Diagnosis and management of comorbid disease in COPD

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Shareable abstract (@ERSpublications)
Comorbid disease is COPD is common and leads to poorer clinical outcomes. A high clinical index of suspicion is required to ensure early diagnosis and management. https://bit.ly/4fN5Mig

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Abstract

COPD is one of the most common chronic respiratory conditions and is associated with high healthcare use, morbidity and mortality. Multimorbidity in COPD is common and confers a worse prognosis. Despite this, there is delayed and often under-diagnosis of comorbid diseases in COPD. Knowledge of the respiratory and non-respiratory pathologies that can coexist with COPD is essential to ensure early detection and appropriate management. This review provides an overview of the comorbidities that have been described in COPD. We discuss their pathogenesis, pitfalls in their diagnosis, and strategies for their prevention and treatment.

Educational aims

1) To learn about the comorbidities commonly seen in COPD patients.
2) To understand pitfalls in the diagnosis of comorbidity in this population, and how to approach management.

Introduction

COPD is one of the most prevalent chronic diseases worldwide affecting an estimated 12.4% of those aged 40 years and above [1]. Comorbidity is common in patients with COPD and is associated with a poorer overall prognosis [2]. The comorbidities commonly described in association with COPD are multisystem and include coexistent respiratory pathology, cardiovascular disease, endocrinopathies, musculoskeletal pathology, and neuropsychiatric conditions (figure 1). While many of these comorbidities have shared risk factors (*e.g.* cigarette smoking in cardiovascular disease), it is increasingly recognised that systemic inflammation is present in COPD, and is an independent mechanism *via* which multimorbidity develops. Abnormally high levels of circulating acute phase inflammatory biomarkers, such as interleukin (IL)-6, C-reactive protein (CRP) and fibrinogen [3], have been detected in patients with COPD, even in those with only moderate disease. Systemic inflammation is associated with an increased risk of cardiovascular disease, infection, diabetes, impaired cognition, anxiety and lung cancer [4]. In addition, low physical activity is associated with higher mortality and hospitalisations in those with COPD and is increasingly recognised as a risk factor for comorbidity [5]. Multimorbidity in COPD leads to reduced quality of life, increased healthcare use and increased mortality. Despite this, many comorbidities remain undiagnosed [2]. Understanding and addressing the presence of comorbidities in COPD is essential to improve the quality of life and survival of individuals. In this review, we outline the comorbidities most commonly associated with COPD, their incidence and prevalence, their impact on clinical course and management, and discuss strategies to effectively prevent and manage them. A summary can be found in table 1.

Respiratory comorbidities

Lung cancer

The association between COPD and lung cancer is probably the most commonly recognised and is supported by data from several epidemiological studies [6, 7]. In one such study, the annual incidence of

