

Extrapulmonary Comorbidities in COPD: A Bidirectional and Multimorbid Perspective

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Abstract

Chronic obstructive pulmonary disease (COPD) remains among the leading causes of death. The systemic characteristics of COPD are becoming clearer every day, and the importance of comorbidities is increasingly well understood. Comorbidities are one of the main causes of mortality in COPD. Although there are specific guidelines for each disease, there is limited literature explaining the effects of comorbidities on one another. Non-respiratory comorbidities associated with mortality in COPD include cardiovascular disease (CVD), metabolic, musculoskeletal, and psychiatric disorders. Both COPD and these comorbid conditions share a common aetiology and are associated with complex clinical and therapeutic interactions. CVD and metabolic comorbidities are more symptomatic and can be easily recognised by patients and physicians. However, osteoporosis, anxiety, and depression are often asymptomatic, despite the fact that these are more common than other comorbidities. Current data suggest that diagnosis and treatment of comorbidities improve prognosis in COPD. Instead of focusing solely on COPD treatment, we should adopt a holistic approach to patient care. This narrative review aims to summarise the bidirectional relationships between COPD and its most common fatal extrapulmonary comorbidities. Another aim of the study is to compile a substantial body of scattered information to provide clinicians with an overview.

Keywords: COPD, cardiovascular diseases, diabetes mellitus, osteoporosis, depression

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a non-homogeneous pulmonary disease characterized by chronic symptoms (dyspnea, cough, sputum, and/or exacerbations) due to abnormalities of the airways and/or alveoli that cause persistent, often progressive, airflow obstruction.¹ However, COPD cannot be defined in a single sentence. Even though new evidence has emerged, COPD requires further research from aetiology to classification and from diagnosis to treatment. COPD is a disease, or more accurately a syndrome, that cannot be explained by a single mechanism and involves numerous gene-environment interactions and many confounding factors, such as comorbidities.

COPD, the third-most common cause of mortality, carries a high comorbidity burden owing to shared aetiological factors and pathophysiological characteristics.² Comorbidities are important in COPD because they increase the risk of exacerbation and mortality.³ The majority of mild-to-moderate COPD patients die from non-respiratory causes.⁴

Today, COPD is recognised as a multimorbid disease. Comorbidities, which are increasingly emphasised in GOLD reports, are important because they share a common aetiology with COPD and contribute to difficulties in disease management. An understanding of comorbidities requires a multifaceted perspective. Just as we consider the impact of comorbidities on COPD, specialists in other fields also consider

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the impact of COPD as a comorbidity. Since comorbid conditions may interact and influence each other, including their diagnosis and treatment processes, a holistic assessment is important.

Both pulmonary and extrapulmonary comorbidities contribute to mortality in COPD. This article is a narrative review based on current evidence from observational studies, randomized trials, and international guidelines. The objective of this article is to review the reciprocal effects of COPD and extrapulmonary comorbidities.

Multimorbidity

The coexistence of multiple chronic conditions is referred to as multimorbidity. When examining the concept of comorbidity, the diagnostic and treatment methods for each disease are discussed. However, when discussing multimorbidity, it is necessary to consider the connections among comorbid conditions. The patient's age, genetic features, and sociocultural background should also be included among these intersecting sets (Figure 1).

The interactions between different morbidities and COPD are complex and can make their effects difficult to predict. In reality, the effect of multimorbidity on an individual's risk profile may be considerably greater than the simple aggregation of the individual effects anticipated from the identified conditions.

In GOLD 2026, the 4M model was introduced as part of the COPD management framework.¹ This model, which consists of mentation, mobility, morbidities, and medications, was initially developed for elderly populations without infectious conditions. Based on the 4M approach, GOLD 2026 offers a detailed assessment of multimorbidity in COPD¹ and organizes COPD-related conditions into five clusters. These include a mental cluster, a respiratory cluster, a multiple-organ loss-of-tissue cluster, a metabolic disease cluster, and a cardiovascular cluster, each encompassing a range of relevant comorbidities. As the present

article specifically addresses extrapulmonary comorbidities associated with mortality in COPD, a condensed version of this framework is illustrated in Figure 1.

Today, multimorbidity is a global health priority, and the number of multimorbid individuals is increasing as the world's population ages.⁵ The concepts of multimorbidity and frailty are often used together. Frailty is a clinical syndrome arising from multiple underlying factors and characterized by reduced strength, endurance, and physiological function that predispose individuals to increased dependency and an elevated risk of death.⁶ It has been argued that multimorbidity and frailty lead to disability, and that their intersection may itself constitute disability.⁶ Large-scale studies have shown that COPD is frequently part of multimorbidity.^{7,8}

According to United Kingdom (UK) Biobank data, which includes nearly half a million participants, the five most common long-term conditions associated with frailty are multiple sclerosis, chronic fatigue syndrome, diabetes mellitus, COPD, and connective tissue diseases.⁷ A multimorbidity study based on data from half a million people in China identified four multimorbidity patterns. The cardiometabolic and respiratory multimorbidity groups experienced a more fatal trajectory.⁷ The gastrointestinal and rheumatological/mental multimorbidity groups were found to have lower mortality.⁷ According to Divo and Celli,⁹ mortality rises as the number of comorbid conditions increases among COPD patients. The main extrapulmonary comorbidities associated with mortality in COPD are cardiac, metabolic, musculoskeletal, and psychiatric.³

