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REVIEW

# Frailty assessment in older adults with chronic obstructive respiratory diseases

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**Abstract:** The number of patients with chronic obstructive pulmonary disease (COPD) has been rising with continued exposure to environmental risk factors and aging of populations around the world. Frailty is a geriatric syndrome with a decline in physiological reserve and often coexists with chronic diseases such as COPD. Frailty is an independent risk factor for the development and progression of COPD, and COPD can lead to frailty; treating one might improve the other. Thus, there is an increasing interest in the assessment of frailty in patients with COPD. Furthermore, early identification and assessment of frailty in patients with COPD may affect the choice of intervention and improve its effectiveness. Based on the current literature, the intent of this review was to summarize and discuss frailty assessment tools used for COPD patients and the relevant clinical practices for predicting outcomes. We ascertain that using suitable frailty assessment tools could facilitate physicians to screen and stratify physically frail patients with COPD. Screening appropriately targeted population can achieve better intervention outcomes and pulmonary rehabilitation among frail COPD patients.

**Keywords:** frailty, COPD, elderly, assessment, intervention

## Introduction

As the world's population ages, frailty is becoming more and more important in health and medical care. Frailty can be regarded as a common sequela of aging; however, it is different from aging and disability as up to 75% of patients >85 years of age are not frail.[1] Frailty is a geriatric syndrome that has been defined as a state of increased vulnerability from age-associated decline in reserve and function, resulting in reduced ability to cope with daily or acute stressors.[2,3] Once stressors strike, frail older adults are more prone to disastrous health outcomes, even disability and death.[4–7] Frailty has been shown to be highly correlated with the quality of life, hospital admissions, and mortality,[8–11] as well as untoward consequences of other geriatric syndromes, such as falls, delirium, depression, cognitive impairment, and incontinence.[12] It should be noted that frailty, in our belief, definitely calls for a practical and a more holistic viewpoint in the care of elderly patients.[13] However, the symptoms of frailty will go unnoticed by physicians in primary care and clinics, unless frailty is actively identified. The authors are happy to see that an international consensus group has suggested that all persons >70 years of age should be screened for frailty.[14]

Frailty often coexists with chronic diseases. Recent studies have suggested a higher prevalence of frailty in people with chronic conditions.[15,16] Despite the fact that more than half of the older people with chronic diseases such as heart failure[17] and chronic obstructive pulmonary disease (COPD) might be frail,[6] most physicians often focus on specific diseases, such as diabetes, heart failure, and COPD, instead of the early diagnosis

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and intervention of frailty, which might lead to the occurrence of unexpected adverse outcomes in older adults. Once frailty develops, a new physiological stressor (eg, acute exacerbation of COPD [AE-COPD] or critical illness) can overwhelm the already diminished physiologic reserve, resulting in disability, severe morbidity, or even death.[18] Therefore, the American Geriatrics Society (AGS), the National Institute on Aging (NIA), and the Alliance for Academic Internal Medicine held a joint conference in 2015 with the purpose to advance the field of frailty research among relevant medical specialties.[19]

COPD is a common, preventable, treatable disease that is characterized by persistent respiratory symptoms and airflow limitations. COPD is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[20] COPD is projected to become the third leading cause of death by 2020. More than 3 million people died of COPD in 2012, accounting for 6% of all deaths globally.[21] The COPD burden is projected to increase in the ensuing decades because of continuing exposure to COPD risk factors and the aging of the population.[22] In the elderly, the diagnosis of COPD is often delayed due to atypical symptoms; the frequency of acute exacerbations is higher than that in the younger people, and respiratory failure is more likely to occur among the elderly.