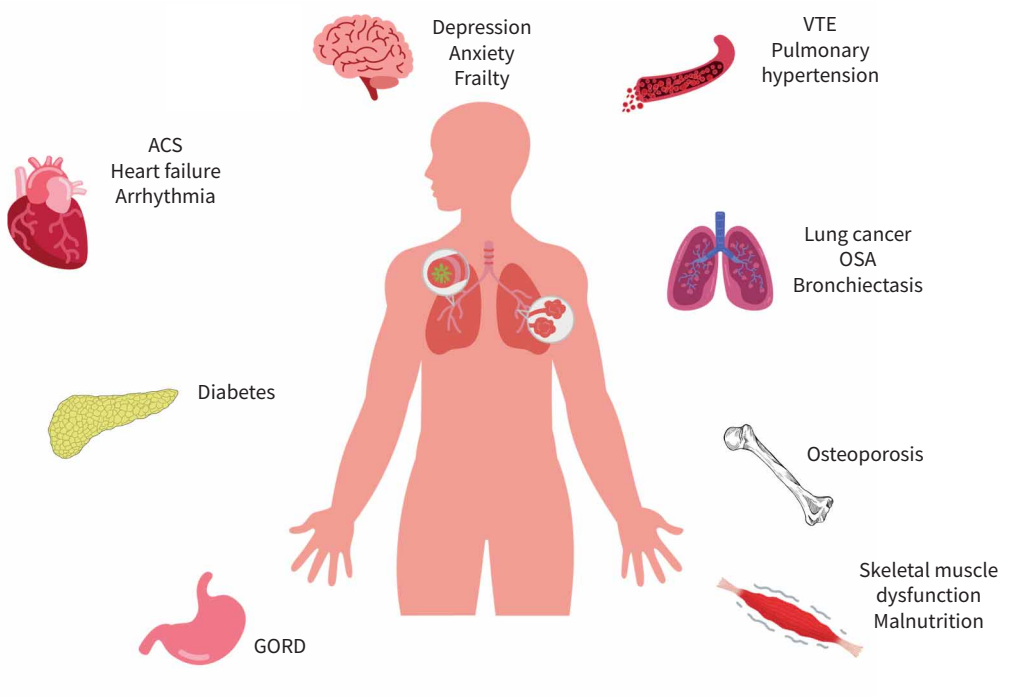

FIGURE 1 The comorbidities of COPD. ACS: acute coronary syndrome; OSA: obstructive sleep apnoea; GORD: gastro-oesophageal reflux disease; VTE: venous thromboembolism.

lung cancer was at least four-fold higher in patients with COPD compared with the general population [6]. Both airflow obstruction and emphysema are important risk factors for the development of lung cancer. However, the risk is greatest with emphysema, independent of the presence of airflow obstruction or smoking history [8, 9]. Lung cancers which develop in association with COPD tend to be more aggressive, demonstrate a shorter volume doubling time [10], and have a poorer prognosis [11].

Smoking cessation is the most effective measure to mitigate lung cancer risk. Pharmacological agents and cognitive behavioural therapy both improve the likelihood of successful smoking cessation in individuals with COPD. Some studies have suggested that inhaled corticosteroids (ICS) have a protective effective against lung cancer development; however, the data is conflicting and insufficient to support any true impact on lung cancer risk in COPD [12].

Screening of smokers for lung cancer reduces mortality by detecting lung cancer at an earlier stage. This was demonstrated in two large, population-based trials: the American National Lung Cancer Screening Trial (NLST), which observed a 20% relative reduction in mortality with screening [13], and the Dutch–Belgian lung cancer screening trial (NELSON), which observed a 24% mortality reduction [14]. On the basis of this data, the US Preventive Service Task Force (USPSTF) recommend annual low-dose computed tomography (CT) for lung cancer screening in adults aged 50–80 years with a 20-pack-year smoking history who currently smoke or have quit withing the past 15 years [15]. Similar screening programmes are now being rolled out internationally.

Patients with COPD are more likely to experience complications following the procedures necessary to make a diagnosis of lung cancer. Emphysema is an independent risk predictor of pneumothorax post CT-guided lung biopsy [16] and those with severe COPD have more frequent respiratory complications following bronchoscopy [17]. This has important implications when considering lung cancer screening in this cohort. Lung cancer screening offers both advantages and potential risks in patients with COPD and reduced lung function. The NSLT data have shown that the benefit of lung cancer screening is greatest in those with normal lung function or only mild-to-moderate COPD, with no mortality benefit in those with severe or very severe disease [10]. In a secondary analysis of the NLST data, patients with COPD who underwent screening were found to be more likely to have an invasive procedure and experience a serious procedure-related complication (OR 1.78, p=0.01) [10, 18, 19]. Liquid biopsy is an emerging technology which may potentially represent a noninvasive way to detect lung cancer [20].

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TABLE 1 Summary of clinical implications of comorbid disease and COPD

