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REVIEW

Frailty in COPD: Clinical Impact, Diagnosis, Biomarkers, and Management Strategies

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Abstract: Frailty is a complex clinical syndrome characterized by reduced physiological resilience and heightened susceptibility to external stressors, culminating in increased risks of functional decline, hospitalization, and mortality. In individuals with chronic obstructive pulmonary disease (COPD), frailty exacerbates disease burden and is closely linked to adverse outcomes, including increased exacerbation frequency, diminished quality of life, and poor prognosis. This review synthesizes current evidence on the interplay between frailty and COPD, emphasizing clinical implications, diagnostic frameworks, emerging biomarkers, and tailored management strategies. A systematic literature search was conducted across PubMed, Scopus, and Embase databases, employing key terms such as "frailty", "chronic obstructive pulmonary disease", "COPD", "frailty assessment", "biomarkers", and "frailty management in COPD". Inclusion criteria targeted English-language studies reporting original data with a direct focus on frailty in the context of COPD. By synthesizing multidimensional assessment strategies and potential therapeutic modalities, this review supports the development of precision-based interventions to reduce frailty and improve outcomes in patients with COPD.

Keywords: frailty, COPD, frailty assessment, frailty scales, frailty biomarkers

Introduction

COPD - According to the definition by GOLD 2024 report, it is a highly heterogeneous lung disease characterized by persistent respiratory symptoms that are caused by abnormalities in the airways (bronchitis, bronchiolitis) and/or air sacs (emphysema), along with worsening airflow obstruction that is generally progressive. Besides its cardinal respiratory features, COPD is well recognized as a systemic disease with many extrapulmonary manifestations, including frailty.[1,2] Frailty, traditionally associated with older adults, has gained recognition as a crucial factor in assessing overall health, even in younger populations with chronic conditions. The estimated prevalence of frailty among individuals aged 65 years and older ranges from 10% to 20%, contingent upon the definitional framework and assessment methodology employed, reflecting the inherent heterogeneity in diagnostic criteria and measurement constructs across clinical and epidemiological studies.[3,4] In contrast, emerging research indicates that frailty may also affect a substantial proportion of younger adults with COPD. In a recent study, frailty was found to impact up to 30% of individuals under the age of 65 who suffer from COPD, which is notably higher than the prevalence in the general population of a similar age.[5] Reported prevalence rates of frailty among individuals with COPD exhibit considerable variability, ranging from approximately 10% to over 70%, largely influenced by the heterogeneity of study populations and the divergent frailty assessment instruments employed across investigations.[3,6] This variability stems from the use of different conceptual models and measurement approaches. Two primary models dominate the field: the phenotype model, typified by the Fried criteria, which defines frailty based on five physical components such as weakness and low physical activity;[7] and the deficit accumulation model, exemplified by the Frailty Index, which quantifies frailty based on the cumulative number of health

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deficits.[8] These differing frameworks capture distinct aspects of vulnerability and contribute to the heterogeneity in frailty prevalence reported in COPD populations. The clinical impact of frailty in COPD is critical.[9] Various crucial factors are associated with frailty in COPD patients, including chronic systemic inflammation, a decrease in physical activity, frequent exacerbation, and the cumulative effects of aging and comorbidities. These factors cooperatively contribute to the decline of cognitive, physical, and physiological function, all hallmark features of COPD.[4,10–12]

Numerous tools and criteria have been developed to evaluate frailty, ranging from simple screening methods such as the Clinical Frailty Scale (CFS) and the Frailty Index (FI) to more comprehensive assessments like the Fried Frailty Phenotype (FFP) and the Edmonton Frail Scale (EFS). To comprehensively assess frailty, these tools integrate multiple areas, including physical function, cognitive status, and psychological well-being.[13] The use of these tools in COPD patients is still being researched, as the specific characteristics of frailty in COPD may necessitate individualized assessment techniques.[11,14]

A multifaceted route addressing both the physiological and psychosocial dimensions of COPD is necessary for the prevention and management of frailty in COPD.[15] Emerging research increasingly recognizes frailty as a critical and independent determinant of adverse outcomes in COPD. Traditionally associated with aging, frailty is now being identified across a broader age spectrum, including younger individuals with COPD, suggesting a complex interplay between chronic systemic inflammation, functional decline, and multimorbidity.[5] This review endeavors to synthesize contemporary evidence on the prevalence, pathophysiological underpinnings, and clinical implications of frailty in COPD, particularly within non-geriatric populations, thereby highlighting its relevance in comprehensive patient assessment, risk stratification, and the development of individualized management strategies.