To date, frailty has been used to assess many chronic diseases, such as cardiovascular diseases, chronic kidney disease, and obesity.[23–25] Increasing attention is being given to frailty assessment in patients with chronic lung diseases.[26] Indeed, several recent studies have shown a significant increase in the incidence of frailty in chronic lung disease.[27,28] The prognostic utility of frailty in patients with chronic respiratory diseases for mortality and hospitalization has been validated,[29–31] and physical frailty has been shown to be amenable to treatment with pulmonary rehabilitation.[32] However, frailty assessment in older adults with COPD is still controversial. In this review, we summarized assessment tools for frailty in patients with COPD, briefly presented the underlying pathological pathways and potential biomarkers for frailty and COPD, and discussed the strategies for prevention and intervention in frail older adults with COPD.

## Prevalence of frailty in patients with COPD

Depending on the assessment methods and heterogeneity of the population, the prevalence of frailty varies greatly.[33,34] The general trend of frailty prevalence increases with age, and the prevalence in women is higher than that in men. Frailty is estimated to affect 10.7% of community-dwelling adults >65 years of age, 15.7% of adults 80–84 years of age, and 26.1% of adults >85 years of age.[35] In frail females, the probability of falling is threefold greater than those who are not frail.[36]

The prevalence of frailty in patients with COPD has been reported to range from 6.6% to 75.5%, depending on the populations studied the frailty screening tools used;[6,28,29,32] frailty has been shown to correlate with the severity of COPD.[4,29] A recent meta-analysis[37] showed that patients with COPD have a twofold greater risk for frailty than patients without COPD. Specifically, the pooled prevalence of pre-frailty with COPD was 56% (95% CI=52%–60%; $I^2$=80.8%) and that of frailty with COPD was 20% (95% CI=15%–24%; $I^2$=94.4%).[37]

## Common pathological pathways and biomarkers for frailty and COPD

COPD and frailty share some important common risk factors. Cumulative exposure to tobacco, respiratory infections, occupational dust, and air pollution and advanced age can lead to respiratory impairment. In turn, respiratory impairment can increase the risk for adverse outcomes. In addition to respiratory tract symptoms, extrapulmonary manifestations in COPD patients are very similar to the symptoms of frailty, such as fatigue, weight loss, reduced physical activities, muscle weakness, and osteoporosis. Once frailty develops, the AE-COPD, as a new physiological stressor, can result in progressively worsening conditions ranging from disability and morbidity to death. The frequent coexistence of COPD and frailty seems to suggest a common underlying pathophysiological mechanism (see later).[29]

## Inflammation

Inflammation is known to play an important role in the development of COPD. Moreover, chronic inflammation is considered to be one of the primary pathobiological changes driving frailty.[38] A number of studies have focused on inflammation and frailty.[39–43] Frail adults have increased serum levels of the proinflammatory cytokine, interleukin-6, compared with non-frail adults,[44] which has been consistently found to be associated with frailty in both cross-sectional[45] and prospective studies.[39–43] The Cardiovascular Health Study (CHS) reported that frail participants had an increased level of C-reactive protein (CRP),[42] and tumor necrosis factor-alpha and receptors were shown to be associated with frailty.[40,46,47] Patients with COPD showed signs of chronic inflammation; higher levels of systemic proinflammation

biomarkers are associated with poorer physical functioning, more exacerbations, and death.[48–50]

## Endocrine dysfunction

Endocrine dysfunction, especially the hypothalamic–pituitary axis, which controls metabolism and energy use through the signaling actions of a series of homoeostatic hormones,[51] has also been found to be associated with frailty. Frail adults have lower levels of IGF-1,[52–56] sex hormones,[57,58] 25-hydroxy vitamin D,[59–62] and dehydroepiandrosterone (DHEA).[63,64] COPD affects the function of the endocrine system through hypoxemia, hypercapnia, systemic inflammation, and glucocorticoid administration. In turn, altered endocrine function may further contribute to the already aggravated clinical manifestations of COPD.[65]

## Sarcopenia

Clinically, frailty may copresent with sarcopenia. Sarcopenia, defined as an abnormally low lean muscle mass combined with low muscle strength or function,[66] is a fundamentally important cause of frailty.[67] The mechanisms underlying sarcopenia include protein and micronutrient deficiencies, chronic inflammation, endocrine dysregulation, and disuse atrophy.[68] Several studies found that sarcopenia is more common in patients with COPD than in matched healthy controls.[69–71] In addition, adults with COPD exhibit skeletal muscle dysfunction at the biochemical, cellular, and structural levels.[72,73] Finally, as the severity of COPD and the concomitant dyspnea worsens, patients can experience decrease in muscle strength, impaired mobility, sarcopenia, and ultimately, frailty.

