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Review Article

Advances in pathophysiology and assessment methods of chronic obstructive pulmonary disease with frailty

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ABSTRACT

Frailty, a multidimensional syndrome characterized by decreased physiological reserves and vulnerability to stressors, presents significant challenges in the management of chronic obstructive pulmonary disease (COPD). COPD and frailty share common risk factors and pathophysiological pathways, such as muscle wasting, chronic inflammation, and malnutrition. Both COPD and frailty lead to a significant reduction in patients' physical functionality and quality of life. Consequently, early screening for frailty and proactive interventions for patients with COPD are increasingly considered essential. There are several methods for screening and assessing frailty in patients with COPD, such as the Fried Frailty Phenotype and the Frailty Index, each with its own advantages and limitations. However, there is currently no unified standard, nor a method specifically tailored to the Chinese population. The treatment of patients with COPD and concurrent frailty currently favors exercise interventions, nutritional interventions, or a combination of both. Further treatment approaches, including pharmacological interventions, are still being explored. Therefore, the development of frailty screening and assessment tools tailored to the Chinese population, along with the exploration of reasonable and effective new intervention measures, represents a crucial direction in China's efforts to prevent and treat frailty.

Introduction

Frailty is conceptually defined as a multidimensional syndrome characterized by diminished physiological reserves and decreased resistance to stressors, which can lead to adverse clinical outcomes such as dependency, disability, falls, and even mortality.[1] This syndrome predominantly afflicts the elderly, with the incidence rate of frailty among them ranging from 4.9 % to 27.3 %, and manifesting multifaceted characteristics across physical, psychological, and social domains.[2–4] As societies age, the population at risk of frailty continues to escalate. Frailty, recognized as one of the most significant global public health challenges of the 21st century, undeniably poses increasingly grave challenges to families, societies, and public healthcare systems.[5] Studies have shown that various factors associated with chronic respiratory diseases can contribute to frailty, and frailty, in turn, can exacerbate the typical functional decline observed in these conditions.[6,7] In the realm of geriatric medicine, comprehensive guidelines for the clinical management of frailty are well-established.[8,9] However, no specific guidelines exist to address the unique needs of individuals with chronic respiratory diseases. Chronic obstructive pulmonary disease (COPD) is a respiratory disorder characterized by partially irreversible airflow limitation and is one of the numerous chronic illnesses linked to frailty.[10–12] This article aims to review the advancements in the epidemiological inquiry, pathophysiological mechanisms, assessment, and rehabilitation interventions for COPD with frailty, to improve the management of frailty in COPD patients.

Epidemiological inquiry into frailty and COPD

According to both domestic and international literature, the prevalence of frailty among COPD patients ranges from 9 % to 28 %, and the prevalence varies significantly based on different assessment methods and criteria.[13–15] This variability is largely due to differences in assessment methods and criteria. Table 1 summarizes the prevalence of frailty in COPD patients across various studies.

A meta-analysis, based on 27 global studies, has indicated that the risk of developing frailty is twice as high in COPD patients compared to those without COPD, highlighting the substantial risk of frailty experienced by individuals with COPD.[12] Furthermore, frailty has been proven to be closely linked to the severity of COPD, acting as an independent risk factor for the acute exacerbation and progression of the disease.[16] Several studies have shown that frailty is highly correlated with the quality of life, hospitalization rates, and mortality, in both stable and intensive care unit (ICU)-admitted patients with COPD.[15,17] It also increases the risk of falls, disability, and depression among the elderly.[6,18–21] Furthermore, the frailty phenotype has been shown to pre-

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Table 1
Prevalence of frailty among COPD patients in various studies.