Search Methods and Selection Criteria

A narrative review methodology was employed. Relevant literature was identified through searches in PubMed, Scopus, and Embase, focusing on studies published in English up to March 2025. Inclusion criteria encompassed original research, reviews, and clinical guidelines addressing frailty and systemic biomarkers in COPD. Exclusion criteria included studies unrelated to COPD or frailty and non-peer-reviewed sources. Approximately 240 articles were screened, with 123 deemed relevant and cited in the final manuscript.

Clinical Implications of Frailty in COPD

The clinical relevance of frailty in chronic COPD extends beyond its mere prevalence, necessitating a critical exploration of its independent association with adverse outcomes, which are pivotal in clinical prognostication and therapeutic decision-making. Increasingly, research underscores frailty as a robust, independent predictor of deleterious events, including exacerbations, prolonged hospitalizations, and mortality, irrespective of the presence of comorbidities or disease severity. Notably, studies consistently demonstrate that frailty, as a distinct clinical syndrome, contributes independently to these negative outcomes in COPD patients.[5,16] A systematic review and meta-analysis by Huang et al[17] highlighted that up to 40% of frail COPD patients have sarcopenia. Frailty in COPD has been quantitatively linked to increased exacerbation frequency, with frail patients experiencing exacerbations 1.5 to 2 times more often than their non-frail counterparts.[6] Frailty amplifies the likelihood of acute respiratory events due to impaired immune function and reduced reserve capacity.[18] Studies show that frail COPD patients are more prone to anxiety and depression, which further impair their ability to manage the disease effectively.[19,20]

Studies have shown that frailty is associated with a 25% longer average hospital stay, a 40% higher risk of poor treatment response, and a 50% increase in 1-year mortality.[21] Jia Luo et al reported that the all-cause mortality risk was more than twofold higher in frail patients (HR = 2.54, 95% CI: 1.01–6.36) than in non-frail patients.[22] These data underscore the critical role frailty plays in exacerbating clinical outcomes in COPD. Bernabeu-Mora and others revealed that frailty was associated with a 3-fold increase in hospital admission rates for acute exacerbation. Severely frail patients were much more likely to be readmitted than non-frail patients (45% versus 18%).[4] The similar findings documented by Almanzar et al the impact of frailty on COPD exacerbation, highlight that frail patients experience more readmission compared to non-frail patients, and highly frail patients have poorer outcomes than their less frail counterparts, including longer ICU lengths of stay and less possibility of discharge home from the hospital.[11] A cross-sectional study by Yogesh

et al[23] observed the intersection of frailty, sarcopenia, and malnutrition in COPD patients, highlighting that these conditions are common and often associated with poorer clinical outcomes. Liu et al[24] evaluated frail patients as having significantly lower functional exercise capacity compared to the control group with non-frail patients.

Additionally, a study by Gephine and others[25] found that frail individuals had lower daily step numbers, exercise tolerance, and functional capacity, and higher fatigue, anxiety, and depressive symptom scores ($p<0.05$) compared to non-frail individuals. Ensrud et al[15] documented a significant financial burden on the healthcare system, with costs, rising from the robust to the frail stage. Frailty remarkably reduces health-related quality of life in COPD patients. A retrospective, cross-sectional study by Roberts and others[26] reported that frailty was a major determinant of poor health-related quality of life outcomes in individuals with COPD. The ECLIPSE study by Hanania et al evaluated a higher rate of depression and social engagement in frail patients. Other researchers reported the interplay between frailty, depression, and social support in COPD individuals.[19]

Assessment Tools for Frailty in COPD

Early evaluation and effective assessment of frailty are crucial for optimizing clinical outcomes. For this purpose, in clinical practice, evidence-based tools are used to assess frailty in COPD (Table 1). One of the most widely used and validated methods for verifying frailty is the Fried Frailty Phenotype (FFP). FFP was first introduced by Fried in 2001, and it has a collective score of five physical and functional criteria: unintentional weight loss, exhaustion, low physical activity, slowness, and weakness, has been used in COPD studies and is associated with a higher risk of exacerbations and functional decline.[10] A criterion of unintentional weight loss is loss of ≥4.5 kg or ≥5% of body weight in the past year, and reflects the majority of catabolic processes, malnutrition, and systemic inflammation in frailty. It has been used in COPD studies and is associated with a higher risk of exacerbations and functional decline. The second criterion is exhaustion, self-reported fatigue, or lack of energy, which indicates impaired energy and physiological homeostasis.[7] Muscle weakness and reduced mobility were measured by using the Minnesota Leisure Time Physical Activity Questionnaire.[27] Slowness of the patients scored by gait speed below defined thresholds based on height and sex (eg, <0.8 m/s), reflects neuromuscular and cardiovascular decline.[28] Weakness is assessed using grip strength below specific