Chronic Obstructive Pulmonary Disease and Cardiovascular Comorbidities

Cardiovascular disease (CVD) includes acute myocardial infarction (AMI), coronary artery disease, hypertension, atrial fibrillation (AF), and heart failure (HF). CVD has been reported in 20-60% of patients with COPD.¹⁰

Processes such as smoking, air pollution, and ageing are common aetiological factors in both COPD and CVD. The pathophysiological relationship between COPD and CVD is explained in two ways (Figure 2). The first is a spillover mechanism. In COPD, local inflammation may spill over from the lungs into the systemic circulation and contribute to CVD.^{10,11} A second in COPD mechanism is that emphysema, airway obstruction, small airway disease, epithelial dysfunction, remodelling, and hypoxia cause systemic inflammation. C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- α), interleukin (IL)-6, IL-8, and fibrinogen, which are responsible for this inflammation, reach the cardiovascular system via the systemic circulation and trigger local inflammation there. However, a causal relationship between COPD and comorbidities may also operate in the opposite direction: for example, atherosclerosis, arterial calcification, endothelial dysfunction, and tissue hypoxia in CVD may lead to the release of inflammatory cytokines similar to those released in the lungs. These may reach the lungs via the systemic circulation and contribute to the development and/or progression of COPD.¹⁰

Chronic obstructive pulmonary disease and acute myocardial infarction

The prevalence of AMI in COPD patients is 3.5 times higher than that in those without COPD,¹² and the prevalence of COPD in people with AMI varies between 7% and 30%.¹³ In patients with COPD, comorbid conditions such as hypertension, diabetes mellitus, and hyperlipidaemia are more

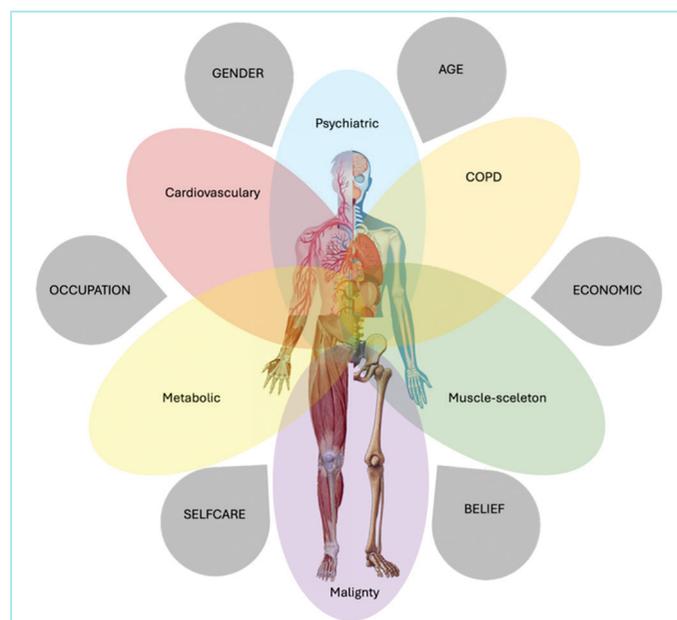


Figure 1. Multimorbidity effect on human body. (Modified from reference 3).

COPD: Chronic obstructive pulmonary disease.

common than in the general population and increase the risk of AMI. In addition, matrix metalloproteinases in COPD may trigger an AMI by rupturing plaques. Furthermore, elevated coagulation factor levels and increased platelet activation in COPD lead to coronary thrombosis and increase the risk of AMI.¹³

Diagnosing AMI in COPD is not always straightforward. Both AMI and COPD may present with similar clinical symptoms, such as dyspnoea and chest tightness. The frequency of typical chest pain in AMI patients with COPD is lower than in those without COPD, which may delay the diagnosis of AMI in patients with COPD and potentially increase myocardial damage or delay reperfusion strategies.¹³ Clinicians should exercise caution in this regard. Making a differential diagnosis swiftly and correctly may prevent unnecessary tests and inappropriate treatment. One of the most commonly used biomarkers for differential diagnosis is cardiac troponin.

Almost 40% of stable COPD patients have elevated cardiac troponin levels compared with the general population.¹ Because cardiac troponin levels can be elevated in infectious COPD exacerbations, their utility in diagnosing AMI in this setting is limited. The mechanism underlying troponin elevation during COPD exacerbations is unclear; further research is needed.^{14,15} The current GOLD 2026 recommendation is to measure troponin levels in patients with COPD who present with unexplained dyspnoea, chest tightness or chest pain, and worsening exercise capacity.¹

The medical treatment of AMI in patients with COPD should be the same as in patients without COPD.⁸ In AMI, percutaneous intervention performed at the appropriate time for the correct indication saves lives. However, it has been reported that patients with COPD presenting with non-ST-segment elevation myocardial infarction undergo fewer percutaneous interventions than patients without COPD, despite being at higher risk.^{15,16} Possible reasons include

the older age of COPD patients and their multimorbidities, which may influence decisions regarding suitability for more aggressive interventions.¹⁶

Chronic obstructive pulmonary disease and atrial fibrillation

AF is the most common cardiac arrhythmia. It is described as a “growing epidemic” because 43 million people worldwide have AF. COPD, affecting 392 million people, is a growing epidemic.²

Various mechanisms have been proposed to explain AF in COPD. COPD is characterised by hyperinflation, ventilation/perfusion mismatch, and airway obstruction. These structural and functional alterations may trigger AF by causing sympathetic nervous system activation, vascular remodelling, and local cardiac conduction disturbances. In a study that analysed over 21 million hospitalised COPD patients, the prevalence of AF was 22.1%, and mortality was 5.7 times higher in patients with AF.¹⁷ In a smaller study of patients with AF, the prevalence of COPD was 11.5%, and mortality was higher among patients with both AF and COPD.¹⁸ In a prospective observational study of 4,000 AF patients in Asia, the risk of all-cause mortality was 3.9-fold higher among those with COPD.¹⁹

In COPD, AF frequently presents with increased dyspnoea. Despite electrocardiogram (ECG) being the primary diagnostic method, Holter monitoring is recommended, especially in patients with intermittent dizziness.¹ The mainstays of AF treatment are anticoagulants and rhythm-control agents. The potential adverse effects of rhythm controllers on COPD are discussed in the following sections.