Population	Country	Sample size	Prevalence of frailty (%)	Notes
Pooled COPD patient population[12]	Various	27 studies involving 60,278 individuals	19%	Patients with COPD exhibited a two-fold increased likelihood of frailty.
Stable COPD patients[15]	USA	280 outpatients with COPD	24.8%	Handgrip strength was predictive of COPD exacerbations.
ICU-hospitalized COPD patients[17]	Australia and New Zealand	7126 patients admitted to the ICU due to COPD exacerbation	54.1%	Frailty was independently associated with a shorter time to death.
COPD patients post-pulmonary rehabilitation[14]	UK	Out of 816 outpatients with COPD, 115 underwent pulmonary rehabilitation.	15.7%	Pulmonary rehabilitation has been shown to significantly ameliorate frailty symptoms

COPD: Chronic obstructive pulmonary disease; ICU: Intensive care unit.

dict the progression of COPD, with handgrip strength emerging as a key indicator of disease exacerbation.[15] Moreover, the mortality rate among frail patients with COPD is higher than that among frail individuals without COPD, suggesting that frailty and COPD can mutually influence each other.[6] Studies indicate that both frailty and respiratory impairments in COPD patients can be managed through interventions such as pulmonary rehabilitation and nutritional support.[14,22,23] Although COPD is inherently a chronic disease characterized by partially irreversible airflow limitation, effective management or treatment of frailty in COPD patients can enhance overall physical function and quality of life, potentially alleviating some respiratory symptoms.[24] The presence of frailty holds significant value in research for altering the prognosis and developing therapeutic approaches for individuals with COPD.[14,25]

Therefore, a deeper understanding of the relationship between frailty and COPD, accurate early identification of frailty, and the implementation of targeted, effective intervention measures to guide respiratory rehabilitation can reduce the risk of the aforementioned adverse outcomes and may even reverse some of these effects.[26,27]

Pathophysiological links between COPD and frailty

The onset and progression of frailty may result from the physiological dysfunction of multiple interrelated systems, manifesting as a constellation of symptoms including fatigue, weight loss, reduced physical activity, muscle weakness, and osteoporosis.[28] Indeed, frailty is increasingly recognized not only as a common comorbidity in COPD but also as a frequently observed comorbidity in other chronic conditions, such as cardiovascular disease, diabetes, and chronic kidney disease.[29,30] This often leads to multimorbidity.

COPD, characterized by partially irreversible airflow limitation, includes not only respiratory symptoms but also fatigue, anxiety, depression, and sleep disturbances.[15,31] These symptoms contribute to an increased risk of frailty, potentially leading to malnutrition and a reduction in muscle mass.[32] Beyond respiratory symptoms, the extrapulmonary manifestations in COPD patients bear a striking resemblance to frailty, indicating associated underlying mechanisms. Currently, the pathophysiological mechanisms of frailty are not fully understood. However, it is recognized that COPD and frailty share common risk factors and pathophysiological pathways, including aging, smoking, muscle atrophy, chronic inflammation, immunosenescence, and endocrine disorders.[33–36] The interaction of these factors results in a synergistic deterioration of bodily functions, significantly impairing the physical functioning and quality of life of patients.

At the molecular level, the relationship between COPD and frailty involves several key pathways, ultimately leading to the development of sarcopenia, which forms the physiological basis of frailty. Chronic systemic inflammation is a biological hallmark of patients with pulmonary diseases, and higher levels of systemic pro-inflammatory biomarkers in patients with COPD are associated with worse outcomes.[37] Pro-inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP), are significantly increased in COPD.[38] These inflammatory markers can activate proteolytic pathways, including the ubiquitin-proteasome system and the autophagy-lysosome pathway, leading to an increased catabolic state of certain muscle and adipose tissues.[39–41] This triggers a decline in the function of respiratory and skeletal muscles and a reduction in physical activity, resulting in respiratory distress and decreased activity levels, further contributing to a decline in muscle mass and function, creating a vicious cycle that precipitates sarcopenia.[42] Compared to non-frail COPD patients, frail COPD patients often exhibit higher levels of inflammation, such as elevated levels of plasma IL-6.[11,43,44] The increase in IL-6 may lead to a higher incidence of ventilatory disturbances or even result in the impairment of bronchial smooth muscle cell function, thereby exacerbating the severity of airflow limitations experienced by these patients.[45] This implies that frailty and chronic respiratory diseases mutually reinforce each other.