Comorbidity	Prevalence	Associated phenotype	Impact on COPD outcomes	Investigations	Management	Reference
Lung cancer	5%	Emphysema	Increased mortality	Screening with LDCT of the chest considered in those aged 50–80 years with >20 pack-year smoking history	Smoking cessation Screening with LDCT	[6]
OSA	56–66%		Higher prevalence of pulmonary hypertension Decreased QoL Increased risk of cardiovascular comorbidities especially atrial fibrillation	Polysomnography or polygraphy as the gold standard Overnight oximetry is less reliable	Positive pressure ventilation Bilevel noninvasive ventilation	[26]
Bronchiectasis	20–69%	Chronic bronchitis Frequent exacerbator	Increased exacerbation frequency Decreased lung function Decreased QoL Increased colonisation with PPMs (*e.g. P. aeruginosa*)	CT thorax Sputum culture	Macrolide antibiotics Chest physiotherapy for airway clearance techniques	[37]
VTE	3–29%		Prolonged hospitalisation during exacerbations Increased mortality	CT pulmonary angiogram D-dimer	Anticoagulants	[11]
Pulmonary hypertension	5–40%	Emphysema	Increased hospitalisations Increased mortality	Screening: echocardiography and NT-ProBNP Right heart catheterisation for definitive diagnosis but rarely has therapeutic implications Arterial blood gases	Long-term oxygen therapy	[52]
Acute coronary syndromes	7–33%	Chronic bronchitis	Increased mortality Increased hospitalisations	Elevations of Troponin and ECG changes common during exacerbations; do not necessarily reflect primary cardiac event	Reperfusion therapy, β-blockers, ACE inhibition and statins	
Heart failure	20–30%		Increased hospitalisations Increased symptom burden Worse QoL	Echocardiography Cardiac MRI	Guideline-directed medical therapy for heart failure	[77]
Arrythmia	20%		Increased mortality Increased risk of adverse cardiac events Increased risk of recurrence following ablation	ECG Cardiac monitor	β-blockers Anti-arrhythmic agents Ablation	[62]
Osteoporosis	24–69%	Emphysema	Decreased QoL Increased exacerbation risk	DEXA FRAX risk score	Calcium and vitamin D supplementation Anti-resorptive treatments	[11]
GORD	17–78%	Chronic bronchitis	Increased exacerbation risk	Usually a clinical diagnosis Consider OGD pH manometry in severe cases	Proton pump inhibitors	[98, 99]

Continued

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TABLE 1 Continued

Comorbidity	Prevalence	Associated phenotype	Impact on COPD outcomes	Investigations	Management	Reference
Malnutrition	5–30%	Emphysema	Increased mortality	Nutritional assessment including BMI estimation	Nutrition support	[93]
Diabetes	10–25%		Decreased QoL	Fasting glucose and HbA1c	Guideline-directed management	[100]
Skeletal muscle dysfunction			Increased mortality Decreased QoL Increased symptom burden	Limb muscle function testing (*e.g.* handgrip dynamometry) DEXA can evaluate skeletal muscle mass Exercise testing: 6 min walk test, ergometry Spirometry: MIP, MEP, SNIP	Pulmonary rehabilitation Neuromuscular electrical stimulation Inspiratory muscle training	[91]
Anxiety and depression	20–60%		Increased exacerbations Increased hospitalisations Increased symptom burden, especially dyspnoea	Anxiety Inventory for Respiratory (AIR) Disease and Brief Assessment Schedule Depression Cards (BASDEC)	Pharmacotherapy Psychological interventions Pulmonary rehabilitation	[102, 103]
Frailty	20–50%		Increased mortality	Clinical Frailty Score Comprehensive Geriatric Assessment	Rehabilitation Nutritional interventions Minimise polypharmacy	[105]

OSA: obstructive sleep apnoea; VTE: venous thromboembolism; GORD: gastro-oesophageal reflux disease; QoL: quality of life; LDCT: low-dose computed tomography; PPM: potentially pathogenic microorganisms; *P. aeruginosa*: *Pseudomonas aeruginosa;* CT: computed tomography; NT-proBNP: N-terminal pro-brain natriuretic peptide; ACE: angiotensin-converting enzyme; MRI: magnetic resonance imaging; DEXA: dual energy X-ray absorptiometry; FRAX: Fracture Risk Assessment Tool; OGD: oesophagogastroduodenoscopy; BMI: body mass index; HbA1c: haemoglobin A1C; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; SNIP: Sniff nasal inspiratory pressure.

The presence of COPD significantly impacts the management of lung cancer. Patients with COPD are at an increased risk during surgical resection for early stage cancers and are often deemed inoperable due to their high perioperative mortality. Pre-operative spirometry, diffusing capacity of the lung for carbon monoxide (D_{LCO}) and cardiopulmonary exercise testing are used to assess tolerance for resection [19]. In those with early stage cancers who are deemed inoperable, stereotactic ablative radiation therapy (SBRT) has emerged as the standard treatment with high rates of long-term disease control [21]. Optimisation of COPD treatment is associated with improved overall lung cancer survival, underlining the importance of identifying comorbid COPD in patients with lung cancer [22].

