/minute)	0	85 (48.3)	64 (97.0)	<0.001 <sup>a,b,c</sup>
Peak Performance, mean (SD) <sup>###</sup>	36.1 (5.0)	31.6 (7.5)	20.8 (6.8)	<0.001 <sup>a,b,c</sup>
SF-36 Vitality Score				
Mean Vitality Score (SD)	60.9 (5.4)	46.2 (11.7)	39.2 (9.9)	<0.001 <sup>a,b,c</sup>
Low Vitality Score ( $\leq 55$ )	0	124 (70.5)	62 (93.9)	<0.001 <sup>a,b,c</sup>
Handgrip strength, Kg				
Mean Handgrip strength (SD)	35.2 (8.3)	33.9 (9.6)	26.2 (7.8)	<0.001 <sup>b,c</sup>
Low handgrip strength by Fried criteria	0	38 (21.6)	48 (72.7)	<0.001 <sup>a,b,c</sup>
Low handgrip strength by Dodd criteria	3 (7.5)	52 (29.6)	50 (75.8)	<0.001 <sup>a,b,c</sup>

**Notes:** \*P-value for Wald test with robust standard errors of linear regression models for continuous variables, and Wald chi-square test for categorical variables. \*\*Non-skin cancer, no lymphoma or leukemia. <sup>#</sup>Multiple sclerosis or Parkinson's. <sup>###</sup>Peak performance is defined as the top steps/minute during the top 30 one-minute periods each day. <sup>a</sup>p<0.0167 comparing not frail and pre-frail participants. <sup>b</sup>p<0.0167 comparing not frail and frail participants. <sup>c</sup>p<0.0167 comparing pre-frail and frail participants. **Abbreviations:** SD, standard deviation; BMI, body mass index; mMRC, Modified Medical Research Council Dyspnea Scale; SF-36, Short Form Health Survey 36.

2). In unadjusted analysis, there was an association between weakness as defined by Dodd and increased risk of mortality (HR 2.36, 95% CI 1.03–5.38). In all other unadjusted and adjusted analysis, there was no significant association between frailty measures and death (Table 5).

## Discussion

In this prospective cohort study of COPD patients, the prevalence of pre-frailty and frailty was high. The frailty phenotype was associated with an increased risk of non-COPD hospitalizations, but not with the risk of moderate-to-severe

**Table 2** Mean Annual Exacerbation, Hospitalization Rates and Mortality by Frailty Category

Outcome	Not Frail n=40	Pre-Frail n=176	Frail n=64	P-value*
Moderate-to-severe exacerbations per year, mean (SD)	0.59 (0.70)	0.75 (0.89)	0.87 (1.16)	0.27
All-cause hospitalizations per year, mean (SD)	0.20 (0.41)	0.34 (0.65)	0.49 (0.68)	0.02 <sup>b</sup>
Non-COPD hospitalizations per year, mean (SD)	0.10 (0.23)	0.17 (0.41)	0.22 (0.37)	0.12
Mortality, n (%)	3 (7.5)	8 (4.6)	10 (15.2)	0.02 <sup>c</sup>

**Notes:** \*P-value for Wald test with robust standard errors of linear regression models for continuous outcome variables and Wald chi-square test for mortality frequency. <sup>b</sup>p<0.0167 comparing not frail and frail participants. <sup>c</sup>p<0.0167 comparing pre-frail and frail participants.