Increased oxidative stress caused by smoking and chronic hypoxia can result in mitochondrial dysfunction, which further impairs both respiratory and skeletal muscle function.[46] Moreover, immunosenescence contributes to dysregulated immune responses, characterized by elevated levels of senescent T cells and decreased tissue regenerative capacity, which further exacerbates chronic inflammation and muscle degradation in COPD.[47] Future studies should aim to further elucidate these molecular pathways, especially the role of chronic inflammation and its connection to sarcopenia in the pathogenesis of frailty associated with COPD. The detailed pathogenesis in patients with COPD and frailty is illustrated in Fig. 1.

In addition, between 17% and 49% of the frail population with chronic respiratory diseases suffer from malnutrition.[6] The exact relationship between malnutrition and frailty remains unclear, as it could serve as both a significant risk factor for and a consequence of frailty.[48,49] Malnutrition impairs immune function and increases the risk of infections, which may exacerbate the progression of COPD.[50] This increases vulnerability and susceptibility to systemic functional decline, consequently intensifying the vicious cycle of frailty.[51,52]

Screening and assessment of frailty in COPD

The consensus among American and European experts in 2012 advocates that all individuals over the age of 70 years, and those who have experienced a significant unexplained decline in body mass exceeding 5%, should undergo screening for frailty.[1] Frailty screening refers to the use of a quick and simple method to identify elderly individuals who, although they may seem healthy, are actually frail. This process can slow down the progression of frailty and improve adverse outcomes associated with it. However, the assessment of frailty involves a variety of methods, and there is no universal standard determining which one should be used for patients with COPD. Currently, the Fried Frailty Phenotype (FFP) and the Frailty Index (FI) are recognized as the consensus standards, from which other frailty screening and assessment methods are derived.[53]

The FFP is the primary clinical method for assessing frailty. It diagnoses frailty based on five criteria: involuntary weight loss, self-reported exhaustion, low physical activity, slow walking speed, and weak grip strength.[54] This method primarily focuses on the physiological aspects of frailty in the elderly, providing a manageable number of objectives

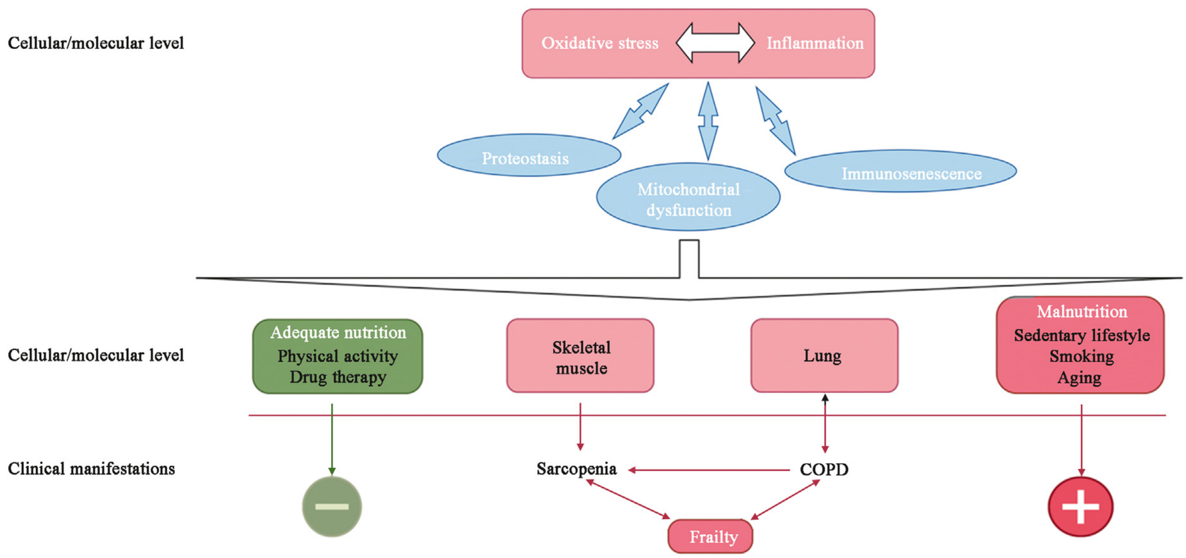

Fig. 1. Pathogenesis for patients with COPD and frailty. COPD: Chronic obstructive pulmonary disease.

and quantifiable indicators suitable for outpatient settings or stable COPD patients.[54] Nonetheless, the FFP has its limitations. Certain measures, such as grip strength, are not suitable for frequent clinical evaluation. Additionally, it does not encompass non-physical factors contributing to frailty, such as environmental, psychological, and cognitive elements.