Table 1 Commonly Used Frailty Assessment Tools in COPD and Their Clinical Relevance

Tool	Assessment Domains	Advantages	Limitations	Clinical Use in COPD
Fried Frailty Phenotype (FFP)	Weight loss, exhaustion, low physical activity, walking speed, grip strength	Widely validated; based on objective physical criteria	Requires equipment; less sensitive to early frailty	Common in research; predicts exacerbation risk and functional decline
Clinical Frailty Scale (CFS)	Overall clinical impression of physical performance and comorbidities	Quick; practical for clinical settings	Subjective; inter-rater variability	Applied for frailty screening in hospitalized COPD patients
Frailty Index (FI)	Accumulated health deficits across multiple domains	Comprehensive; quantifies frailty severity	Time-consuming; data intensive	Used to assess frailty burden and mortality risk
Short Physical Performance Battery (SPPB)	Gait speed, chair stand test, balance assessment	Objective; prognostic value for hospital outcomes	Limited to lower-body function	Predicts hospitalization, disability, and mortality
Edmonton Frail Scale (EFS)	Function, cognition, nutrition, mood, medication use, social support	Multidimensional; efficient screening tool	Contains subjective items; less specific to COPD	Assesses multidimensional frailty in elderly COPD patients
Kihon Checklist (KCL)	Physical function, nutrition, cognition, mood, social activities	Adapted for older adults in primary care	Region-specific; limited global validation	Emerging tool in Asian populations with COPD

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thresholds based on gender and BMI (eg, <20 kg for women and <30 kg for men).[29] Each construct is assigned 1 point if present or 0 if absent. Thus, the FFP score ranges from 0 to 5, with higher scores reflecting increased frailty. The FFP can be evaluated as a binary (frail, FFP ≥ 3), categorical (frail, FFP ≥ 3; prefrail, FFP = 1–2; not frail, FFP = 0), or ordinal scale (0–5). Numerous studies validated the association of FFP-defined increased risk of hospitalization and mortality.[7,30] The limitations of FFP are narrow focus and as it does not consider the psychosocial aspects of frailty, such as isolation, depression, and mental well-being. Moreover, this may not fully apply to the younger population.

The Clinical Frailty Scale (CFS) is a clinical judgment-based frailty tool developed for the Canadian Study of Health and Aging in 2005 by Rockwood et al.[31] It has since become widely used for assessing frailty in clinical settings, especially in older individuals,[32] with further validation in acute COPD settings.[33] CFS provides a quick and subjective assessment based on clinical judgment, considering cognitive status, physical function, and comorbidities. The Rockwood Clinical Frailty Scale is a 9-point ordinal scale ranging from 1 (very fit) to 9 (terminally ill). Descriptive criteria and visual cues accompany each level to assist in determining the frailty status of patients. An observational cohort study analyzed the CFS prediction of 30-day mortality admitted to the intensive care unit (ICU) with an accuracy comparable to more complex frailty indices.[34] Disadvantages of the Rockwood CFS may be less sensitive in assessing young individuals with atypical presentation (eg, COPD patients with non-physical manifestations of frailty).

Another widely used validated tool to assess physical performance and functional status in COPD is the Short Physical Performance Battery (SPPB).[35] The SPPB is a 3-part (gait time, chair stand, and balance) quick and objective physical function test with excellent test-retest reliability, predictive validity, and clinical applicability with defined clinically important difference values.[36] It was developed as a part of Established Populations for Epidemiologic Studies of the Elderly (EPESE)[37] and has been shown to be feasible in COPD patients and is predictive of hospitalization and mortality.[38] The Balance Test evaluates by using the side-by-side stand, semi-tandem stand, and tandem stand, and measures the ability to maintain balance for up to 10 seconds in each position. The tester demonstrates each stance before the participant attempts it; clear instructions are given regarding what the participant can and cannot do to maintain his/her balance.[39]