## Assessment tools for frailty used in COPD and clinical practice

Increasing evidence supports the use of frailty assessment to predict clinical outcomes in patients with chronic lung diseases, especially with COPD (Table 1). Screening for frailty can be used as a prognostic tool to help with treatment decision-making and risk stratification; this will have

**Table 1** Summary of the selected studies on frailty and COPD in different populations

| First author, year (reference no) | n | Country | Design | Frailty tool | % frail with COPD | Main results |
|---|---|---|---|---|---|---|
| **Based on community dwelling** | | | | | | |
| Vaz Fragoso, 2012[31] | 3,578 participants, 13.8% airflow limitation and 9.3% restrictive pattern | USA | Cross-sectional and longitudinal analysis | FFP | No COPD frail data Pre-frail 48.3% and frail 5.8% in CHS data | Frailty and respiratory impairment were strongly associated with one another. When frailty and respiratory impairment were both present, it will increase the risk of death |
| Lahousse, 2016[29] | 2,142 participants, 402 with COPD and 1,740 without COPD | The Netherlands | Prospective population-based cohort study | FFP | Pre-frail 51.2% and frail 10.2% | Frailty identified those COPD participants at high risk of mortality |
| Park, 2013[6] | 20,470 participants, 211 with COPD | USA | Cross-sectional study | TFI | Pre-frail 21.8% and frail 57.8% | Individuals with COPD who had self-reported shortness of breath and comorbid diabetes were more likely to be frail than those who did not. Frail people tended to have a greater number of disabilities |
| Galizia, 2011[102] | 1,288 (489 with COPD and 799 without COPD) | Italy | Cross-sectional study, 12-year follow-up | FSS | Frailty 48.9% with COPD and 36.8% without COPD | Clinical frailty COPD had a high risk of mortality |
| Akgün, 2016[81] | 3,538 HIV-infected participants and 3,606 HIV-uninfected participants, 4% and 5% had COPD | USA | Cross-sectional | aFRP | No COPD frail data Pre-frail 32.2% and frail 3.0% in HIV infected; pre-frail 33.0% and frail 2.6% in HIV uninfected | COPD was strongly associated with frailty and physical limitations. The association was stronger among those with both HIV infection and physical limitation than among those without HIV infection |

(*Continued*)