**Table 3** Associations Between Frailty Measures and Acute COPD Exacerbations and All-Cause Hospitalizations Using Handgrip Strength Based on Fried et al Criteria

Frailty Measures*	Moderate-Severe COPD Exacerbations		All-Cause Hospitalizations		Non-COPD Hospitalizations	
	Adj. IRR (CI)**	p-value	Adj. IRR (CI)**	p-value	Adj. IRR (CI)**	p-value
Number of frailty measures						
Non-frail (0)	ref		ref		ref	
Pre-frail (1–2)	1.13 (0.74–1.72)	0.57	1.36 (0.70–2.64)	0.36	1.58 (0.68–3.70)	0.29
Frail (≥3)	1.14 (0.69–1.89)	0.62	1.96 (0.92–4.19)	0.08	2.62 (1.00–6.84)	0.05
Individual frailty components						
Exhaustion (SF 36-vitality score <55)	1.25 (0.93–1.69)	0.14	1.49 (0.95–2.33)	0.09	1.51 (0.86–2.66)	0.15
Weakness (Low HGS based per Fried)	1.46 (1.09–1.97)	0.01	1.27 (0.81–2.01)	0.30	1.23 (0.70–2.18)	0.47
Slowness (Cadence <30 steps/min)	0.86 (0.64–1.16)	0.32	1.14 (0.74–1.76)	0.55	1.96 (1.13–3.38)	0.02
Low activity (Total daily steps <2500)	0.55 (0.35–0.88)	0.01	1.03 (0.56–1.91)	0.93	1.33 (0.61–2.90)	0.48
Undernutrition (BMI ≤21)	0.95 (0.61–1.47)	0.80	0.93 (0.47–1.85)	0.84	0.83 (0.34–2.04)	0.69

**Notes:** \*Each frailty measure represents an independent model. \*\*Adjusted for Age, Sex, Charlson comorbidity index ≥ 1, FEV1, nMRC, Home O2, Prior COPD hospitalizations in the past year.

**Abbreviations:** IRR, incidence rate ratio; CI, confidence interval; SF-36, Short Form Health Survey 36; HGS, handgrip strength; BMI, body mass index.

**Table 4** Sensitivity Analysis: Associations Between Frailty Measures and Acute COPD Exacerbations and All-Cause Hospitalizations Using Handgrip Strength Based on Dodd et al Criteria

Frailty Measures*	Mod-Severe COPD Exacerbations		All-Cause Hospitalizations		Non-COPD Hospitalizations	
	Adj. IRR (CI)**	p-value	Adj. IRR (CI)**	p-value	Adj. IRR (CI)**	p-value
Number of frailty measures						
Non-frail (0)	Ref		Ref		Ref	
Pre-frail (1–2)	1.13 (0.73–1.75)	0.59	1.16 (0.59–2.27)	0.67	1.30 (0.55–3.08)	0.54
Frail (≥3)	1.12 (0.67–1.87)	0.65	1.83 (0.86–3.88)	0.12	2.62 (1.02–6.74)	0.05
Weakness (Low HGS based per Fried)	1.40 (1.05–1.85)	0.02	1.27 (0.83–1.96)	0.27	1.47 (0.87–2.49)	0.15

**Notes:** \*Each frailty measure represents an independent model. \*\*Adjusted for Age, Sex, Charlson comorbidity index ≥ 1, FEV1, mMRC, Home O2, Prior COPD hospitalizations in the past year.

**Abbreviations:** IRR, incidence rate ratio, CI, confidence interval HGS, handgrip strength.

exacerbations in adjusted analyses. Of the five standard measures of frailty, only handgrip strength was independently associated with increased risk of moderate-to-severe AE-COPD.

Our findings add to the existing evidence that pre-frailty and frailty are common among persons with COPD. The prevalence of the frailty phenotype using the criteria of Fried et al in this outpatient cohort of COPD

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**Table 5** Associations Between Frailty Measures and Mortality

Frailty Measures*	Adjusted HR (CI)**	P-value
<b>Number of frailty measures</b>		
0	Ref	
1–2	0.58 (0.15–2.29)	0.43
≥3	1.47 (0.34–6.38)	0.61
<b>Individual frailty components</b>		
Exhaustion (SF 36-vitality scale score <55)	0.83 (0.34–1.99)	0.67
Weakness (Low HGS per Fried)	1.31 (0.33–1.96)	0.30
Weakness (Low HGS per Dodd)	1.49 (0.61–3.61)	0.38
Slowness (Cadence <30 steps/min)	1.93 (0.67–5.53)	0.22
Low activity (Total daily steps <2500)	1.16 (0.36–3.76)	0.81
Undernutrition (Low weight BMI ≤21)	1.87 (0.58–6.01)	0.29

**Notes:** \*Each frailty measure represents an independent model. \*\*Adjusted for Age, Sex, Charlson comorbidity index ≥ 1, FEV1, MMRC, Home O2, Prior COPD hospitalizations in the past year.