Sleep disordered breathing

Sleep disturbance is common in COPD and is one of the most frequently reported symptoms, occurring in up to 75% of patients [23]. When sleep disordered breathing, particularly obstructive sleep apnoea (OSA), coexists with COPD, it impairs overall health status and quality of life [24]. Sleep disordered breathing has negative effects on respiratory control, respiratory muscle function and lung mechanics, which can lead to profound disturbances of gas exchange. This can manifest in several ways, including altered sleep architecture, nocturnal desaturation and nocturnal hypoventilation [25].

The coexistence of OSA and COPD is often referred to as overlap syndrome. It is unclear whether COPD increases the risk of developing OSA, prevalence data vary with some studies estimating OSA to be present in 10–15% of patients with COPD [26]. Patients with both conditions have a worse prognosis compared with either condition alone. Overlap patients have higher incidences of pulmonary hypertension and right ventricular remodelling, and are at an increased risk of arrhythmias, particularly atrial fibrillation [27].

The STOP-BANG questionnaire is recommended as a screening tool for OSA in patients with overlap syndrome [28]. However, these patients often exhibit fewer of the typical OSA symptoms, such as snoring, witnessed apnoeas, daytime somnolence and unrefreshed sleep, compared with patients with OSA alone, reducing the accuracy of screening tools and leading to under-diagnosis [29]. Overnight oximetry is often considered a first-line screening tool for diagnosing OSA. However, it has been demonstrated that in patients with moderate-to-severe COPD, cyclical changes in saturation on oximetry are not a reliable predictor of OSA when confirmed by polysomnography (PSG) [30]. Therefore, PSG or polygraphy should be considered as the investigation of choice in all those with COPD who are at moderate-to-high risk of OSA based on the STOP-BANG questionnaire, as well as in patients with hypertension and nocturnal hypoxaemia.

In managing overlap syndrome, a combined strategy of optimising COPD treatments and implementing positive airway pressure (PAP) therapy when appropriate is advised. Long-acting β-agonists, long-acting muscarinic antagonists and theophylline have all been shown to improve nocturnal oxygenation [31]. Pulmonary rehabilitation also leads to improvements in sleep quality, daytime sleepiness and apnoea–hypopnoea index in patients with OSA [31]. In all patients with moderate or severe OSA, PAP remains the treatment of choice. PAP in this context reduces COPD exacerbations and hospitalisations [31]. PAP therapy improves daytime oxygenation values in those with overlap syndrome and may eliminate the need for long-term oxygen therapy (LTOT). Extra care should be taken when prescribing PAP in COPD patients. High levels of positive end-expiratory pressure can impose an additional expiratory load and worsen hyperinflation [29, 32].

Bi-level PAP should be considered in all patients with nocturnal hypoventilation (with or without coexistent OSA). In stable patients with chronic hypercapnic respiratory failure [33], long-term nocturnal noninvasive ventilation has been shown to improve symptoms, and to reduce hospital readmission and mortality [28, 34].

Bronchiectasis

Bronchiectasis is increasingly recognised as an important comorbid condition in those with COPD. Hurst *et al.* [35] have emphasised the need to consider this distinct clinical phenotype and suggested that the two may exist as an overlap syndrome. Bronchiectasis in patients with COPD is associated with the "chronic bronchitis" phenotype with thicker bronchial walls, greater daily sputum production and an increased number of exacerbations [36]. The variable most consistently associated with the presence of bronchiectasis in patients with COPD is chronic bacterial infection by potentially pathogenic microorganisms (PPMs), particularly *Pseudomonas aeruginosa* [37].

The cause-and-effect relationship between bronchiectasis and COPD is controversial. Chronic bronchitis, as well as the presence of bacteria such as *P. aeruginosa* in the lower airways, impair host defence mechanisms, resulting in disruption of epithelial integrity, inflammation and structural damage [37, 38].

Chronic infection with *P. aeruginosa* often signals a worse prognosis in patients with COPD due to its association with increased disease severity, frequent infections and accelerated decline in lung function. It is not surprising, therefore, that studies have demonstrated increased mortality in patients with COPD and comorbid bronchiectasis [36].