Chronic obstructive pulmonary disease and heart failure

COPD and HF largely share common aetiologies. In both conditions, progressive dyspnoea is a major symptom and can complicate differential diagnosis and disease management. Some symptoms may be helpful in differential diagnosis and indicative of illnesses, but are not definitive.²⁰ Cough is mainly a symptom associated with COPD, but in HF it may be related to pulmonary congestion or to the use of angiotensin-converting enzyme (ACE) inhibitors. Although night-time symptoms are more common in HF, 20% of patients with severe COPD also experience them. Particular caution is therefore required for elderly patients with a history of smoking.²⁰

COPD and HF share common pathophysiological mechanisms. In COPD, congestion develops due to increased airway obstruction, increased intrathoracic pressure, and a fall in left ventricular function. This reduces cardiac output. On the other hand, increased volume overload and/or myocardial dysfunction in HF lead to increased airway obstruction and worsening of COPD symptoms, and may cause hypoxaemia. In addition, both diseases involve sympathetic overdrive, which increases pulmonary vascular resistance by activating the renin-angiotensin-aldosterone system.^{1,20}

The prevalence of COPD in HF, confirmed by pulmonary function testing, is between 25% and 50%.²⁰ However, the prevalence of COPD based solely on patient self-report, without spirometry, has been reported to be around 10%.²⁰ A recent study from Sweden found that the prevalence of COPD among patients with HF was 13%.²¹ In the same study, the highest prevalence of COPD (16%) was found in HF with preserved ejection fraction (HFpEF). In HF with mildly reduced EF, the prevalence of COPD was 12%, and it was 11% in HF with reduced EF. Although the prevalence of HF confirmed by echocardiography in COPD

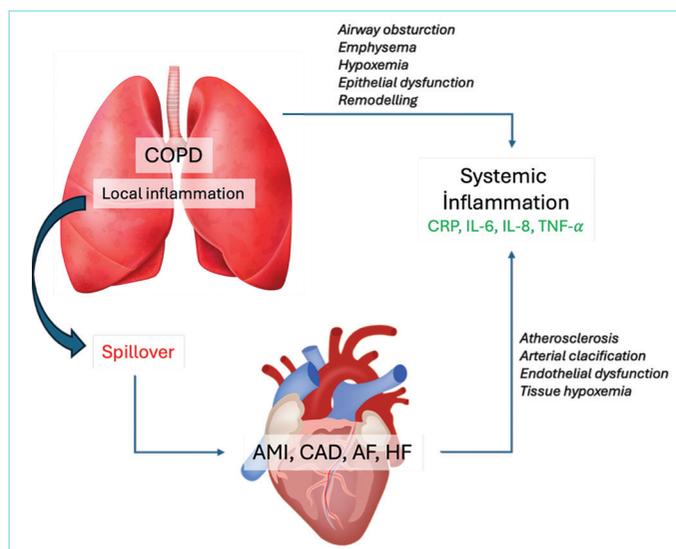


Figure 2. Local and systemic effects of COPD and CVD (This figure was created using the information in references 10 and 11).

COPD: Chronic obstructive pulmonary disease, CVD: Cardiovascular disease, CRP: C-reactive protein, IL: Interleukin, TNF- α : Tumor necrosis factor-alpha, AMI: Acute myocardial infarction, CAD: Coronary artery disease, AF: Atrial fibrillation, HF: Heart failure.

is 5-20%, nearly half of patients with COPD have elevated pro-brain natriuretic peptide (pro-BNP) levels, suggesting myocardial damage.²⁰

The coexistence of COPD and HF is associated with greater mortality than that observed with COPD alone.²² A 15% higher mortality rate was observed among patients with COPD and concomitant HF, independent of EF.²¹ In a study of patients with HFpEF, the prevalence of COPD was found to be 14%, and COPD was associated with increased hospitalisation and mortality.²³

GOLD 2026 recommends the measurement of natriuretic peptides in patients with heart failure, followed by ECHO if natriuretic peptides are abnormal.¹

For clinicians, probably the most important issue is the differential diagnosis between COPD and heart failure. The absence of left HF on ECHO does not exclude HF. It should be borne in mind that HFpEF is common in these patients, and it can worsen symptoms and increase hospital admissions and mortality. Examinations and management strategies should be organised according to current guidelines.

Therapeutic interactions in chronic obstructive pulmonary disease and cardiovascular disease

One of the most controversial issues in the co-occurrence of COPD and CVD is treatment: cardiac drugs can have adverse effects on the lungs, while pulmonary drugs may adversely affect the heart. The most commonly used medication groups in CVD are beta-blockers, ACE inhibitors, angiotensin receptor blockers, and diuretics. There is particular concern regarding pulmonary side effects associated with beta-blockers. It is believed that beta-blockers, which have been proven to decrease mortality in CVD, may worsen COPD, while bronchodilators may trigger arrhythmias.