The Gait Speed test is designed for application in primary and psychiatric care. In the Gait Speed test, the participant walks a 4-meter distance usual walking pace.[40] The patient should be asked to wear comfortable footwear. The patient will be instructed to walk at his usual pace from the starting line to the finish line (4 meters away). The time is recorded using a stopwatch.[39] The time taken is translated into a score ranging from 0 to 4 based on accepted cutoff values: 0 points: unable to walk; 1 point: > 8.70 seconds; 2 points: 6.21–8.78 seconds; 3 points: 4.82–6.20 seconds; 4 points: <4.82 seconds (fastest). The Gait Speed test reflects the ability to move independently and efficiently, and the strength, coordination, and endurance of lower extremity muscles.[41] Guralnik and others[39] reported that gait speed is a powerful tool for predicting mortality and disability. The study by Kon et al[40] concluded that among COPD patients, gait speed correlates with increased dyspnea, reduced exercise tolerance, and poor health-related quality of life. A similar result reported Studenski et al[41] that each 0.1 m/s decline in gait speed is associated with significant increases in mortality and functional decline. The limitations of this test in frailty evaluation specified that gait speed assesses lower extremity function but does not account for upper body impairments or comprehensive frailty dimensions.[40]

The Frailty Index (FI) is a quantitative tool introduced by Rockwood et al in 2001, based on the deficit accumulation model of frailty. FI has been validated in various populations, including community-dwelling adults, hospitalized patients, and long-term care residents, and has proven a useful tool in different medical conditions, including COPD.[21,42] The frailty index is a measure that converts the percentage of deficits present or absent in a particular patient into an index score that varies between 0 and 1, with 0 reflecting no deficits and 1 the presence of all deficits.[43] Deficits include mobility issues, fatigue, comorbidities, cognitive decline, and nutritional deficiencies. Numerous studies consistently demonstrated that a higher FI is strongly associated with increased risk of mortality, hospitalization, long lengths of hospital stay, and functional decline, and its superiority over chronological age in predicting adverse health outcomes. Rockwood[31] and others developed the Clinical Frailty Scale and evaluated its predictive validity for mortality and institutionalization. Mitnitski et al[44] reported that FI is a more sensitive predictor of survival than chronological age. Several studies investigated the relationship between the FI and biomarkers of inflammation, particularly C-reactive protein (CRP) and interleukin-6 (IL-6), supporting the biological basis of frailty.[45] Hubbard et al[46] highlighted that higher

levels of systemic inflammation are associated with increased frailty in older adults. This association underscores the role of inflammatory processes in the development and progression of frailty among older individuals.

The Edmonton Frail Scale[47] is a multidimensional assessment tool including nine domains such as general health status, functional independence, medication use, mood continence, functional performance, nutrition, and social support and has shown associations with prolonged hospital stays and, increased care needs.[48] Its comprehensive approach provides a holistic view of frailty status. Roberto Bernabeu-Mora et al[26] evaluated the utility of the Edmonton Frail Scale in hospitalized patients and highlighted that identifying patients with frailty for targeted interventions may reduce early readmission rates.

As described above, frailty assessment tools have been designed for the majority the general geriatric population. However, COPD patients present unique challenges due to their specific disease characteristics, necessitating tailored adaptations of these tools. COPD patients often experience dyspnea, declined lung function, and exercise intolerance, which are not directly captured by traditional frailty tools.[42] Muscle dysfunction and sarcopenia are common in COPD due to hypoxia, systemic inflammation, and corticosteroid use. Swallow et al[49] found that reduced quadriceps muscle strength is a significant predictor of mortality in COPD patients. Incorporating muscle-specific assessments like the sit-to -stand test or isometric strength tests can provide more accurate frailty measurements.

Fatigue is a common daily experience symptom and a critical component of frailty in COPD and contributes significantly to functional impairment.[50] Fatigue correlates with poor exercise tolerance, reduced quality of life, and increased rate of hospital admissions. Studies reported that self-reported fatigue predicts mortality and healthcare utilization across various frailty contexts, including COPD.[51,52] Avlund et al[53] demonstrated that those who reported tiredness had a higher risk of developing disabilities in mobility and daily activities, and whether self-reported tiredness in daily activities at age 75 is an independent determinant of the onset of the disability over a 5-year follow-up. To assess energy levels and fatigue impact recommended Fatigue Severity Scale (FSS) and Multidimensional Fatigue Inventory (MFI).[54]

COPD is frequently accompanied by multiple comorbidities, including cardiovascular disease, diabetes, osteoporosis, anxiety, and depression, which notably contribute to frailty. These comorbidities exacerbate disease severity, increase healthcare utilization, and reduce health-related quality of life. The Charlson Comorbidity Index (CCI) is a validated tool developed by Charlson et al in 1987 to refine frailty assessment. The CCI[55] includes 19 conditions such as myocardial infarction, congestive heart failure, COPD, diabetes with complications, metastatic cancer, leukemia, peptic ulcer disease, AIDS, liver, renal, neurological disease, and peripheral vascular disease. Each condition is assigned a weight from 1 to 6 based on its impact on 1-year mortality. The total score sums up the weights for all of the present conditions, and a higher score indicates a greater burden of comorbidities and an increased risk of mortality.[56] An additional point is added for every decade of patients who are above 50 years, further refining mortality risk predictions. CCI helps clinicians predict 1-year mortality, guiding decisions on treatment intensity.[57] The limitation of the CCI is that it does not capture dynamic changes in comorbidity burden over time.