The FI uses a cumulative deficit model, digitizing abnormal parameters based on the accumulation of health deficits theory to provide a direct representation of an individual's health status and predict the likelihood of adverse events.[55] This model's distinct advantage lies in its broad applicability and comprehensive assessment scope, encompassing 92 potential issues ranging from symptoms and signs to laboratory markers.[55,56] Subsequent research has demonstrated that, without compromising predictive accuracy, 92 assessment indicators can be reduced to 30.[57] This makes it suitable for community screening and epidemiological studies on frailty. However, the FI's extensive and intricate evaluation requirements make it time-consuming and more susceptible to confounding factors. In addition, it lacks the capability to differentiate frailty from disability and comorbidities.

The Clinical Frailty Scale (CFS) allows healthcare professionals to assign scores ranging from 1 (very healthy) to 9 (very frail) following a comprehensive assessment of the patient.[58] During acute COPD exacerbation, patients often suffer from chest tightness, breathing difficulties, and require multiple monitoring devices, often rendering them unable to cooperate with complex frailty assessments. In such instances, the CFS, a simple, rapid, and non-physical examination-based method of assessing frailty, is often advantageous and recommended for hospitalized patients with COPD.[59] Given its subjective nature, the CFS requires physicians with specialized expertise to minimize assessment bias.

The Kihon Checklist (KCL) is a multidimensional, self-reported screening method developed in Japan and widely used within the country.[60,61] It evaluates seven dimensions: functional daily living abilities, physical activity, nutritional status, oral function, social conditions, cognitive abilities, and emotional state. Each domain is equipped with its own frailty threshold, offering references for more targeted frailty assessments in subsequent evaluations.[62,63] More and more scholars are advocating for a multidimensional conception of frailty that encompasses physical, psychological, emotional, social, and cognitive aspects.[64,65] Methods for assessing frailty across multiple dimensions, like the KCL, are recognized for their higher efficiency in identification and superior predictive power regarding adverse outcomes.[66–68] Given that both China and Japan are located in East Asia and share the same ethnic background, this method can serve as a reference for frailty screening and subsequent targeted interventions among the elderly population in Chinese communities.

Traditional frailty screening methods also include the Short Physical Performance Battery (SPPB), the Edmonton Frailty Scale (EFS), and the fatigue, resistance, ambulation, illness, loss of weight (FRAIL) scale, which should be selected by existing literature and specific clinical or community settings through detailed analysis.[6,69–71] The specific advantages and limitations of each method are presented in Table 2.

In addition, certain questionnaires related to the respiratory system also serve as screening tools for frailty in patients with COPD.[14,72,73] For example, findings from several studies demonstrate a correlation between the frailty level of COPD patients and their scores on the modified British Medical Research Council (mMRC) and the COPD Assessment Test (CAT).[74,75] According to the Greek UNLOCK study, the prevalence of frailty escalates with increasing mMRC and CAT scores, signifying them as the more potent predictors of frailty.[76] This underscores the critical importance of symptom burden and health status in the management of COPD. By correlating mMRC and CAT scores with frailty, we can better identify patients at higher risk of adverse outcomes, enabling more targeted interventions aimed at prevention or improvement. Further research comparing frailty assessment methods and respiratory questionnaires in screening, diagnosing, and prognosis of COPD patients is eagerly anticipated.

Rehabilitation interventions for COPD with frailty

Given the incompletely elucidated pathogenesis of frailty, there is currently a lack of specific curative treatments. Efforts are instead focused on prevention and slowing disease progression. The general strategies include managing triggers, medication, rehabilitation exercises, dietary adjustments, and psychological support, among others. At present, there is a lack of specific medications for frailty. Considering that a portion of elderly COPD patients are in poor health and have numerous medication contraindications, non-pharmacological interventions prove to be safer and more effective. These mainly include exercise interventions, nutritional interventions, and a combination of both.