The first meta-analysis, showing that beta blockers do not adversely affect lung function, was published 22 years ago; however, there is still hesitation today in prescribing beta blockers to patients with COPD.²⁴ An increasing number of studies have shown that the bronchoconstrictor effect of B1-cardioselective beta-blockers is less than that of B2-selective ones.²⁵ A review of 23 observational studies and 14 randomized controlled trials (RCTs) concluded that beta-blockers can be used safely in patients with COPD with respect to adverse effects, exacerbation risk, and mortality.²⁶

In terms of cardiac side effects of antimuscarinic bronchodilators, the 4-year Understanding Potential Long-term Impacts on Function with Tiotropium study provided reassurance about the use of tiotropium,²⁷ and the Acclidinium Safety and Cardiovascular Endpoints Trial study found that, after a three-year follow-up period, patients using acclidinium had a cardiac side-effect profile similar to that of patients receiving placebo.²⁸ In contrast, concerns regarding beta-2 agonists persist due in part to conflicting study results. The SUMMIT study, which examined 16,485 COPD patients with existing CVD or at high risk of it, compared placebo, long-acting beta-2 agonist (LABA), and inhaled corticosteroid (ICS) groups.²⁹ LABA was not found to affect cardiovascular outcomes (AMI, mortality, or AF). In contrast, a recently published cohort study involving 180,367 patients from the UK Clinical Practice Research Datalink reported that initiation of short-acting beta-agonist (SABA), LABA, or ICS plus LABA therapy in patients with COPD was associated with major adverse cardiac events (MACE).³⁰ A meta-analysis published in 2019 that examined 43 RCTs concluded that long-acting

bronchodilators did not cause major cardiac adverse effects in stable COPD, but that LABA increased the risk of HF.³¹ However, a more recent publication, including 74,974 asthma patients, 46,907 COPD patients, and 27,047 patients with asthma-COPD overlap, reported a low risk of arrhythmia, hypertension, heart failure, and cerebrovascular diseases among COPD patients using LABA.³² In summary, although findings regarding MACE associated with beta-agonists are conflicting and it has been emphasised that LABAs should be used cautiously in patients with COPD and HF, the overall findings indicate that LABAs are safe to use in COPD. When interpreting these studies, researchers should pay attention to the methodology. The clinician's own experience is also important in the choice of treatment.

Ensfentrine is a novel inhaled treatment option introduced to relieve dyspnoea in patients with stable COPD. It is a phosphodiesterase-3 and -4 inhibitor.¹ There is no evidence that it causes adverse cardiovascular events. Ensifentrine is currently only available in the US.¹

Due to shared aetiological and pathophysiological characteristics, CVD may be common among patients with COPD. If there is unexplained worsening of symptoms in a COPD patient, CVDs should be investigated, and vice versa. These patients should be carefully monitored for adverse drug effects and drug-drug interactions. The GOLD 2026 report recommends annual ECG and pro-BNP screening for patients with COPD. Although it is necessary to act in accordance with current guidelines, we need further research on this subject.

Chronic Obstructive Pulmonary Disease and Diabetes Mellitus

COPD and DM are among the most prevalent chronic diseases worldwide. The prevalence of DM in COPD has been reported to be between 20% and 30%.^{1,33} Smoking is a common aetiological factor, and both systemic oxidative stress (associated with increased fibrinogen, CRP, IL-1, IL-6, and TNF- α) and chronic inflammation occur in COPD and DM.^{33,34} However, the relationship between them is not well understood. Various mechanisms have been proposed. Smoking leads to oxidative stress, systemic inflammation and insulin resistance. Pro-inflammatory biomarkers such as CRP, TNF- α , and IL-6, which are released during systemic inflammation, promote COPD progression and disrupt insulin signalling. Oxidative stress impairs glucose uptake in skeletal muscle by causing mitochondrial dysfunction and thereby increases insulin resistance.³³ In COPD, recurrent acute hypoxic episodes activate the sympathetic nervous system, leading to increased catecholamine release and insulin resistance. Chronic hypoxia reduces skeletal muscle insulin sensitivity by causing permanent mitochondrial dysfunction and decreased adenosine triphosphate production.³³

In COPD, physical inactivity caused by chronic dyspnoea and fatigue contributes significantly to insulin resistance, muscle atrophy, and metabolic dysfunction.³⁴ Because skeletal muscle plays a significant role in glucose homeostasis, the ability to regulate blood sugar levels is impaired. A sedentary lifestyle worsens systemic inflammation and impairs mitochondrial function. These factors increase the risk of metabolic complications in patients with COPD and type 2 DM.³³ Additionally, it has been suggested that the autonomic neuropathy caused by diabetes may reduce airway calibre by inducing parasympathetic dysfunction, impairing the respiratory response to hypoxia, increasing the risk of lung infection by causing mucociliary dysfunction, and reducing the strength of the diaphragm and other respiratory muscles.³⁵

The most reliable methods for DM diagnosis are measurements of fasting glucose and glycated hemoglobin A1c (HbA1c). It is recommended that fasting glucose and HbA1c levels be monitored every 3-5 years in COPD patients in GOLD 2026.

Therapeutic interactions in chronic obstructive pulmonary disease and diabetes mellitus

When examining the relationship between two diseases, researchers must consider the negative impact of treatments on those diseases.