The COPD-Specific Comorbidity Test (COTE) is a validated tool designed to quantify the comorbidity burden in COPD, and COTE focuses on 12 conditions most relevant to COPD outcomes.[58] COTE is a cornerstone predictor of all causes of mortality in COPD patients, focusing on the conditions most relevant to COPD outcomes.[59] Divo et al[60] identified 12 comorbidities that negatively influence survival in COPD, and a COTE score of 4 or higher increased the risk of mortality by 2.2 times across all BODE index quartiles. de Torres et al in the study "Prognostic evaluation of COPD patients: GOLD 2011 versus BODE and the COPD comorbidity index COTE"[61] suggested that the BODE index had a better survival prediction than the ABCD GOLD categories. Adding the COTE to the BODE index was complementary and significantly improved outcome prediction.

Frailty frequently coexists with sarcopenia, a syndrome characterized by the progressive decline in skeletal muscle mass, strength, and functional capacity. This coincidence negatively impacts functional status and quality of life in COPD patients.[62,63] Schols et al[64] reported that about half of the patients with mild to severe COPD had a reduced body weight, which could be related to both a loss of muscle and adipose tissue. One of the validated tools to screening sarcopenia is the SARC-F questionnaire.[65] SARC-F was presented by Morley,[66] a simple questionnaire including five items: strength (S), assistance walking (A), rising from a chair (R), climbing stairs (C), and falls (F) on a scale of 0 to 2; the recommended cutoff value is ≥4 points.[14] Li et al[67] validated the SARC-F against multiple definitions of sarcopenia,

establishing its advantages as a community screening tool. In the context of COPD, studies indicate that patients with higher SARC-F scores often manifest declines in exercise capacity and impaired activities of daily living. While specific studies detailing these findings are not provided in the available sources, the correlation between high SARC-F scores and decreased physical performance in COPD patients is recognized in clinical observations.[68] The Turkish study concluded that the SARC-F is well-suited as a screening tool for functional measures, rather than for definitive sarcopenia diagnosis.[69] The SARC-F is especially valuable in excluding muscle function impairment and may complement other muscle mass assessment tools. These results are consistent with Kurita et al.[70] They validated that the SARC-F questionnaire alone is not adequate for finding cases in musculoskeletal disease settings.

Dual-energy X-ray absorptiometry (DEXA) remains the gold standard for non-invasive measurement of appendicular skeletal muscle mass, offering precise and reliable results.[71] In contrast, bioimpedance analysis (BIA) provides a more accessible and cost-effective alternative, making it particularly valuable in clinical practice.[72] de Blasio et al[73] highlighted that bioimpedance index is a significant independent predictor of handgrip strength (HGS) and respiratory muscle strength in COPD patients. These findings underscore that the BI index could provide useful information for evaluating body composition and better assessing muscle strength and physical fitness in COPD.

Association Between Systemic Biomarkers and Frailty in COPD

Frailty in COPD has been increasingly conceptualized as a manifestation of complex systemic processes, with a growing body of evidence suggesting potential associations with specific circulating biomarkers. Although biomarkers have not been validated as a definitive diagnostic tool for frailty, several candidates, including inflammatory biomarkers (C-reactive protein (CRP), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), fibrinogen, and Growth Differentiation Factor-15 (GDF-15)), oxidative stress biomarkers (Malondialdehyde, 8-Isoprostane, and Glutathione (GSH)),[74] muscle and metabolic biomarkers (serum creatinine and Cystatin C, Insulin-like growth Factor-1 (IGF-1), Albumin, prealbumin, Leptin, and Adiponectin),[75] gut microbiome and nutritional biomarkers (short-chain fatty acids (SCFAs))[76] provide valuable insight into disease mechanisms and progression. Table 2 provides a concise overview of key systemic biomarkers that have been studied in the context of COPD and summarizes their potential, though not yet definitive, relevance to frailty. Observational studies by Yogesh et al[77] and Gandhi et al[78] concluded that elevated CRP levels are linked to systemic inflammation and poor outcomes. A prospective study by Singh and others[79] reported that frailty in COPD patients was also significantly associated with serum IL-6 (p=0.033) and CRP (p=0.010) but not with TNF-α (p=0.077). Baldi et al indicated that raised IL-6 mediates some of the association between lower forced expiratory volume in 1 second (FEV1) and shorter six-minute walk distance (6MWD) in patients with COPD.[80]