Exercise intervention

The decline in skeletal muscle mass and function represents a crucial intermediary in the vicious cycle between COPD and frailty. The strength of the respiratory muscles is negatively correlated with both frailty and its precursory states.[77] Hence, exercise-based pulmonary

Table 2
Commonly used methods to evaluate frailty with COPD.

Method	Domains assessed	Score range	Advantages	Limitations
Fried Frailty Phenotype (FFP)	Nutritional status, physical activity, mobility, strength, and energy	Range: 0–5	Simple, validated for clinical use, focuses on physical frailty, widely used.	Limited to physical domains, doesn't assess psychological or social factors; time-consuming for clinical practice due to performance-based tests (e.g., grip strength).
Frailty Index (FI)	Distinct diseases and their consequences including nutritional status, physical activity, mobility, strength, energy, cognition, mood, and social relations or social support	Range: Varies widely depending on specific measure but includes at least 30 items for a valid Frailty Index	Comprehensive, considers a wide range of health aspects, good for epidemiological studies.	Time-consuming, requires extensive data, harder to apply in clinical settings.
Clinical Frailty Scale (CFS)	Nutritional status, physical activity, mobility, strength, energy, cognition, mood, and social relations or social support	Range: 0–7	Quick, easy to use, particularly effective during acute COPD exacerbation	Subjective, requires expert judgment to avoid bias.
Kihon Checklist (KCL)	Instrumental, social activities of daily living, physical strength, nutritional status, oral function, cognitive status, depression risk	Range: 0–25	Multidimensional, more comprehensive in capturing the full scope of frailty, suited for community use.	Self-reported, relies on patient accuracy, limited validation in populations outside of Japan.
Short Physical Performance Battery (SPPB)	Physical activity, mobility, strength, and energy	Range: 0–12	Objective measurement, simple scoring system, suitable for outpatient settings, validated in COPD.	Primarily focused on physical function; does not include cognitive or psychological assessments. Variability in cut-off scores can lead to different frailty categorizations.
Edmonton Frail Scale (EFS)	Cognition, general health, functioning, social support, medication use, nutrition, mood continence, physical performance	Range: 0–17	Holistic, covers multiple dimensions, suitable for hospital settings.	Requires more clinical time, less specific to COPD.
FRAIL Scale	Fatigue, resistance, ambulation, illness, loss of weight	Self-reported	Easy to administer, self-reported, suitable for large-scale community screening.	Limited scope; focuses predominantly on physical frailty; self-reported data may introduce bias, less accurate in predicting clinical outcomes compared to more objective tools.

COPD: Chronic obstructive pulmonary disease; FRAIL: Fatigue, resistance, ambulation, illness, loss of weight.

rehabilitation programs are instrumental in enhancing the respiratory function, swallowing capability, and limb muscle function of patients, thereby improving the state of COPD-associated frailty.[78–80] Research conducted by Maddocks *et al*[14] demonstrates that approximately 60 % of patients with COPD and concurrent frailty show improvement following pulmonary rehabilitation training, affirming the long-term efficacy of pulmonary rehabilitation exercise. Furthermore, compared to non-frail patients with respiratory diseases, frail patients who engage in pulmonary rehabilitation treatments show enhancements in physical condition, along with a decrease in symptoms of anxiety and depression.[14,81] This highlights the significant role of pulmonary rehabilitation in alleviating symptoms of anxiety and depression in patients with COPD, particularly those who are also dealing with frailty.[82] Exercise training, used as an intervention for frailty, is cost-effective and easy to administer. However, elderly patients with COPD exhibit significant variability in their baseline health statuses, resulting in diverse levels of tolerance towards physical activity. Therefore, Wang *et al*[34] have pointed out that pulmonary rehabilitation treatment plans should be tailored to the individual, as personalized treatment strategies contribute to maximizing benefits. The "frailty rehabilitation paradox" indicates that patients with COPD and frailty are approximately twice as likely to be unable to complete pulmonary rehabilitation programs due to physical reasons.[14,83] The use of mobile or telehealth services to enhance program adherence warrants further investigation. Overall, aerobic exercises or endurance training, can enhance exercise tolerance and alleviate dyspnea in patients with COPD. These exercises also improve mitochondrial function, as well as pulmonary function and sarcopenia.[84–86]

Nutritional intervention

Malnutrition, a common comorbidity in patients with COPD and frailty, may be associated with a decline in muscle strength, exercise capacity, and fatigue due to deficiencies in nutrients such as protein, vitamin D, and carbohydrates.[48] Therefore, the early implementation of nutritional support plays a positive role in improving the state of frailty among the elderly population. Nutritional supplementation in malnourished COPD patients can significantly improve maximum inspiratory pressure and maximum expiratory pressure, enhancing the recovery of skeletal muscle quality, exercise capacity, and respiratory muscle strength.[87,88] Therefore, nutritional intervention offers specific benefits for patients with COPD who are frail and malnourished.