• Chronic obstructive pulmonary disease medications in diabetes mellitus

Although bronchodilators form the basis of COPD treatment, ICSs are used particularly in eosinophilic COPD, and systemic corticosteroids (SCSs) are used during COPD exacerbations.¹ Adherence to COPD guidelines is lower than expected, resulting in higher-than-anticipated use of inhaled steroids.

SCSs such as prednisone increase glucose production by promoting hepatic gluconeogenesis and reduce peripheral glucose uptake, thereby impairing insulin sensitivity.³⁶ This effect is dose-dependent: as the dose increases, the risks of hyperglycaemia, weight gain, and visceral fat accumulation increase. This also means that each dose of prednisone administered during an exacerbation increases the patient's risk of developing diabetes.

ICS also impairs glycaemic control, although less commonly than SCS; this impairment is dose-dependent.³³ A meta-analysis concluded that the risk of DM or impaired glucose control increased by 34% in patients using >1,000 µg/day of fluticasone or its equivalent.³⁷ Although corticosteroids are the main group of medications expected to have an adverse effect on DM in COPD, beta-agonists may affect glucose metabolism.³³ Both LABAs and SABAs may increase insulin resistance and hepatic glucose production through activation of beta-adrenergic receptors.^{33,38} It is recommended that the effects of these medications be regularly monitored, particularly in COPD patients with DM and impaired glucose regulation. However, no adverse effect of antimuscarinics on glucose metabolism has been demonstrated. Considering these metabolic outcomes, it has been reported that LAMAs may be suitable as the first-choice for stable COPD to mitigate harmful metabolic effects.³³

• Diabetes mellitus medications in chronic obstructive pulmonary disease

Metformin, which is the main medication option for type 2 DM, has been found to exhibit anti-inflammatory properties that can help in COPD by reducing systemic inflammation and oxidative stress.³⁹ Although metformin has been shown to improve lung function and reduce COPD exacerbations,^{40,41} further well-designed research is needed in this area.

Semaglutide and liraglutide, glucagon-like peptide-1 receptor agonists, have anti-inflammatory effects that can be beneficial in the lungs.^{33,41,42} Furthermore, it may help reduce breathing difficulties in obese individuals with COPD by facilitating weight loss.^{33,41,42}

Thiazolidinediones, a class of antidiabetic drugs, are associated with fluid retention in patients with COPD and may worsen pulmonary congestion and exacerbate respiratory symptoms.^{33,43} Therefore, its use is not recommended in DM patients with COPD.

Sodium-glucose cotransporter-2 inhibitors confer cardiovascular and renal protection but require careful monitoring in patients with COPD because of potential risks, such as electrolyte imbalance and dehydration, which can adversely affect the respiratory system.^{33,43}

DM may develop in patients with COPD because of both shared aetiological factors and medication use. Increased risk of infection and autonomic neuropathy caused by DM can have a negative impact on COPD prognosis. GOLD 2026 recommended that systemic steroids be used for less than 6 days because of the risk of glucose imbalance.¹

Chronic Obstructive Pulmonary Disease, Osteoporosis and Fracture

Osteoporosis is one of the most commonly reported comorbidities in COPD; its prevalence has been reported to be between 38% and 58%, while osteopenia prevalence has been reported as 18-65% and increases with COPD severity, reaching approximately 84% in patients with severe COPD.⁴⁴

The key risk factors for osteoporosis include nutritional deficiencies, reduced physical activity, cigarette smoking, weight loss, air pollution, and SCS use (Figure 3), which are all associated with COPD.⁴⁵ In addition, vitamin D deficiency, hypoxia, hypercapnia, and forced expiratory volume in 1 second (FEV₁) loss contribute to the development of osteoporosis in COPD.⁴⁰ Smoking is a major risk factor for osteoporosis by increasing osteoclastic activity and osteoblastic apoptosis. There is also evidence that nicotine disrupts bone structure by inhibiting oestrogen synthesis.⁴⁶ FEV₁ is the respiratory function parameter most closely associated with osteoporosis. The lower the FEV₁, the higher the risk of osteoporosis. This condition has been associated with the severity of COPD.^{47,48}

The most controversial issue regarding the coexistence of COPD and osteoporosis is the use of CS. The risk of fractures increases significantly with the use of SCS.⁴⁷ The relationship between chronic glucocorticoid

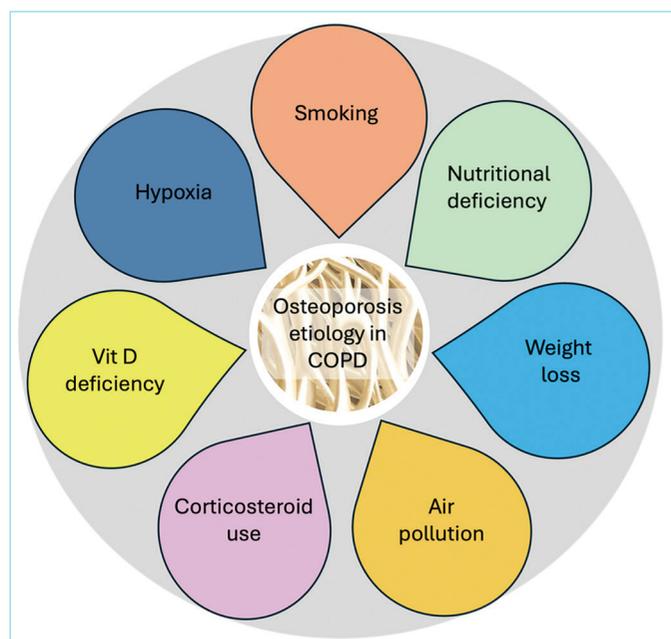


Figure 3. Osteoporosis etiology in COPD (This diagram was created using references numbered 40, 45 and 47).

