Frailty Assessment in a Stable COPD Cohort: Is There a COPD-Frail Phenotype?

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The frailty syndrome increases the morbidity/mortality in older adults, and several studies have shown a higher prevalence of this syndrome in patients with Chronic Obstructive Pulmonary Disease (COPD). The aim of this study was to identify the characteristics of frail patients with COPD to define a new phenotype called "COPD-frail." We conducted a cross-sectional study in a cohort of patients with stable COPD, classified as either frail, pre-frail, or non-frail. Sociodemographic, clinical, and biochemical variables were compared between the three groups of patients. The study included 127 patients, of which 31 were frail, 64 were pre-frail, and 32 non-frail. All subjects had FEV1/FVC below the lower limit of normal (range Z-score: -1.66 and -5.32). Patients in the frail group showed significantly higher scores in the mMRC (modified Medical Research Council) scale, the CAT (COPD Assessment Test), and the BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity) index. They also showed differences in symptoms according to GOLD (Global Initiative for Chronic Obstructive Lung Disease), as well as more COPD exacerbations, less physical activity, more anxiety and depression symptoms based on HADS (Hospital Anxiety and Depression Scale), and lower hemoglobin, hematocrit, and 25-hydroxycholecalciferol levels. Variables with independent association with frailty included the mMRC score, the HAD index for depression and age. In summary, differential characteristics of frail patients with COPD encourage the definition of a "COPD-frail" phenotype that—if identified early—would allow performing interventions to prevent a negative impact on the morbidity/mortality of these patients.

Keywords: COPD, frailty, phenotype, COPD-frailty

Running Title: Identifying a COPD-Frailty Phenotype.

Introduction

According to the consensual definition, frailty is "a medical syndrome with multiple causes that is characterized by diminished strength, endurance, and reduced physiological function, or reserve, that increases an individual's vulnerability for developing increased dependency and/or death" [1], with Geriatrics being one of the medical specialties that pioneered the development of its definition. Frailty has been wrongly considered a synonym of aging, comorbidity, or disability. However, this condition is not limited to older people, and it may also be identified in middle-aged adults. Likewise, we can find frail and non-frail profiles among older adults, irrespective of their age.

Frailty is also associated with chronic diseases in both ways: the presence of chronic conditions increases the risk of frailty [1–3], and the presence of frailty may increase morbidity and mortality by accelerating the physical decline of these patients [4, 5]. Hence, the assessment of frailty is of paramount importance, regardless of the main diagnosis [5]. Pneumology is one of the specialties in which this diagnosis becomes more necessary due to the increasing evidence of a relationship between frailty and chronic respiratory diseases [6, 7].

Consequently, in recent years a remarkable interest in the study of frailty in patients with chronic obstructive pulmonary disease (COPD) has arisen. Recently, a systematic review and meta-analysis showed the risk of frailty among patients diagnosed with COPD is two-fold that of adults of the same age without this diagnosis [8]. This relationship may be because COPD and frailty share some risk factors, including aging, smoking, inflammation [9], and clinical manifestations such as fatigue, anorexia, muscle weakness, and slow walking speed [10]. In this sense, Lahousse et al. suggested that both pathologies might have a common physiopathology [11]. However, none of the articles found refers to the term COPD-frail phenotype.

Nevertheless, some of the above-mentioned symptoms may remain unnoticed if frailty is not assessed in COPD patients. Thus, early assessment and diagnosis of frailty might help physicians identify patients at higher risk of experiencing adverse events and establish early interventions and treatments to mitigate or reverse the frailty condition. For this reason, this study aimed to identify sociodemographic, clinical, and biochemical characteristics of patients with a concomitant diagnosis of COPD and frailty to identify a patient phenotype that we have called "COPD-frail."

Methods

Study Design and Population

This was a cross-sectional study based on a consecutive screening of COPD outpatients followed-up in the Pneumology Service of the University Hospital La Ribera (Valencia, Spain) between April 2018 and July 2018.

We included patients aged ≥ 40 years and diagnosed with COPD according to the Global Initiative for Chronic Lung Disease (GOLD) [12]. Exclusion criteria were patients who experienced a COPD exacerbation within four weeks before the initial visit, presented with any other clinically relevant respiratory disease and/or a concomitant oncological disease, and had a life expectancy of fewer than six months.