Elevated IL-6 levels correlate with reduced muscle mass, lower exercise tolerance, and increased risk of hospitalization, making it a reliable predictor of systemic frailty and clinical deterioration in COPD patients.[81] A systematic review and meta-analysis recognized fibrinogen as a COPD biomarker of severe exacerbation, and shorter 6MWD, higher heart rate.[82] However, there is insufficient study of the relationship between frailty and plasma fibrinogen level.

In the pathogenesis of COPD, oxidative stress plays a key role.[83] Malondialdehyde (MDA) is a biomarker of lipid peroxidation, meaning it indicates damage to cell membranes caused by reactive oxygen species (ROS). In normal conditions, MDA levels in COPD patients are not significantly different from healthy individuals.[84] However, after maximal incremental exercise, MDA levels rise significantly, indicating oxidative stress-induced tissue damage.[85] Isoprostanes are physiopathologic mediators of oxidative stress, resulting in lipid peroxidation. 8-isoprostane is especially useful for measuring oxidative stress damage. Antczak et al[86] reported a significant fall in the concentration of 8-isoprostane after treatment of COPD exacerbation. These results are consistent with the study by Ashmawi and others.[87]

One of the biomarkers of oxidative stress is GSH. Authors Bellanti et al[88] studied that low GSH levels are associated with sarcopenia patients with cardiovascular disease. However, there is insufficient study of the relationship between frailty in COPD and GSH.

The serum creatinine/cystatin C (Cr/CysC) ratio has attracted attention as a surrogate marker for sarcopenia.[89] This was first reported as a surrogate marker of muscle mass in 2013.[90] A study by He et al[91] reported that a low Cre/Cys C ratio was associated with a prolonged hospital length of stay and admission to the intensive care unit in AECOPD patients, and indicated that the Cre/Cys C ratio is an easy, cheap, repeatable, and promising biomarker that allows the evaluation risk of AECOPD.

Table 2 Systemic Biomarkers Investigated in COPD and Their Proposed Relevance to Frailty

Biomarker	Biological Domain	Findings in COPD	Proposed Significance in Frailty	Clinical Applicability & Diagnostic Accuracy
CRP, IL-6, TNF-α	Inflammation	Elevated levels linked to systemic inflammation and poor outcomes	Suggested association via chronic inflammation and functional decline	Routinely measured; CRP/IL-6
MDA, 8-Isoprostane	Oxidative Stress	Increase post-exercise; markers of lipid peroxidation	Proposed link to oxidative tissue damage affecting frailty	Used in research; 8-Isoprostane more reliable than MDA
Glutathione (GSH)	Antioxidant Defense	Reduced in sarcopenia, cardiovascular patients	Hypothesized connection; role in COPD frailty unconfirmed	Not standardized clinically; limited availability
Cr/CysC Ratio	Muscle Metabolism	Low ratio linked to sarcopenia and longer hospitalization	Emerging surrogate for sarcopenia-related frailty	Simple, cost-effective; moderate predictive value
IGF-1	Anabolic Signaling	Decreased levels in COPD; affects growth/ apoptosis pathways	Suggested as indicator of muscle wasting, not specific to frailty	Research use; variable values; poor diagnostic accuracy
Leptin, Adiponectin	Metabolic-Inflammatory Cytokines	Elevated during COPD exacerbation	Proposed as systemic inflammation mediators influencing frailty	Experimental stage; no frailty-specific cut-offs
Short-Chain Fatty Acids (SCFAs)	Gut/Nutrition	Decreased in COPD; linked to systemic inflammation	Proposed impact on immunosenescence and inflammation in frailty	No clinical use; emerging in microbiome/ frailty research
Fibrinogen	Coagulation & Inflammation	Elevated in severe exacerbations; reduced exercise tolerance	Unclear role in frailty; more studied as a COPD risk marker	FDA-qualified for COPD risk; frailty link insufficient
GDF-15	Mitochondrial Dysfunction	Elevated in older COPD patients; predicts poor outcomes	Proposed as a novel aging/frailty biomarker	High prognostic potential; not specific to COPD frailty

Abbreviations: CRP, C-Reactive Protein; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-alpha; MDA, Malondialdehyde; 8-Isoprostane, 8-iso-Prostaglandin F2α; GSH, Glutathione; Cr, Creatinine; CysC, Cystatin C; Cr/CysC Ratio, Creatinine-to-Cystatin C Ratio; IGF-1, Insulin-like Growth Factor 1; Leptin, Leptin; Adiponectin, Adiponectin; SCFAs, Short-Chain Fatty Acids; GDF-15, Growth Differentiation Factor 15.