**Abbreviations:** HR, hazard ratio; SF-36, Short Form Health Survey 36; HGS, handgrip strength; BMI, body mass index.

patients was similar to the pooled prevalence described in a systematic review by Marengoni (23% vs 19%, respectively).<sup>19</sup> Similarly, the prevalence of pre-frailty in this study was 64%, compared to 56% described by Marengoni et al.<sup>19</sup>

Like other studies we found that frailty is associated with non-COPD hospitalizations, however, the frailty syndrome as a whole was not associated with the key COPD outcome of exacerbations. When the individual components of the frailty syndrome were examined separately, however, handgrip strength was predictive of COPD exacerbations. To the best of our knowledge, this is the first study that describes an association between low HGS and increased risk of AE-COPD in a prospective analysis, and the results are consistent with a cross-sectional study that found that HGS was associated with risk of COPD exacerbations in the past year.<sup>23,38</sup> HGS is also associated with quality of life measured with the EuroQOL EQ-5D in COPD,<sup>39</sup> and another measure of limb muscle strength, quadriceps strength, predicted mortality in COPD.<sup>25</sup> Limb muscle dysfunction is common in COPD, and is related to poor exercise tolerance.<sup>24</sup> The exact mechanism in which low HGS contributes to increased risk of AE-COPD has not been well understood, however. The relationship between HGS and exacerbations was similar whether we used the same cut-offs for low HGS from Fried's original study, or using the reference range by Dodd et al that defined low HGS as 2 standard deviations below the predicted peak handgrip strength as an adult.<sup>14,33</sup>

Frailty is a broader syndrome than low handgrip strength and is characterized by a physiologic state of

decreased reserve causing vulnerability to adverse events.<sup>40,42</sup> Overall the relationship between frailty and COPD outcomes is unclear.<sup>19,42</sup> We used Fried's framework to define frailty based on the presence of ≥3 out of 5 frailty measures.<sup>14</sup> Since we did not have identical measures used to define the Fried criteria, we used externally validated criteria. We defined frailty measures of slowness and low activity with objectively measured data obtained through a validated accelerometer, undernutrition by baseline BMI, and exhaustion by the SF 36-vitality scale score.

Interestingly, we found that except for handgrip strength, the other 4 measures of physical frailty were not associated with a significantly increased risk of AE-COPD. Exhaustion showed a trend towards increased risk of exacerbations, but slowness, low activity and undernutrition were not associated with exacerbations. Low physical activity, defined as total daily steps <2500,<sup>36</sup> was associated with a decreased exacerbation risk (IRR 0.55, 95% CI 0.35–0.88), but there was no association between low physical activity and risk of non-COPD hospitalizations. This result was unexpected as prior studies have shown that decreasing step count is associated with an increased risk of acute exacerbations and COPD hospitalizations.<sup>43–45</sup> The reason why low physical activity might reduce exacerbation risk is unclear, although patients with low step counts may theoretically be limiting potential environmental exposures triggering exacerbations.

We had few participants with undernutrition (10%) and were not able to assess weight loss prior to baseline visit, limiting the utility of this frailty measure. Therefore, in

COPD, physical measures of frailty such as slowness, low activity, and undernutrition appear to be less predictive of AE-COPD than weakness or exhaustion. The participants in this study had moderate-to-severe COPD and therefore it is possible that some of the frailty components such as slowness and low activity are already captured in the COPD severity measures of FEV1, dyspnea (mMRC) and home oxygen use. We found that frailty was associated with increased risk of non-COPD-related hospitalizations. This suggests that the frailty phenotype is still an important risk factor for non-COPD-related hospitalizations.