No studies have examined therapies for COPD complicated by bronchiectasis, leaving therapeutic consequences unclear. However, studies of bronchiectasis have included adult smokers with airflow obstruction from which we can draw parallels. These suggest that the use of long-term macrolide antibiotics and inhaled antibiotics may be beneficial in reducing exacerbations in this cohort [37, 39]. The use of ICS is associated with an increase in the bronchial bacterial load in patients with COPD and chronic bacterial infection [40]. It is on this basis that the Global Initiative for Chronic Obstructive Lung Disease (GOLD) currently advises against the use of ICS in patients with comorbid bronchiectasis and bacterial colonisation [41].

Peripheral eosinophilia has been observed in 20% of patients with bronchiectasis [42] and there is increasing interest in eosinophilia as a treatable trait in bronchiectasis. In 2023, a study demonstrated that in bronchiectasis patients with eosinophils >300 per μL, treatment with ICS reduced the number and severity of exacerbations [43]. Neutrophilic inflammation is felt to play a key role in COPD with bronchiectasis. Recent phase 2 clinical trials of dipeptidyl peptidase-1 inhibitors, novel drugs that target neutrophilic inflammation, showed promise in reducing exacerbation frequency in bronchiectasis [44]. These medications may represent a much needed novel, therapeutic approach for these conditions.

Venous thromboembolism

COPD is an established risk factor in the development of pulmonary embolism (PE) [45]. It has been suggested that this risk is mediated by shared risk factors such as immobilisation, repeated hospitalisations, right ventricular failure, venous stasis and systemic inflammation [46]. The prevalence of PE is higher during acute exacerbations of COPD. A large multicentre French study of 740 COPD patients admitted with symptoms of an exacerbation identified PE in 6% [47]. In patients with COPD, PE is the most frequent clinical presentation of venous thromboembolism (VTE), in contrast with the general population where deep vein thrombosis is more common [48].

The overlap between the symptoms of a COPD exacerbation and a PE (dyspnoea, cough) means the diagnosis of acute PE can be missed [47]. Fernández *et al.* [49] found that patients with COPD and PE more often had a lower pre-test probability than those without COPD and that COPD was associated with a significant delay in the diagnosis of PE. Physicians should maintain a high index of suspicion for PE in patients hospitalised with symptoms of a COPD exacerbation, in particular in those who fail to improve as expected with standard exacerbation therapy.

COPD patients who present with VTE experience poorer outcomes compared with the general population, with an increase in 3-month mortality [48]. In addition, when compared with COPD patients without PE, 1 year mortality is significantly increased [50]. Some studies had suggested a higher risk of VTE recurrence in patients with COPD [48]. However, a large prospective study of 1400 patients, published in 2017, did not find a higher rate of recurrence [51]; and therefore, the guidelines for duration of anticoagulation are the same as for patients without COPD. Ultimately, clinicians should be aware of the heightened risk of VTE in patients with COPD and be vigilant regarding thromboprophylaxis.

Pulmonary hypertension

The development of pulmonary hypertension (PH) in COPD is closely linked with the severity of airflow obstruction and chronic hypoxaemia, and is an important prognostic factor [52]. Pulmonary vascular remodelling in COPD, due to the combined effects of hypoxia, inflammation and loss of capillaries in emphysema, is the main driving factor in the development of PH in these patients.

PH should be suspected in patients with dyspnoea, desaturation with exertion and a disproportionate reduction in D_{LCO} on pulmonary function tests. Echocardiography can be a useful screening tool for PH; however, it can be limited by the presence of hyperinflation leading to poor acoustic windows. Right heart catheterisation is the gold standard test to confirm a diagnosis of PH and assess its severity.