According to the Declaration of Helsinki and the Spanish Organic Act on Data Protection (LOPD 3/2018), the study was conducted. The study protocol was approved by the University Hospital La Ribera Clinical Research Ethics Committee, and all patients signed informed consent.

Variables and Assessments

At the beginning of the study, the following demographic and clinical characteristics of participants were collected: age, sex, date of COPD diagnosis, number of COPD exacerbations during the previous year (recorded both at outpatient visits and hospital admissions), and the exhaled nitric oxide fractions. The comorbidity burden was assessed using the modified Charlson Comorbidity Index; dependence, using the Lawton and Brody scale; anxiety and depression, using the Hospital Anxiety and Depression Scale (HADS); dyspnea, using the modified Medical Research Council (mMRC) scale; the impact of symptoms, using the COPD Assessment Test (CAT); and physical activity, using the Spanish Short Version of the Minnesota Leisure Time Physical Activity Questionnaire (VREM). We also included data from a recent (i.e., up to six months before inclusion) spirometry and six-minute walk test in patients without available results within the specified time window underwent the test in the study visit.

In the study visit, fasting blood samples were collected to determine hemoglobin, hematocrit, white blood cells, neutrophils, platelets, fibrinogen, total protein, albumin, C-reactive protein, brain natriuretic peptide, lactate dehydrogenase, and 25-hydroxycholecalciferol. We also performed a nutritional screening of study participants by assessing the controlling nutritional status (CONUT) using albumin, total cholesterol, and lymphocyte values, as described by Ulíbarri et al. [13].

COPD patients were classified based on the GOLD guidelines 2017, including lung function and symptoms [12]. Frailty was assessed using the Fried scale [5], which rates the frailty degree based on five items: involuntary loss of ≥5 kg of weight in the past year, fatigue (i.e., affirmative response to one of the two questions of the CES-D scale), low physical activity (i.e., weekly kcal bellow 383 in men and 270 in women), slow gait (i.e., the average velocity for walking 4.5 m < 20% of the sex- and height-adjusted normal limit), and weak grip strength (i.e., < 20% of

the sex- and body mass index-adjusted normal limit). Patients were classified: 1) as frail if they met three or more criteria; 2) pre-frail if they met one or two criteria; and 3) non-frail if they did not meet any criteria.

Sample size

The power of the study was calculated, and with the Insize macro for SPSS, Insize type = CI1p / p0 = 11 / apre = 5, the estimated sample size was 106. The sample size was increased by 20% to compensate for possible losses. Finally, the sample size was 127 participants. With this sample size, the power of the study was 94.56%.

Statistical Analysis

Qualitative variables were described as frequencies and percentages, and quantitative variables as mean and standard deviation (SD). Differences between groups of qualitative variables were analyzed using the Chi-square test. The corresponding differences of quantitative variables were analyzed using unifactorial ANOVA after verification of normality using the Kolmogorov-Smirnov test. Post hoc analyses were conducted using Bonferroni and Tukey methods. Associations between clinical and biochemical variables and frailty were determined using binary logistic regression by estimating the odds ratio (OR) adjusted by sex, age, and the Charlson Comorbidity Index score. A conditional forward stepwise binary logistic regression was used to build a multivariate model. First, the full model was considered with all variables significantly associated with frailty in the univariate analysis. In a second step, any variable not causing an important change—defined as the absence of an adjusted effect of more than 10%—or not improving estimation's standard error upon adjusting the model without this variable was removed from the model. All comparisons were bilateral, and the threshold of statistical significance was set at 0.05. All statistical analyses were performed using the SPSS 23.0 software (IBM Corp, Armonk, NY).

Results

Characteristics of the Study Population

Demographic and Clinical Characteristics

The study included 127 patients diagnosed with COPD, the majority of which were male (n=108; 85.0%), with a mean (SD) of 66.5 (7.9) years, a body mass index (BMI) of 27.6 (5.4) kg/m^2 and a mean of 60.0 (31.4) packs of cigarettes smoked per year. Considering the age range of our sample, we calculate the lower limit of normal (LLN) of each subject, and in all of them, the LLN was lower than -1.645 (range Z-score: -1.66 and -5.32). The study cohort showed high comorbidity and good functionality based on the Charlson Comorbidity Index (mean [SD] of 4.5 [1.8]) and the Lawton and Brody scale (mean [SD] of 6.7 [1.7]) respectively.