COPD: Chronic obstructive pulmonary disease.

(GC) use and osteoporosis is well known. The prevalence of long-term oral GC treatment-related osteoporosis or fractures is approximately 30-50%, indicating that GC treatment is the most common cause of osteoporosis.⁴⁹ Bone loss occurs rapidly during the first few months of GC treatment. The risk of fracture increases within the first 3-6 months of treatment. This risk remains high as long as GC treatment continues. Discontinuing GC treatment rapidly reduces the risk of fractures,^{50,51} but the risk may not return to baseline levels. Although maintenance treatment with SCS in COPD is not routine, it is frequently prescribed during exacerbations, and the cumulative dose is important. Because high cumulative doses of extraoral GCs cause increasing fracture risk.⁴⁹ SCS use in COPD patients with frequent exacerbations may accelerate the development of osteoporosis. No safe dose of CS with respect to osteoporosis development exists. The risk of fracture doubles in the 30 days following a course of SCS⁵² and reaches a maximum level at 3-6 months after initiating SCS use.⁴⁹ GOLD recommends a course of SCS lasting fewer than 6 days for the treatment of COPD exacerbations.¹

In a comprehensive meta-analysis involving 17,513 patients, ICS was found to be associated with a significant increase in fracture risk (OR: 1.21).⁵³ However, a systematic review that examined 26 RCTs involving 61,380 participants concluded that ICS use did not increase the incidence of fractures or osteoporosis in COPD patients.⁵⁴ Perhaps greater reliance should be placed on randomised controlled trials rather than observational studies because ICS-containing treatment (including triple therapy) is more likely to be given to more severe patients, who are also at increased risk of osteoporosis due to COPD.

Bone fractures are the most significant clinical outcomes of osteoporosis. In COPD, in addition to a procoagulant tendency, immobilisation due to fractures further increases the risk of venous thromboembolism and thus contributes to mortality. The most common type of fracture in osteoporosis is the vertebral compression fracture (VCF), which not only causes back pain but also contributes to increased symptoms because vital capacity is reduced by 9% with each vertebral fracture.⁵⁵ As VCF increases, kyphosis develops, and when it (the kyphotic angle) exceeds 55 degrees, spirometric deterioration is most pronounced. VCFs are rarely diagnosed because 60-70% are asymptomatic. In patients with VCFs associated with osteoporosis, the risk of a subsequent vertebral fracture increases at least fivefold, while the risk of hip fracture increases threefold.⁵⁶

GOLD 2026 states that chest computed tomography scans can be used as a preliminary assessment tool for low bone mineral density to identify individuals requiring further investigation for osteoporosis.¹

Osteoporosis is a common clinical manifestation in COPD, associated with numerous factors ranging from aetiology to treatment, and contributes to increased mortality. It is particularly important to avoid systemic steroids in patients with COPD because of the increased risk of osteoporosis. A healthy skeletal system is a mainstay of mobility, and mobility is one of the five key components of COPD management. It is recommended that osteoporosis screening with a DXA scan be performed every 3-5 years in patients with COPD, according to GOLD 2026.¹

Chronic Obstructive Pulmonary Disease, Anxiety and Depression

Anxiety and depression are prevalent, yet frequently underdiagnosed, comorbidities in COPD.⁵⁷ These conditions do not directly affect lung function, but they can have numerous adverse effects on symptom

perception and treatment compliance.⁵⁷ The prevalence of anxiety in stable COPD patients receiving outpatient treatment is reported to range from 13% to 46%, and to reach up to 55% in hospitalised patients.⁵⁸ As COPD severity increases, the prevalence of anxiety also increases; nearly 75% of patients with end-stage COPD experience anxiety.⁵⁷ The prevalence of depression in stable COPD ranges from 27% to 40%, increasing to 86% during exacerbations.⁵⁷

Various aetiological factors may be implicated in anxiety and depression in COPD. Systemic inflammation in COPD is also believed to affect neurobiological mechanisms through proinflammatory mediators such as IL-6 and CRP.⁵⁷ Another aetiological factor associated with both COPD and depression is smoking. In addition, the frequent co-occurrence of other chronic conditions such as CVD, DM, and muscle weakness with COPD further increases susceptibility to anxiety and depression.⁵⁹

Anxiety and depression are frequently observed together in COPD patients.⁵⁷ As these patients' perceptions of symptoms are worse, their ability to cope with their illness is lower and their risk of hospitalisation is higher.⁴⁹ Both of them significantly affect COPD, leading to worsening respiratory symptoms, frequent exacerbations, hospital admissions, reduced quality of life, and increased risk of death.⁵⁹ Depression has been shown to be an independent risk factor for readmission within 30 days following a COPD exacerbation.⁶⁰ Similarly, depression has been identified as a factor that increases the risk of hospitalisation within one year after discharge for COPD exacerbations⁶¹ and has been reported to increase mortality risk in COPD by 40%.⁶²

Treatment Options of Anxiety and Depression in Chronic Obstructive Pulmonary Disease