**Table 1** (*Continued*)

| First author, year (reference no) | n | Country | Design | Frailty tool | % frail with COPD | Main results |
|---|---|---|---|---|---|---|
| **Stable COPD outpatients in clinic or rehabilitation center** | | | | | | |
| Gale, 2018[92] | 520 diagnosed with COPD and 150 comparator group | UK | Cross-sectional analysis Community-based patients with COPD | FI-CGA | Frail 28% | Patients with COPD were more likely to be frail than comparators. Frailty could be predicted by the number of comorbidities and the number of exacerbations per year as well as physical function |
| Limpawattana, 2017[86] | 121 COPD patients | Thailand | Cross-sectional study of COPD in clinic | FRAIL | Frail 6.6% and pre-frail 41.3% | Fatigue was the major component of frailty in these populations |
| Kusunose, 2017[96] | 79 COPD patients | Japan | Prospective, consecutive COPD outpatients | KCL | Pre-frail 30.4% and frail 21.5% | Frailty was significantly related with SGRQ. Frailty assessment should be included in the multidimensional assessment of COPD and separated from lung function assessment |
| Mittal, 2016[28] | 120 participants with chronic lung disease, 56% with COPD | USA | Prospective | FFP | Pre-frail 64% and frail 18% | Frailty was common in patients with chronic lung diseases. Exhaustion and slow gait speed were the two most common markers of frailty |
| Maddocks, 2016[32] | 816 | UK | Prospective | FFP | Pre-frail 64.3% and frail 25.6% | Frail patients responded favorably to rehabilitation, and their frailty can be reversed in the short term |
| **Clinically advanced COPD in hospital** | | | | | | |
| Baldwin, 2017[79] | 618 with advanced lung disease, 130 older ICU survivors | USA | Prospective, multicenter cohort | FFP-MLTA and FFP-DASI | Advanced frail 42%–1% and ICU 49%–12% | MLTA had a substantially greater floor effect than the DASI. The DASI improved the construct and predictive validity of frailty assessment |
| Uchmanowicz, 2016[4] | 102 | Poland | Prospective, hospitalized due to exacerbation | TFI | 75.5% | Elderly patients with severe COPD may be more prone to frailty and decreased acceptance of their disease in comparison to patients suffering from other chronic diseases |
| Bernabeu-Mora, 2017[99] | 103 | Spain | Prospective, hospitalized | REFS | Mild frailty 25%, moderate frailty 27.8%, and severe frailty 66.7% | Identifying patients with frailty for targeted interventions may reduce early readmission rates |
| Valenza, 2016[121] | 212 (104 stable and 108 exacerbation) | Spain | Cross-sectional study | Modified FFP Modified Baecke physical activity | Stable 64.8% and exacerbation 62.6% | Physical activity level can predict the absence or presence of frailty in subjects with stable and exacerbated COPD |

**Abbreviations:** aFRP, adapted frailty-related phenotype; COPD, chronic obstructive pulmonary disease; FFP, Fried frailty phenotype; CHS, Cardiovascular Health Study; TFI, Tilburg Frailty Indicator; FSS, Frailty Staging System; FI, Frailty Index; CGA, Comprehensive Geriatric Assessment; KCL, Kihon Checklist; SGRQ, St George's Respiratory Questionnaire; MLTA, Minnesota Leisure Time Physical Activity Questionnaire; DASI, Duke Activity Scale Index; REFS, Reported Edmonton Frail Scale.

importance in differentiating patients who will benefit from the treatment from those who may obtain no benefit or even experience harmful consequences from interventions and pulmonary rehabilitation.[32,74]

## Fried frailty phenotype (FFP)

Most studies involving the interactions between COPD and frailty were assessed by the FFP. The FFP,[75] often known as the CHS index, has five core domains, including slowness

(slow gait speed), weakness (low grip strength), low physical activity (Minnesota Leisure Time Activity), exhaustion (Center for Epidemiologic Studies-Depression [CES-D] questionnaire), and weight loss (self-reported weight loss of 4.5 kg or recorded weight loss of 5% in the last year). Patients with 3–5, 1–2, and 0 factors are classified as frail, pre-frail, and robust, respectively. The FFP is the most frequently cited frailty tool[76] and has been used to predict mortality and adverse clinical outcomes in large cohorts of community-dwelling elders.[77,78]

In the following, we describe several studies to demonstrate the relevance and impact of FFP frailty assessment; these studies were each carried out with a different participant group, ie, community-based, stable COPD outpatients, and advanced COPD in hospital and immunodeficient patient group, respectively.