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IGF-1 plays a vital role in the pathogenesis of lung diseases; nevertheless, the relationship between circulating IGF-1 and lung disease remains unclear. IGF-1 is released systemically in response to autocrine/paracrine signaling and acts by binding to and activating the IGF-1 receptor, which triggers growth-promoting and antiapoptotic pathways.[92] Authors from China reported that circulating IGF-1 levels were significantly lower in COPD patients.[93] These findings align with the findings of Kythreotis et al.[94] Leptin and adiponectin are pleiotropic cytokines thought to play a role in host response to inflammation. Several studies declared that leptin and adiponectin are associated with the systemic inflammatory process during exacerbations of COPD, and these are involved in the local inflammatory response in COPD.[95,96]

SCFAs and oxidative stress biomarkers represent emergent tools in the paradigm of precision medicine for COPD, offering nuanced insights into patient-specific inflammatory and metabolic phenotypes. Diminished SCFA concentrations have been implicated in the amplification of systemic inflammatory cascades,[76,87,97] whereas elevated oxidative stress indices have demonstrated robust associations with heightened exacerbation susceptibility and accelerated pulmonary function decline.[98,99] These biomolecular signatures hold translational potential in stratifying disease phenotypes, guiding therapeutic intensification, and enabling dynamic monitoring of intervention efficacy.[100] Frailty in chronic COPD is underpinned by a complex interplay of oxidative stress, chronic low-grade inflammation, skeletal muscle catabolism, and metabolic dysregulation, with an expanding repertoire of biomarkers elucidating the underlying pathobiology, disease trajectory, and potential points of therapeutic intervention.[82] GDF-15 has emerged as a novel biomarker that reflects mitochondrial dysfunction and chronic inflammation; studies show it predicts mortality, hospitalization, and decline in functional status, particularly in older COPD populations.[101]

Strategies for Management of Sarcopenia and Frailty in COPD

Frailty and sarcopenia are common contributors to poor outcomes in COPD patients. Muscle wasting and other complications that arise from COPD. Early diagnosis and effective management of these conditions can remarkably reduce exacerbations, improve quality of life, and enhance overall survival.[62] Nutritional support, exercise programs, pharmacological therapies, and multidisciplinary approaches are key strategies for improving muscle strength and enhancing quality of life.[102] COPD frail patients are at high risk of malnutrition due to increased energy expenditure from the disease and poor appetite. Nutritional interventions play a key role in managing COPD frailty. A randomized clinical trial concluded that specific nutritional supplementation had additional effects on the nutritional status, inspiratory muscle strength, and physical activity compared with placebo.[103] Numerous studies highlighted that oral nutritional supplements enriched with proteins, vitamins, and minerals significantly improve the nutritional status of COPD patients.[104,105] Møgelberg and others[106] described that in COPD patients with sarcopenia a high protein diet showed improvements in muscle strength and function. Controversially, a meta-analysis by Bernardes et al[107] revealed, with limited evidence, that increased protein and/or energy intake positively impacts anthropometric measures and handgrip strength of COPD patients. Several studies demonstrated that a high-fat, low-carbohydrate diet helped reduce dyspnea and improve exercise tolerance in COPD patients.[108] Numerous studies reported that nutritional interventions, including protein, vitamin D, omega-3 fatty acids, and energy supplementation, play a crucial role in managing COPD and improving the quality of life.[109,110] However, these findings are contradictory to a meta-analysis by Stockton and others.[111] They concluded that vitamin D supplementation does not have a significant effect on muscle strength in adults.