Nutritional management is an integral component of a multidisciplinary holistic care approach. Beyond just addressing nutrition, it involves tackling issues like managing symptoms like nausea, fatigue, or pain, enhancing cognition, and offering psychological and social support. These efforts may alleviate anxiety and depression, influencing a patient's energy intake.[89,90] This, in turn, enhances the role of good nutritional management in aiding the rehabilitation of frailty.[91]

Combined interventions

Combining exercise and nutritional interventions is crucial for the prevention and treatment of frailty. Studies have shown that oral nutritional supplements, combined with physical exercise, can enhance physical function, nutritional status, and quality of life in frail elderly individuals.[92] Providing nutritional support during high-intensity interval training for COPD patients with reduced muscle mass can increase lower limb muscle strength and exercise capacity.[93,94] Therefore, increasing physical activity and ensuring adequate nutritional supplementation have beneficial effects in improving conditions for COPD patients with frailty.

In addition, the role of therapeutic drugs related to sarcopenia, such as angiotensin-converting enzyme inhibitors, growth hormones, testosterone, and vitamin D, in the treatment of frailty remains in the exploratory stage, and no definitive conclusion has been reached yet.[95,96]

In the future, rehabilitation interventions for frailty should focus on exploring the efficacy of personalized, home-based rehabilitation programs and telemedicine-delivered interventions, especially for patients who are unable to attend in-person treatments. These approaches aim to maximize adherence and improve outcomes for frail patients with COPD. Furthermore, combining innovative pharmacological methods with established non-pharmacological strategies, such as exercise and nutrition, could provide comprehensive solutions for more effectively managing frailty symptoms in COPD. Investigating these multifaceted interventions through well-designed clinical trials will be crucial for establishing evidence-based guidelines to improve frailty outcomes in COPD populations.

Summary and prospect

Frailty, as a syndrome of dysfunction across multiple organ systems, significantly deteriorates the quality of life and clinical outcomes for patients with COPD. Building upon the foundation of prior research, this article succinctly summarizes the pathophysiological characteristics of COPD associated with frailty, alongside the assessment methods and intervention measures available. Given the close association between the pathogenesis and clinical manifestations of frailty and COPD, treating or preventing one condition may likely benefit the other. The early stages of frailty present a prime opportunity for pulmonary rehabilitation interventions.[97] Early assessment, identification, and intervention of frailty is crucial in preventing or slowing down its progression, thereby improving the adverse outcomes for patients with COPD. Although there are various screening and assessment methods for frailty, including the FFP and FI, each with its own advantages and disadvantages, the absence of a unified standard highlights the need for further standardization and regulation. Moreover, there is a phenomenon of using a mix of various screening and evaluation methods. Moreover, most of them, proposed by foreign experts and institutions, do not adequately address the needs of the Chinese population. Studies have shown that the prevalence and characteristics of COPD with frailty in the Chinese population can differ significantly from those observed in Western populations. For instance, COPD patients with frailty in China tend to have a higher prevalence of malnutrition, lower body mass index, and a greater burden of comorbidities such as cardiovascular diseases and diabetes.[98–101] In addition, cultural factors and disparities in healthcare access are key determinants in the management and outcomes of frailty for COPD patients in China.[100,101] Therefore, the development of frailty screening and assessment methods tailored for the Chinese population, followed by appropriate interventions based on screening and assessment results, represents a focused direction for the prevention and treatment of frailty in China.

CRediT authorship contribution statement

Xia Wang: Writing – original draft. **Weiping Hu:** Writing – review & editing. **Jing Zhang:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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