## Community-based population

Vaz Fragoso et al[31] used the CHS data for their community-based, large population study and evaluated the relationship between a modified version of the FFP and respiratory impairment in 3,578 participants; respiratory impairment included airflow limitation or restriction as measured by spirometry using contemporary protocols of the American Thoracic Society. Participants completed a battery of assessments at baseline and 4 years thereafter and underwent up to 12 years of vital status follow-up evaluations. After adjusting for relevant covariates, pre-frail and frail participants were found to have a 42% higher likelihood of developing respiratory impairment than participants who were non-frail. Conversely, participants with respiratory impairment at baseline had a 58% higher likelihood of developing pre-frailty or frailty than participants without respiratory impairment at baseline. The impact of baseline respiratory impairment and frailty status on mortality appeared to be synergistic as well. Compared with non-frail subjects with normal respiratory function, frail subjects with respiratory impairment had a nearly fourfold higher risk for death. The risk for death was at least twofold higher for frail subjects with respiratory impairment than that for non-frail subjects with respiratory impairment or frail subjects without respiratory impairment. Another population-based study evaluated 2,142 community-dwelling older adults (402 with COPD and 1,740 without COPD) who had an FFP assessment and underwent spirometry.[29] The participants with COPD were more than twice as likely to be frail as those without COPD; this association was stronger with COPD of increased severity according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. During an average follow-up of 805 days, frail participants with COPD had a nearly threefold higher mortality rate than non-frail participants without COPD. Notably, frailty status was a stronger determinant of mortality than the $FEV_1$% or comorbidity.

## Stable COPD outpatients

FFP was also used for assessing frailty in stable COPD outpatients. Mittal et al[28] reported that frailty is relatively common in ambulatory patients with chronic lung diseases recruited from clinics and a rehabilitation center. Patients with COPD accounted for 56% of the total patients. Frail patients had higher self-reported hospitalizations and falls and lower gait speeds. Based on FFP, self-reported exhaustion (90.5%) and slow gait speed (76.2%) were the most common frailty criteria. The simple screening tool, gait speed, can be used to screen frail patients with a high sensitivity but a low specificity. To evaluate the rehabilitation outcomes of stable COPD outpatients, a study[32] showed that frail patients with stable COPD appropriate for a pulmonary rehabilitation referral had more difficulty engaging in pulmonary rehabilitation. Frailty is both a strong and an independent risk factor for failure to complete pulmonary rehabilitation than smoking status, breathlessness, or low mood. Although frail patients with COPD were more unlikely to complete rehabilitation, the frailty phenotype was reversed for stable COPD patients who did complete pulmonary rehabilitation. In addition, they appeared to have more favorable rehabilitation outcomes, including physical, psychological, and global health improvement.[32] Therefore, proactively screening frail stable COPD patients and researching a better means to support frail patients through rehabilitation will direct clinicians to make a greater effort to identify suitable patients for pulmonary rehabilitation referral who are more likely to benefit from the intervention.

## Clinically advanced and critical patients

For frailty assessment in patients with advanced and critical lung disease, the FFP has limitations. Baldwin et al[79] showed that the Minnesota Leisure Time Physical Activity Questionnaire (MLTA) has a significant floor effect in patients with advanced lung disease and in critical care survivors. In this study,[79] they measured frailty physical activity using the Duke Activity Scale Index (DASI) and the MLTA in two cohorts of patients (advanced lung disease patients awaiting lung transplantation and survivors of acute respiratory failure). The results[79] showed that the DASI performed better and had a less pronounced floor effect than MLTA in this patient population and was more predictive of frailty outcome. The DASI queries activities more relevant to adults with

advanced lung disease or to survivors of critical illness, and thus can minimize misclassification of frailty attributable to low activity and can better discriminate between different levels of activities relevant to the fields of pulmonary and critical care medicine.[79] The FFP is based on the experience of suburban community-dwelling older adults who had fewer activity limitations than adults with advanced lung disease or older survivors of acute respiratory failure.[79] Because of this fundamental context, it is perhaps not surprising to see that FFP has proven limited utility for the care of this category of patients.