The patients of the study population were classified as frail (n=31; 24.4%), pre-frail (n=64; 50.4%) and non-frail (n=32; 25.2%). Table 1 shows the main baseline characteristics of the three groups. Compared with pre-frail and non-frail groups, frail patients showed higher dependence in daily instrumental activities, —estimated using the Lawton scale score. Likewise, the *post hoc* analysis revealed higher HADS-DEP and HADS-ANX scores among frail patients than pre-frail and non-frail patients. Conversely, no between-group differences were observed regarding the Charlson Comorbidity Index scores, social condition, BMI, percentage of active smokers, age, sex, or packs of cigarettes smoked per year.

Respiratory and Physical Activity Characteristics

Table 2 summarizes the respiratory and physical activity variables in the study cohort. Frail patients reported a higher sensation of dyspnea and impact of symptoms than pre-frail and non-frail patients (Figure 1 and Figure 2). Furthermore, all frail patients were symptomatic based on the GOLD classification and had experienced more exacerbations during the previous year

than the other two patients groups. Frail patients were the only ones with more than two hospitalizations due to these exacerbations. Likewise, frail patients showed a higher percentage of prescribed domiciliary oxygen therapy than the pre-frail and non-frail groups (Table 2). We did not observe significant differences regarding respiratory function (FEV1%) between study groups; however, frail patients reported a higher BODE score (Figure 3) and shorter distance walked in the six-minute walk test. Physical activity, estimated using VREM, was lower in frail and pre-frail patients than non-frail patients (Figure 4).

Biochemical and Nutritional Characteristics

Regarding the analytical parameters of nutrition and inflammation, frail patients showed lower hemoglobin, hematocrit, and albumin levels than pre-frail and non-frail patients and a higher number of neutrophils in the blood than in non-frail patients. The ANOVA analysis showed significant differences regarding total protein between study groups; the *post hoc* analysis did not reveal between-group differences pairwise. Frail patients had lower plasma levels of 25-hydroxycholecalciferol than pre-frail and non-frail patients (Table 3).

Factors That Influence Frailty

Table 4 summarizes the univariate and multivariate analyses' results to predict frailty based on demographic, clinical, and biochemical characteristics. Variables associated with a decreased risk of frailty included the Lawton scale score and hemoglobin levels (Table A4). On the other hand, variables associated with a higher risk of frailty include the HAD-DEP scores, mMRC, CAT, BODE, GOLD symptoms, the number of hospital admissions due to exacerbations and treatment with additional oxygen (Table 4A). In the parsimonious predictive model, age, mMRC, and HAD-DEP scores were the three variables more strongly associated with frailty (Table 4B).

Discussion

In this cross-sectional study in patients with COPD, we observed a 24.4% prevalence of frailty. Our analysis revealed various characteristics of frail patients that significantly differed from pre-frail and non-frail ones: a higher dependence in daily instrumental activities, a higher number of anxiety and depression symptoms, a higher sensation of dyspnea, a higher impact of COPD symptoms, a higher number of exacerbations during the previous year, a higher BODE score, less distance walked in the six-minute walk test, a higher number of drugs prescribed for COPD, and lower hematocrit, hemoglobin, albumin, and 25-hydroxycholecalciferol in plasma values. The variables more strongly associated with frailty were mMRC and HAD-DEP index scores and age. Nevertheless, given that a phenotype should be a stable condition, it cannot be demonstrated in a cross-sectional study. Indeed, a number of attributes used to define the frailty phenotype may represent disease activity at the time of study.

The prevalence of frail and pre-frail subjects observed in our study are consistent with those found in a recent study, which reported frailty and pre-frailty frequencies ranging from 9% to 28% and 48% to 64%, respectively.[8] Of note, frail patients in our cohort were not older nor showed higher comorbidity than pre-frail or non-frail patients. This finding, which is consistent with those reported by Limpawattana et al. [14] and Kennedy et al. [15], emphasize that the frailty syndrome is not due to age or comorbidity *per se*, although both factors are associated with a higher prevalence of frailty [16,17]. In line with previous studies, we did not observe any differences between groups concerning patients' BMI or social condition [7,14,15].