The majority of patients with COPD have non-severe PH [53]. Severe PH, defined as pulmonary vascular resistance (PVR) >5 WU (Wood units), is observed in 1–5% of cases of COPD [54]. A distinct pulmonary vascular phenotype in COPD has been proposed, characterised by milder airflow obstruction, low D_{LCO}, hypoxaemia and significant exercise limitation [55]. There is conflicting evidence regarding the use of PH

specific medications in patients with COPD as pulmonary vasodilators may cause worsening ventilation/perfusion (V'/Q') mismatch and thus hypoxaemia [55]. The 2022 European Society of Cardiology/European Respiratory Society guideline suggests that phosphodiesterase-5 inhibitors (*e.g.* sildenafil) may be considered in a subset of COPD patients with severe PH, however, this decision should be made on an individual patient basis, in specialist PH centres [53]. It has been proposed that inhaled pulmonary vasodilators may be beneficial in this cohort as they have less potential to cause V'/Q' mismatch; however, a recent 2024 study in patients with COPD did not show evidence of positive benefit [56]. LTOT is the only treatment currently recommended for COPD patients with PH, with studies showing oxygen use for >15 h per day can stabilise PH in those with severe COPD [57].

Cardiovascular comorbidities

COPD is an independent risk factor for cardiovascular morbidity and mortality. Even after adjustments for confounding cardiovascular risk factors, such as cholesterol, obesity, smoking status and hypertension, patients with COPD have a 2–3-fold increased risk of cardiovascular events, including death [58]. Studies have demonstrated that just having symptoms of chronic bronchitis increases cardiovascular mortality [59].

There is mounting evidence that COPD exacerbations are associated with a period of increased cardiovascular risk. It is hypothesised that this increased risk is driven by an increase in systemic inflammation and increased cardiac workload during an exacerbation. A Danish study with 118 000 participants found a four-fold increased risk for major adverse cardiac events in the period following an exacerbation [60]. This increased risk is independent of pre-exacerbation cardiovascular risk status, and time dependent, with the greatest risk in the first 30 days but persisting for up to 1 year post-exacerbation [61, 62]. In this population the risk was greatest in those with severe exacerbations requiring hospitalisation.

Acute coronary syndrome

Patients with COPD are at higher risk of acute coronary syndrome (ACS). The relative risk of ACS is estimated to be 1.4-fold higher in COPD patients compared with those without COPD [63].

The association between COPD and ACS persists even when statistically adjusted for shared risk factors. Both disease processes share several pathophysiological features. Systemic inflammation drives endothelial dysfunction, oxidative stress and coagulopathy, and plays an important role in atherosclerosis and the development of cardiovascular disease [64]. Pro-inflammatory markers promote vascular endothelial dysfunction and ultimately contribute to plaque formation and rupture. In addition, the systemic inflammation in COPD, as well as oxidative stress due to hypoxia, appears to induce a "pro-coagulant" state with increased levels of coagulation factors, mainly fibrinogen contributing to thrombosis due to endothelial injury. Studies have also demonstrated that COPD patients have an increased platelet count and increased platelet activity, as well as impaired fibrinolysis, thereby increasing the risk of thrombotic events occurring [11, 64, 65].

Patients with COPD are known to have poorer medium- and long-term outcomes following ACS compared with those without COPD [66]. There are multiple reasons for the difference in outcomes in those with COPD. Biological factors and differences in clinical presentation certainly play a role. Patients with COPD are more likely to present with atypical chest pain or dyspnoea during an ACS. Studies have found that patients with ACS and concurrent COPD are more likely to not receive or to have delays in reperfusion therapy, and are less likely to be prescribed β-blockers as secondary prevention, all of which increase mortality [66, 67].

Elevated troponin levels and ECG abnormalities are common findings in patients presenting with an acute exacerbation of COPD [64, 68]; indeed one study of patients admitted with an exacerbation found one in 12 met the criteria for an acute myocardial infarction (MI) [69]. The challenge for physicians lies in differentiating ECG and troponin abnormalities that are due to transient myocardial ischaemia (or "Type 2 MI") from a primary cardiac event [70]. One study advised that physicians screen for cardiovascular risk factors in those presenting with exacerbations [62]; however, this has not been incorporated into formal guidelines and further research into a diagnostic strategy for these patients is warranted.