## Immunodeficient population

An adapted FFP (Multicenter AIDS Cohort Study [MACS]-based survey with four domains [physical shrinking, exhaustion, slowness, and decreased physical activity]) was used to measure frailty in an immunodeficient population drawn from the Veterans Aging Cohort Study (VACS) by comparing HIV-infected individuals with HIV-uninfected individuals. COPD was an independent risk factor for frailty in HIV-infected patients;[80] it was diagnosed in 4% of 3,538 HIV-infected participants and 5% of 3,606 HIV-uninfected participants. Using the adapted frailty-related phenotype (aFRP) assessment tool, 59% of HIV-infected patients and 58% of HIV-uninfected patients with COPD met the criteria for pre-frailty vs 34% of HIV-infected patients and HIV-uninfected patients without COPD. The association between COPD and the physical limitation scale was stronger in HIV-infected participants compared with HIV-uninfected participants.[81]

Overall, FFP is a practical assessment tool for frailty patients with COPD and has been widely adopted by the research and clinical communities.

## FRAIL scale

FRAIL, proposed by the International Association of Nutrition and Aging,[82] comprises five components (fatigue, resistance, ambulation, illness, and loss of weight). FRAIL is administered in the format of a simple, self-report questionnaire based on the phenotype model. Patients reporting 3–5, 1–2, and 0 factors are classified as frail, pre-frail, and robust, respectively. In addition, FRAIL is an independent risk factor for predicting mortality and adverse outcomes in specific populations.[83–85]

Using the FRAIL scale, a cross-sectional study in Thailand reported that the prevalence of frailty in COPD patients was 6.6%. Each component of the FRAIL scale showed a greater rate in frail patients than that in non-frail patients, and fatigue was the main factor of frailty in these populations. Interestingly, this study was a sub-study of "Sarcopenia in COPD", which found that sarcopenia was indeed associated with frailty. Therefore, in theory, frail COPD patients might benefit from the prevention of sarcopenia.[86] Although the FRAIL scale is a simple, self-report tool to measure frailty based on the phenotype, there have not been any validated studies involving hospitalized participants.

## Frailty Index (FI) and the FI derived from a Comprehensive Geriatric Assessment (FI-CGA)

The Rockwood Accumulative Deficits Index,[87] also referred to as the FI, was developed on the basis of the Canadian Study of Health and Aging (CSHA) as a multidimensional measure of frailty. The FI expresses the theory of gradation of frailty with progressive accumulation of deficits, each of which has an equal weight in mathematical modeling;[88] FI involves the accumulation of 20–70 age-related indicators of health, including comorbidities, symptoms, diseases, disabilities, or any deficiency in health.[89] The deficit model enables the use of clinical data collected from medical records for frailty assessment, thus making it possible to identify frail elderly people who will achieve improved outcomes from interventions.[90] Despite this, the calculation of FI is time consuming, and its mathematical nature renders the FI unpopular in clinics.[91] CGA is the global standard clinical assessment for older people. FI-CGA is a simple FI using data from a CGA. The FI-CGA was calculated by dividing the total number of CGA deficits.

In a community-based cross-sectional analysis, all participants, including 520 patients diagnosed with COPD and 150 comparators, completed a modified version of the CGA questionnaire. Using FI-CGA assessment and the age-adjusted cutoff for frailty from the Survey of Health, Aging, and Retirement in Europe, the study showed that the prevalence of frailty was 28% in COPD patients and 0% in comparators. Frail participants also had poorer lung function and physical activity (handgrip and 6-minute walking distance), greater inflammation (fibrinogen and high-sensitivity CRP) and more exacerbations, symptoms, and a poorer health-related quality of life than comparators.[92]

## Kihon Checklist (KCL)

KCL is a validated frailty measurement tool consisting of 25 yes/no questions proposed by the Ministry of Health, Labor, and Welfare of Japan.[93] The 25 self-report

questions are grouped into seven categories including instrumental (three scores) and social activities of daily living (four scores), physical functions (five scores), nutritional status (two scores), oral function (three scores), cognitive functions (three scores), and mood (five scores).[94] The KCL showed predictive utility for the incidence of dependency and mortality in community-dwelling older people.[95]

Using the KCL frailty assessment tool, Kusunose et al[96] showed a significant association between frailty status and St George's Respiratory Questionnaire in patients with stable COPD. Frailty appeared to have developed via an independent mechanism except for age-related deterioration in patients with COPD. Frailty assessment was recommended to be included as a part of multidimensional measurements of COPD.[96] However, similar to FRAIL scale, further validation studies of the KCL in hospitalized COPD patients need to be undertaken.