The most commonly used medications in the treatment of anxiety and depression are mirtazapine, serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), benzodiazepines, and opioids.^{57,58} It has been reported that the majority of COPD patients are diagnosed with anxiety and/or depressive disorders, but only 31% receive treatment for these conditions.^{63,64}

The effect of mirtazapine, a tetracyclic antidepressant, on reducing dyspnoea in COPD has been investigated. A phase-3 RCT found that it did not reduce dyspnoea; rather, it caused significant adverse reactions.⁶⁵ Similarly, a study involving 31,253 patients with COPD found that SSRIs, SNRIs, and TCAs were associated with an increased risk of pneumonia and COPD exacerbations, and that this risk decreased after discontinuation of antidepressants.⁵⁹ Several mechanisms have been proposed to explain the increased risk of COPD exacerbations and pneumonia associated with antidepressant use. These include sedation; nausea and vomiting; suppression of T-cell activity; decreased serotonin uptake; dry mouth and other anticholinergic effects; increased sensitivity to carbon dioxide in chemoreceptors; bidirectional systemic inflammation; and changes in the microbiota.⁶⁶

One of the groups of drugs used for psychiatric problems in COPD is benzodiazepines. They are prescribed for insomnia, anxiety, and chronic dyspnoea caused by COPD.⁶⁴ The effects of benzodiazepines on the respiratory system include decreased minute ventilation, hypoxaemia, hypercapnia, and reduced respiratory muscle endurance and strength. COPD patients who use benzodiazepines have an increased risk of exacerbation and death.⁶⁶ The GOLD strategy document currently states that "there is no evidence that anxiety and depression should be treated

differently in the presence of COPD.¹¹ However, this situation stems from a lack of evidence.

Opioid use has been advocated as a treatment option for COPD patients with refractory dyspnoea. However, adverse respiratory outcomes pose a potential concern associated with opioid medications.⁶⁷ In a cohort of 130,979 elderly patients with COPD, the group that had started opioid treatment experienced more respiratory events and higher mortality.⁶⁸

Another drug, gabapentin, has been frequently used in recent years, particularly in the treatment of neuropathic pain. Another large cohort study has shown that gabapentin was associated with an increased risk of exacerbations and death in patients with COPD.⁶⁹ In summary, care should be taken in the selection and use of antidepressants in COPD; pharmacological approaches should be implemented only after ensuring that non-pharmacological approaches have been fully applied.

A more proactive multidisciplinary approach is required to provide psychological support in addition to pharmacological methods, pulmonary rehabilitation, cognitive behavioural therapy, and group therapy, all of which have been shown to be beneficial.⁵⁹ In addition, a recently published systematic review and meta-analysis has concluded that tele-based interventions appear to be effective in reducing anxiety and depression in patients with COPD.⁵⁹

Anxiety and depression in COPD are two cardinal clinical conditions associated with mortality and frequently remain undiagnosed. It is recommended that the Patient Health Questionnaire-2 depression scale be used annually and the Generalised Anxiety Disorder-2 anxiety scale be used every 3-5 years as screening tools for depression and anxiety in people with COPD in GOLD 2026.¹ Treatment decisions should be made according to current guidelines.

CONCLUSION

The multifactorial nature of COPD, its shared aetiological and pathophysiological characteristics with comorbidities, and the need for specific clinical and therapeutic treatments and their possible interactions necessitate a thorough examination of comorbidities (Figure 4). The prevalence, key mechanisms, and management implications of extrapulmonary comorbidities associated with mortality in COPD are shown in Table 1. Symptoms associated with certain comorbid conditions may remain silent or be attributed to COPD. Cardiac and metabolic comorbidities are more easily recognisable by both patients and physicians, but physicians should be vigilant in identifying musculoskeletal and psychiatric conditions. All the extrapulmonary comorbidities discussed here may be related to increased mortality in COPD, so investigating and intervening in these comorbidities before symptom onset may improve prognosis in COPD.

Table 1. The features of mortality related extrapulmonary comorbidities in COPD

	Epidemiology	Key mechanism	Management implications
Acute MI	The prevalence of COPD in AMI varies between 7-30%. ¹³ AMI in patients with COPD is 3.5 times higher than in patients without COPD. ¹²	Other comorbidities that increase MI risk (DM, HPL), MMPs, increased coagulation factors, and platelet activation are key factors for AMI in COPD. ¹³ Myocardial damage during AMI exacerbates COPD symptoms.	Cardiac troponin measurement (in unexplained worsening symptoms). Treatment should be administered according to current guidelines; standard AMI treatment should be applied.
Atrial fibrillation	Prevalence of AF among hospitalized COPD patients is 22.1%. ¹⁷ Prevalence of COPD among AF patients is 11.5%. ¹⁸ Mortality rate is 3.9-5.7 times higher in co-occurrence with COPD and AF. ¹⁷⁻¹⁹	COPD-related structural and functional alterations may trigger sympathetic nervous system activation, vascular remodelling, and local cardiac conduction disturbances. ¹⁷ It resulted in AF. In AF, pulmonary congestion may be triggered by tachycardia, while in COPD, dyspnoea increases.	Unexplained increase in dyspnoea, intermittent dizziness: ECG and/or Holter monitoring. ¹ Cardioselective beta-blockers are recommended for AF patients with COPD. Beta-agonists should be used with caution in COPD patients with AF.
Heart failure	The prevalence of COPD confirmed by spirometry in patients with HF ranges from 25% to 50%. ²⁰ HF confirmed by ECHO in COPD is between 5-20%. ²⁰	Smoking and ageing are common etiologic factors. Increased intrathoracic pressure in COPD may cause reduced cardiac output, increased sympathetic activity, and RAAS activation. It results in HF. ²⁰ Increased volume overload and/or myocardial dysfunction in HF can lead to increased airway obstruction, worsening COPD symptoms, and hypoxaemia. ²⁰	Natriuretic peptides are essential. If it is abnormal, it should be followed by ECHO. In COPD, both HFpEF and HFrEF are common. HF and COPD treatment should be administered in accordance with guidelines.
DM	The prevalence of DM in COPD is almost 30%. ³³	Smoking, chronic inflammation, and systemic oxidative stress - reflected by CRP, TNF- α , IL-1, IL-6, and fibrinogen - are common.	Fasting glucose and HbA1c measurements are essential. Systemic steroid use should be minimized in COPD. In DM, Blood sugar regulation should be ensured to prevent symptoms and exacerbations of COPD.
Osteoporosis and fracture	Osteoporosis in COPD is between 38-58%. ⁴⁴ Osteopenia prevalence is between 18-65%. ⁴⁴	The key risk factors for osteoporosis in COPD are nutritional deficiencies, reduced physical activity, cigarette smoking, weight loss, air pollution, systemic corticosteroid use, vitamin D deficiency, hypoxia and hypercapnia, and decline in FEV ₁ . ^{44,45}	The dose and duration of systemic steroids used in COPD exacerbations should be kept to a minimum. The cumulative effect of systemic steroids may accelerate the development of osteoporosis. Loss of vertebral density may be observed on a thoracic CT scan. DEXA is the gold standard for diagnosis.