Heart failure

The prevalence of COPD in patients with heart failure (HF) ranges from 20% to 30%, which is significantly higher in the general population [71]. Data from the PARADIGM-HF trial demonstrated that in HF with reduced ejection fraction (HFrEF), patients with comorbid COPD had a worse burden of symptoms and overall quality of life despite an overall similar ejection fraction [72]. Subclinical haemodynamic changes have been observed in individuals with emphysema who demonstrate impaired left

ventricular filling and thus a reduced cardiac output without any reduction in ejection fraction [73]. COPD has a significant prognostic impact on HF and increases HF mortality and hospitalisations [11, 72, 74].

The presence of COPD has been found to delay the diagnosis of concurrent HF [11]. This is often attributed to the shared mechanisms and overlapping symptoms of the two conditions. The concurrence of these conditions can also lead to significant challenges in interpreting crucial diagnostic investigations. Echocardiography is considered the most important tool for making a diagnosis of HF. In COPD, interpretation can be impeded by poor acoustic windows caused by emphysematous hyperinflation. One study found that up to 34% of patients with severe COPD had inadequate views on transthoracic echocardiography. Cardiac magnetic resonance imaging should be considered in those with poor quality images [75, 76].

Studies suggest that spirometry is underused to identify COPD in those with HF [77]. Interpretation of spirometry in the setting of HF can be challenging. Patients with decompensated HF often demonstrate an obstructive ventilatory pattern, which can mimic COPD. The presence of congestion can lead to a more significant reduction in forced expiratory volume in 1 s (FEV_1), due to interstitial and alveolar oedema compressing the airways with associated bronchial hyperresponsiveness [62]. Conversely, those with stable HFrEF often demonstrate a reduction in both FEV_1 and forced vital capacity. Gas trapping and hyperinflation, as demonstrated by a high residual volume/total lung capacity ratio, can be a reliable indicator of COPD. As air trapping is not influenced by interstitial oedema, body plethysmography has been suggested as a useful investigation to improve diagnostic accuracy for COPD in HF patients [78]. β-blockers are a cornerstone in the treatment of HF, but they remain underutilised in patients with COPD, despite extensive safety data in patients with moderate-to-severe COPD [71, 77].

Arrhythmia

COPD is associated with a two-fold increase in atrial fibrillation (AF) risk [79]. COPD and AF share several common risk factors; however, the association goes beyond this. It is hypothesised that COPD directly contributes to the onset of AF through changes in cardiac function triggered by right ventricular strain. The severity of airflow obstruction and degree of hypoxaemia is strongly associated with the frequency of AF [79, 80]. Exacerbations of COPD are associated with a temporary increase in the risk of AF and, in turn, AF can trigger exacerbations of COPD [74]. Patients hospitalised with a COPD exacerbation who have a history of AF are at increased risk of in-hospital mortality [81].

The treatment strategy in AF is unchanged by the presence of COPD. However, rhythm control strategies using cardioversion or catheter ablation are associated with reduced success rates in patients with COPD [82]. Bronchodilators were historically considered as being potentially pro-arrhythmic; however, there is now substantial evidence supporting the acceptable safety profile of long-acting β-agonists, long-acting muscarinic antagonists and ICS [74]. Caution is however advised when prescribing short-acting β-agonists and theophylline as these medications may trigger arrhythmia and judicious use of bronchodilators is advised.

Musculoskeletal comorbidities

Osteoporosis

Osteoporosis is an important systemic comorbidity in COPD. The two conditions share a number of risk factors including advanced age, smoking, physical inactivity, low body mass index (BMI), sarcopenia, systemic inflammation and frequent use of corticosteroids [83]. Emphysema is a strong predictor of low bone mineral density (BMD), independent of airflow obstruction and other osteoporotic fractures, suggesting a mechanistic link between the two disease processes [84].

Oral corticosteroids and ICS are commonly employed in COPD with robust data on their efficacy for preventing and treating exacerbations. Corticosteroids are also the most common iatrogenic cause of osteoporosis. Repeated courses of oral prednisolone (with a cumulative dose of >1 g) have been shown to be associated with a reduced BMD at the spine ($p<0.0001$) [85]. The impact of ICS on BMD is dose dependent, with one meta-analysis demonstrating a modest but statistically significant increase in the likelihood of fractures with ICS treatment [86]. However, it is important to take into account the role ICS play in reducing the rate of exacerbations (and thus the need for treatment with oral corticosteroids) when making therapeutic decisions.