## Edmonton Frail Scale (EFS) and Reported Edmonton Frail Scale (REFS)

The EFS, extracted from CGAs, is a valid and reliable screening tool for the identification of frailty. The EFS has a maximum score of 17 and consists of the following domains: cognition, general health status, functional independence, social support, medication use, mood, continence, nutrition, and functional performance.[97] The REFS adapted the domain "get up and go" to a report of physical function, which was developed in acute care. The reported physical function increased the functional score, and therefore, the component scores are summed from items 1 to 18. The severity of frailty is classified as follows: "not frail (0–5), apparently vulnerable (6–7), mildly frail (8–9), moderately frail (10–11), and severe frailty (12–18)".[98]

A prospective study was designed to observe COPD patients hospitalized with exacerbations in acute medical wards and during follow-up within 90 days after hospital discharge. Frailty of patients with AE-COPD was assessed within 48–96 hours of hospital admission using the REFS. Frailty was categorized into the following four predefined categories: not frail or vulnerable (44.7%), mild frailty (19.4%), moderate frailty (17.5%), and severe frailty (18.4%). The 90-day readmission rates were found to increase with the severity of frailty. Patients with "severe frailty" were approximately fivefold more likely to have readmission than those with "non-frail" status. In addition, frailty was an independent predictor of readmission within 90 days in patients with AE-COPD.[99]

## Frailty Staging System (FSS)

The FSS, as an index of functional impairment severity, was modified from a previous screening method for functional disability in elderly people.[100] The FSS covers the following seven core categories: disability, mobility, cognitive function, visual function, hearing function, urinary continence, and social support.[101]

The FSS frailty assessment tool was used in a study involving 489 patients with COPD with a follow-up period of 12 years.[102] The severity of frailty was classified according to the number of frail domains: mild, one domain; moderate, two or three domains; and severe, four or more domains. Mortality was increased from 48.1% in patients without COPD to 60.7% in patients with COPD. In patients with increasing severity of frailty, mortality increased from 54.3% in patients without COPD to 97.0% in patients with COPD. Therefore, clinical frailty may be considered as a prognostic factor when identifying COPD patients at high risk for mortality.[102]

## Tilburg Frailty Indicator (TFI)

The TFI has been proven to have good validity and reliability for community-dwelling older people.[103] The TFI is an easy-to-administer questionnaire based on an integral conceptual model of frailty containing 15 self-report categories (eleven "yes/no" questions and four "sometimes" questions). The TFI refers to the following three categories of frailty: physical frailty (health, unexplained weight loss, difficulty in walking, balance, poor hearing, vision, lack of strength in the hands, and tiredness), psychological frailty (problems with memory, feeling down, anxiety, and inability to cope with problems), and social frailty (living alone, lack of social relations, and social support). A score >5 is the best cutoff point indicative of frailty.[104,105]

Nine-item criteria modified from the TFI were used in a community-based study that included 211 participants with COPD and a history of smoking from the National Health and Nutrition Evaluation Survey (NHANES) dataset (2003–2006) of 20,470 participants.[6] Of the 211 participants, 57.8% were diagnosed with frailty among the participants with COPD. The study showed that patients with COPD who had shortness of breath were more likely to be frail than patients who did not have COPD. Frail people with COPD were associated with impairments in activities of daily living/instrumental activities of daily living.

Uchmanowicz et al used the TFI to evaluate the association between the level of acceptance of illness and frailty in 102 COPD patients hospitalized with an exacerbation.