Like previous studies investigating frailty in COPD patients [7,11,14,18,19], frail patients in our cohort showed more symptoms and exacerbations and less physical activity, factors that have been associated with higher mortality in COPD patients [20-22]. Aside from the influence of individual symptoms or clinical characteristics, frailty itself has also been identified as a good predictor of COPD adverse events, with increasing evidence regarding its relationship

with COPD-related mortality [7,11,15,23,24].

It is worth noting that physical activity was the only variable that showed statistically significant differences among pre-frail and non-frail patients, which is consistent with a recent study [25]. The authors of this mentioned study pointed out that the level of physical activity could predict the presence or absence of frailty in COPD patients. In our study, as can be seen in Table 4, the limits of the confidence interval are near to non-significance.

The relationship between functional results and frailty is more controversial, with some studies reporting an association between frailty and poorer respiratory performance [8,18], and others—like ours—that failed to find significant relationships between the two factors [7, 14]. Still, in our analysis, we identified frail patients in the early stages of the disease (GOLD 1 and 2). This finding, also reported by Mittal et al. [7] and Maddocks et al. [18], suggest that the vulnerability of the "COPD-frail" patient might start in an early stage, regardless of lung function, and highlights the need for a multidimensional assessment—including frailty—from the beginning of the disease management.

Frailty status is a dynamic process, as shown in a recent systematic review in community-dwelling older adults [26], but the likelihood of reversing frailty without intervention is minimal [3]. Although there are no guidelines for treating frail COPD patients, different studies support that it is possible to reverse frailty in COPD patients [19,27,28].

Early assessment and diagnosis of frailty might help physicians identify patients at higher risk of experiencing adverse events and establish early interventions and treatments to mitigate or reverse the frailty condition.

Taken together, our results and the cumulative evidence on the role of frailty in some COPD patients encourage the definition of a COPD-frail phenotype, understood phenotype as “a single or combination of disease attributes that describe differences between individuals with COPD

as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death)" [29].

This study corroborates previously reported information about the relationship between frailty and COPD. Additionally, we provide new data, including the association between frailty and COPD severity and the possibility of early onset of frailty in COPD patients, which encourages frailty assessments at the beginning of COPD management.

Despite these strengths, our study also has limitations that should be highlighted. The main limitation of our study is the cross-sectional design that is not able to observe patients' temporary evolution, and cannot allow us to confirm the presence of the COPD-frail phenotype. For this reason, we are currently conducting a longitudinal study to obtain this information.

Although we have used a standardized and validated frailty measure, applying the same cut-off points described by Fried for another population might underestimate of overestimate the characteristics of this study population. The reporting bias has been limited using a well-trained staff in the use of scales and measurements, thus reducing the bias due to limited expertise and the influence of participants' subjectivity. Likewise, we established broad selection criteria that minimize screening biases. The real-world approach of our analysis also limited the number of patients.

Nevertheless, the sample size achieved allowed powered statistical comparisons between groups. Probably, we should have included cardiovascular disease in the analysis and do not use only Charlson Index. Also as we measured frailty, the scope of the study should not have been only in a hospital setting but also in primary care, where patients are managed from the early stages. On the other hand, all patients were recruited at the same site, so the results of our study might not be extrapolated to other areas. Finally, due to our recruitment's single-center approach, caution should be taken when extrapolating our results to other areas.

Conclusions

In our study, patients considered "COPD-frail" showed a higher deterioration of their nutritional, functional, and clinical statuses. Higher severity and longer time of evolution of COPD in these patients determined a phenotype with a poorer prognosis, highlighting the significance of identifying frailty in COPD patients. However, it is necessary to conduct longitudinal randomized clinical trials to confirm the presence of this frailty phenotype and quantify the benefit of early assessment and interventions on frailty in COPD patients.

Abbreviations:

BMI: Body Mass Index; BODE: Body mass index, airflow Obstruction, Dyspnea and Exercise capacity; CAT: COPD Assessment Test; CONUT: Controlling Nutritional status; COPD: Chronic Obstructive Pulmonary Disease; FeNO: Exhaled Nitric Oxide; FEV1: Forced Expiratory Volume in one second; FVC: Forced Vital Capacity; GesEPOC: Spanish Guidelines for COPD; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HADS: Hospital Anxiety and Depression Scale; mMRC: modified Medical Research Council; VREM: Spanish Short Version of the Minnesota Leisure Time Physical Activity Questionnaire.

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