Pulmonary rehabilitation programs are a cornerstone intervention in the management of COPD-related frailty and are beneficial in improving health-related quality of life and exercise capacity.[112] A comprehensive Cochrane review by McCarthy[113] highlighted that pulmonary rehabilitation relieves dyspnoea and fatigue, improves emotional function, and enhances the sense of control that individuals have over their condition. These improvements are both moderately large and clinically significant, underscoring the efficacy of PR in managing COPD. A similar conclusion was noted in the meta-analysis about resistance training on subjects with COPD,[114] indicating that resistance training leads to significant improvements in dyspnea, skeletal muscle strength, and lung function in COPD patients. As a newly studied intervention in clinical practice, a home-based exercise program, particularly tele-rehabilitation. Ora et al[115] reported that in COPD patients, tele-R is effective in improving exercise tolerance and patient-reported outcomes, and it seems to be a valid alternative to center-based rehabilitation, but more studies are needed to better understand how to select the right patients and which kind of tele-R is more appropriate. A study using the 12-month HOMEX exercise program intervention

demonstrated that no effect on dyspnea, but provided benefits in functional exercise capacity.[116] In brief, evidence supports that incorporating both aerobic and resistance training into pulmonary rehabilitation programs yields notable improvements in muscle strength, exercise capacity, and overall quality of life for COPD patients. Tele-rehabilitation represents a viable, evidence-based option for COPD patients unable to attend traditional PR programs.

Cognitive Behavioral Therapy (CBT) has been shown to improve psychological well-being in various populations. A meta-analysis by Chen et al[117] demonstrated that CBT improves the lung function, anxiety, and depressive symptoms, treatment compliance, and quality of life of patients with COPD and can be used widely in the clinical treatment of this disease. This concept aligns with other recent meta-analyses.[20,118,119] CBT is the most studied psychological intervention for COPD, originally developed for the management of depression and anxiety. Over time, it has been adapted for various somatic and psychiatric conditions. CBT helps patients manage psychological distress by addressing the interplay of thoughts, emotions, physical sensations, and behaviors. Anxiety symptoms are often exacerbated by catastrophic thinking and avoidance behaviors (eg, "I avoid activities that make me breathless"). A key CBT strategy for anxiety is systematic exposure to feared situations. For depression, inactivity and isolation worsen low mood and negative thinking (eg, "I'm useless, so I stay alone"). CBT tackles this through behavioral activation and restructuring negative thought patterns into more realistic and less distressing ones.[120] However, in world literature, direct evidence on the impact of CBT specifically for frailty in elderly patients with chronic respiratory diseases is limited.

Patient motivational interviewing (MI) and education are thought to be effective approaches in COPD management. A randomized controlled study by Tülüce and others[120] highlighted that one-to-one education and motivational MI enhanced physical activity levels by increasing patient motivation for adopting healthier behaviors.

As a multifactorial condition, frailty and sarcopenia arise from a complex interplay of factors, including nutritional deficiencies, hormonal changes, poor physical activity, and aging. Managing frailty and sarcopenia in COPD patients necessitates a multidisciplinary approach, integrating the expertise of physiotherapists, pulmonologists, nutritionists, and geriatricians to develop personalized care plans.[12] Furthermore, a study of *Frailty in Older Adults: Evidence for a Phenotype* in *The Journals of Gerontology*, defined frailty as a clinical syndrome in which three or more of the following criteria were present: unintentional weight loss (10 lbs in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. This definition underscores the necessity for comprehensive management plans that incorporate multiple disciplines to address both respiratory and muscular health.[7] To sum up, integrating medical and allied health services through a multidisciplinary, patient-centered approach is essential for enhancing outcomes in COPD patients with frailty.

Conclusion

Frailty in COPD represents a multidimensional, systemic phenotype that significantly exacerbates morbidity, accelerates functional decline, and heightens the risk of adverse clinical outcomes. The intricate interplay between systemic inflammation, musculoskeletal wasting, neuroendocrine dysregulation, and impaired resilience underscores frailty as not merely a comorbidity but an integral manifestation of disease progression in COPD. Despite advances in clinical characterization and emerging stratification tools, current diagnostic paradigms remain overly reliant on functional indices, which may lack sensitivity and specificity in heterogeneous COPD populations.

Crucially, the absence of validated, disease-specific biomarkers of frailty in COPD constitutes a major translational gap. While inflammatory mediators such as IL-6, CRP, and TNF-α have been inconsistently associated with frailty, they remain non-specific and poorly predictive at the individual level. No robust biomarker panels have yet been integrated into routine clinical algorithms to identify frail COPD patients early, guide therapeutic decision-making, or monitor response to targeted interventions. This deficiency hampers the development of precision-based management strategies, particularly in tailoring rehabilitative, pharmacologic, and nutritional interventions to frailty severity and biological underpinnings.

Future research must prioritize longitudinal, multi-omic studies to elucidate the pathobiological signatures that define frailty within the COPD spectrum. Integrating biomarkers derived from proteomics, metabolomics, and epigenetic profiling may offer transformative insights into the mechanistic underpinnings of frailty and enable earlier, individualized interventions.

Disclosure

The authors report no conflicts of interest in this work.

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