Frailty was diagnosed in >75% of the COPD patient group. Elderly patients with severe COPD were more prone to frailty and had lower levels of disease acceptance than other chronic diseases. Patients with a higher level of frailty in physical and social domains correlated with a lower level of acceptance of illness.[4]

## Summary

Frailty evaluation in patients with COPD is a feasible prognostic utility for mortality and hospitalization. Physical frailty screening may help identify those patients who will be more likely to benefit from available interventions for other illnesses as shown in the study with frail COPD patients.[31]

The FFP is the most widely used frailty assessment tool and has been validated in many studies. However, in the case of severe COPD exacerbations, it is still very difficult to predict intensive care unit (ICU) outcomes. Identifying patients who are likely or indeed unlikely to benefit from admission to ICU wards would greatly improve the quality of care provided to these patients, enable patients to make better advance directives and allow health care workers to offer palliative care in a timely manner to patients with a high risk for severe morbidity and mortality. As a first step, it is a reasonable strategy to consider using various tools, in their original or modified form, or with different cutoff values to evaluate the effect of frailty on outcomes from intervention delivered to the specific populations.

## Intervention

Frailty is an independent risk factor for exacerbations and progression of COPD, and patients with COPD are also more prone to frailty. Although frailty and COPD affect each other, both frailty and respiratory impairment can be modulated and treated. When one is treated and/or prevented, the other may be improved. Therefore, a more thorough understanding of the relationship between frailty and COPD can help clinicians better prevent and intervene in patients with these two conditions and may reduce the occurrence of poor outcomes.[31]

Muscle wasting, weakness, and malnutrition are common in patients with lung disease and could be responsive to physical exercise training and nutrition optimization. This underscores the importance of rehabilitation. Moreover, pulmonary rehabilitation has been shown to reverse frail patients with COPD who responded well to treatment.[32] Similarly, many factors related to frailty can also be improved through prevention and supportive treatment, such as suitable exercise and nutritional support. Positive treatment effects among these frailty constructs may partially explain why pulmonary rehabilitation improves exercise capacity, disability, and health-related quality of life and reduces hospitalizations and mortality.[106,107] Recent work in older populations has shown that frailty may be reversible through targeted exercise and nutritional interventions.[108–110] It has been postulated that nutritional interventions may be suitable for frail patients with nutritional deficiency and weight loss; however, the evidence for this has been scarce. A systematic review showed that sustained nutritional supplementation had no significant effect on pulmonary function, respiratory muscle strength, and functional exercise capacity in patients with stable COPD.[111] Individual nutrition supplementation may not be able to reverse the decline in muscle strength and function if the intervention is given too late.[112,113] Further research is needed to determine what constitutes effective nutrition interventions.[114]

Some studies have reported the effects of various pharmacotherapies targeting the biological frailty pathway, including angiotensin-converting enzyme inhibitors,[115] DHEA, testosterone, recombinant human growth hormone,[116] and vitamin D.[117] There are no sufficient data to recommend any of these agents for routine use.

There is increasing evidence to support the notion that a comprehensive assessment can help to mitigate the risk factors associated with frailty.[118,119] Frailty and pre-frailty are common in patients with COPD; however, using multidisciplinary intervention, patients with frailty can be reversed, especially at the pre-frailty stage.[120] Therefore, it is critical to diagnose frailty at an early stage. Furthermore, early intervention through comprehensive assessments, referral exercise, and nutritional interventions would prevent and delay the progression of frailty.

## Conclusion

Frailty and COPD have a strong association in aged population. Treating the frailty syndrome will likely reduce risk for poor COPD outcomes. Early recognition of frailty is important in patients with COPD, as early and effective interventions can prevent or delay functional deterioration, institutionalization, disability, and death. Assessment of frail COPD patients can provide better stratification of risks and individual management and improve patient outcomes. There remains controversy in the literature regarding the best frailty assessment tool in older adults with COPD. Some frailty assessment tools are suitable for screening the health status of community populations, whereas others are suitable for assessing outpatients or emergency patients. Further research in this field is warranted, and it should target specific

patient groups in order to establish more effective assessment tools, which would improve the effectiveness of screening and identifying patients at different stages of frailty, thus allowing health care workers to apply individual-specific treatment regimen.

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