Table 1. Continued

	Epidemiology	Key mechanism	Management implications
Anxiety and depression	Anxiety in COPD is between 13-55%, rising during 55%. ^{57,58} Depression affects 27-40% of patients with COPD, rising to 86% during exacerbations. ⁵⁷	Smoking, systemic inflammation, co-occurrence of other chronic comorbidities are major common related factors. ^{57,59}	PHQ depression scale annually and GAD anxiety scale every 3-5 years use as a screening tool. ¹

COPD: Chronic obstructive pulmonary disease, AMI: Acute myocardial infarction, DM: Diabetes mellitus, HPL: Hyperlipidemia, MMPs: Matrix metalloproteinases, AF: Atrial fibrillation, RAAS: Renin-angiotensin-aldosterone system, ECHO: Echocardiography, HF: Heart failure, HFpEF: Heart failure preserved ejection fraction, HFrEF: Heart failure reduced ejection fraction, HbA1c: Glycated hemoglobin A1c, FEV₁: Forced expiratory volume in 1 second, DEXA: Dual-energy X-ray absorptiometry, PHQ: Patient Health Questionnaire-2 depression scale, GAD: Generalised Anxiety Disorder-2, CRP: C-reactive protein, IL: Interleukin, ECG: Electrocardiogram, CT: Computed tomography.

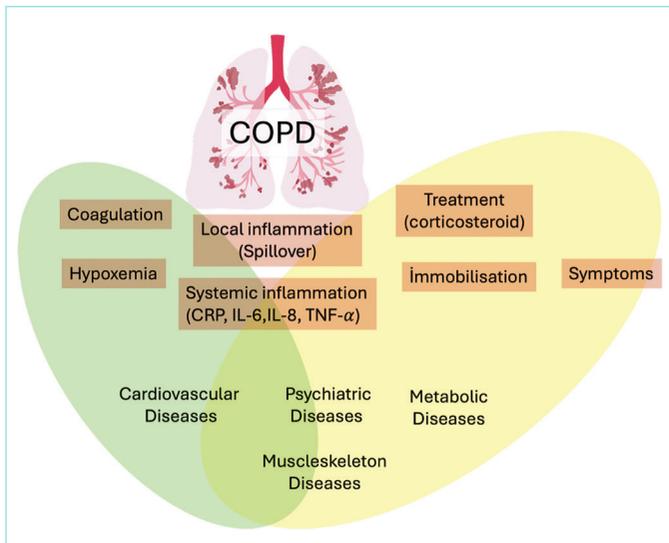


Figure 4. The relationship between inflammatory and clinical characteristics in COPD and extrapulmonary comorbidities (This figure was created using information from references numbered 3, 10, 11, 33, 34, 45, 46, 57, and 59).

COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, IL: Interleukin, TNF- α : Tumor necrosis factor-alpha.

MAIN POINTS

- Chronic obstructive pulmonary disease (COPD), the third leading cause of death among chronic diseases worldwide, is considered a multisystem disease because it affects multiple organ systems via systemic inflammation and hypoxia.
- The multifactorial nature of COPD, which shares common aetiological and pathophysiological characteristics with its comorbidities, coupled with the need for specific clinical and therapeutic treatments and the consideration of their possible interactions, necessitates a thorough examination of comorbidities.
- The main extrapulmonary comorbidities associated with mortality in COPD are cardiac, metabolic, musculoskeletal, and psychiatric.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.B., P.J., N.K., Concept: A.B., P.J., N.K., Design: A.B., P.J., N.K., Data Collection and/or Processing: A.B., N.K., Analysis and/or Interpretation: A.B., P.J., N.K., Literature Search: A.B., P.J., Writing: A.B., P.J.

DISCLOSURES

Conflict of Interest: One author of this article, Ayşe Baha, is a member of the Editorial Board of the Cyprus Journal of Medical Sciences. However, he did not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other author declared no conflict of interest.

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