Although the frailty phenotype was associated with increased risk of mortality, this were not statistically significant. We suspect this was largely driven by a lack of statistical power given the low number of deaths (21 deaths) over the two-year course of the study. This is supported by the fact that two factors that commonly associated with mortality in COPD (low BMI<sup>29</sup> and weakness<sup>46</sup>) had increased point estimates for mortality but were not statistically significant.

Our finding that HGS is the main frailty measure predictive of AE-COPD supports other studies that have suggested that HGS alone may be a useful marker of frailty and those with decreased physiologic reserve.<sup>47,48</sup> Assessing weakness by measuring handgrip strength can be easily done in clinical practice for COPD patients and could provide important prognostic information and identify patients who may benefit from targeted interventions.<sup>18,19</sup> Prior studies have shown reversibility in frailty and sarcopenia status with pulmonary rehabilitation.<sup>19,40,41,49</sup> More detailed longitudinal studies on frailty, weakness, and COPD-related outcomes are warranted in addition to further study on the potential impact of pulmonary rehabilitation on COPD outcomes in frail patients.

Several limitations are worth noting. The majority of our sample were men and frailty is more common in older women.<sup>50</sup> Additionally, due to the primary aim of the main study, participants were excluded if they were chronically using oral corticosteroids or had chronic inflammatory states other than COPD. Although these exclusion criteria reduced the confounding because of steroids or other inflammatory states on the relationship between frailty and COPD outcomes, they may limit the generalizability of our findings and may have selected for a healthier baseline study population. Another potential limitation is the use of frailty measure definitions that did not exactly match the original Fried definitions. However, similar to others,<sup>22</sup> we were careful to use externally

developed criteria to represent the measures of exhaustion, slowness, low physical activity, and undernutrition/weight loss.

The use of accelerometer data from a 7-day period to define slowness and low physical activity may be biased by the Hawthorne effect, in which participants behave differently initially due to being observed but over time return to their usual physical activity not captured by the accelerometer. In the final model to predict non-COPD hospitalizations, we were not able to adjust for prior non-COPD hospitalizations which may have influenced the results. As previously discussed, the low number of deaths over the study duration likely resulted in an underpowered analysis for evaluation between frailty and mortality. Finally, exacerbation and hospitalization data were obtained through regular surveys, but ultimately reliant on patient self-report.

## Conclusion

The results of this longitudinal cohort study show a high proportion of patients with COPD are either frail or pre-frailty of frailty, and that the individual frailty measure of weakness, as defined by low handgrip strength, was significantly associated with increased risk of moderate-to-severe acute exacerbations of COPD. The frailty phenotype was not associated with COPD exacerbations but was associated with an increased risk of non-COPD-related hospitalizations. Evaluating weakness as measured by low handgrip strength in patients with COPD identifies a high-risk population that could potentially benefit from targeted interventions to prevent exacerbations and for interventions that can improve muscle weakness in COPD such as pulmonary rehabilitation. Future studies should examine whether interventions for frailty and weakness may reduce adverse outcomes in COPD.

## Abbreviations

AE-COPD, acute exacerbations of chronic obstructive pulmonary disease; BMI, body mass index; CASCADE Study, COPD Activity: Serotonin Transporter, Cytokine, and Depression Study; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume; FVC, forced vital capacity; HGS, handgrip strength; IRR, incident rate ratio; SD, standard deviation.

## Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. N. Y. contributed data to analysis and interpretation, preparation

of the manuscript, and served as principal author. E.R. L. contributed to the study design, data acquisition, data analysis and interpretation, and preparation of the manuscript. K. C.P, J.L., and Z.C. contributed to the data analysis and interpretation. J.C.H contributed to the preparation of the manuscript. H.Q.N. contributed to the study design and preparation of the manuscript. V.S.F. contributed to the study design, data analysis and interpretation, and preparation of the manuscript.

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