Osteoporosis is associated with an increased risk of fractures which have important implications for morbidity and mortality in COPD. Vertebral compression fractures leading to pain and kyphosis have a marked impact on patients with COPD. There is an estimated 9% loss of vital capacity with each vertebral

compression fracture, the impact of which is amplified in those with already reduced lung function due to COPD. Rib fractures may precipitate COPD exacerbations due to difficulties expectorating and pain related to hypoventilation [87].

Early recognition of vertebral compression fractures is important, especially in patients with COPD. Measurement of BMD using a dual energy X-ray absorptiometry (DEXA) scan is the gold standard for making a diagnosis of osteoporosis. However, DEXA does not detect microarchitecture changes in the bone and therefore BMD alone does not reliably predict osteoporotic fractures. It can also take over 2 years to detect statistically significant changes in BMD on a DEXA scan. The World Health Organization has developed the FRAX score, which is an algorithm designed to estimate a patient's 10-year probability of a fracture. In 2012, a study demonstrated that neither FRAX score or BMD alone could predict vertebral compression fractures in individuals with moderate-to severe-COPD [88]; highlighting an unmet need for a disease-specific algorithm to predict osteoporotic fractures [83, 88]. SARKAR *et al.* [83] suggested the following algorithm for the investigation and management of osteoporosis in COPD. Patients are assessed for the following criteria:

- Minor: BMI <21 $kg \cdot m^{-2}$, current smoking, alcohol use >3 units per day, age >65 years, hip fracture in a parent, rib fracture, menopause, inactivity, FEV_1 <50% predicted
- Major: systemic corticosteroids (3 months per year), fragility fracture (spine/hip)

If patients meet at least one major or three minor criteria then BMD should be assessed using a DEXA scan along with serum vitamin D levels. SARKAR *et al.* [83] suggest that pharmacotherapy is initiated in the following conditions:

- Documented fragility fractures;
- T-score below 2.5 standard deviations; or
- T-score between −1 and −2.5 standard deviations with one major criterion

In terms of pharmacotherapy, calcium and vitamin D supplementation are first-line therapy. Guidelines suggest a minimum intake of 1200 mg calcium and 800 UI vitamin D in those over 50 years of age, with one metanalysis finding a 12% reduction in fractures of all types and a reduced rate of bone loss [89]. Guidelines advocate for early anti-resorptive therapy in those with corticosteroid-induced osteoporosis.

Bisphosphonates are usually employed in the first instance, with zoledronic acid giving the overall best fracture protection [83]. However, teriparatide has greater efficacy than bisphosphonates in steroid-induced osteoporosis, with a greater increase in BMD and fewer new vertebral fractures [90].

Malnutrition and skeletal muscle dysfunction

One of the main systemic manifestations of COPD is malnutrition and a change in body composition that develops as the disease progresses. Low BMI (<20 $kg \cdot m^{-2}$) is associated with a higher mortality, poorer exercise tolerance and an increase in hospitalisations [91]. Malnutrition leads to a reduction in lean body mass (muscle). Even without loss of muscle mass, patients with COPD may exhibit skeletal muscle dysfunction, which has a negative impact on morbidity and disease prognosis [11, 91]. Both skeletal muscle dysfunction and malnutrition are more prevalent in those with an emphysematous phenotype. The aetiology of skeletal muscle dysfunction is multifactorial. In the case of respiratory muscles, altered fibre type, metabolism and remodelling due to hyperinflation are contributing factors. Physical inactivity and deconditioning contribute to limb muscle weakness. Systemic factors including smoking, nutritional deficiencies, exacerbations, anabolic insufficiencies and medications also play an important role [91].

Peripheral muscle wasting is associated with increased mortality and a poorer prognosis than ventilatory muscle loss [92]. COPD exacerbations can precipitate accelerated loss of muscle mass due to immobility, which is worsened by the additional effects of steroids. This loss of muscle mass often fails to recover to the pre-exacerbation baseline, mirroring the effect of exacerbations on lung function [91].

Multimodal treatment incorporating nutritional support and exercise-based training through pulmonary rehabilitation are the cornerstones of treatment of malnutrition and muscle dysfunction in COPD. Nutritional support has been shown to improve body mass, muscle strength, quality of life and walk distance; however, it has not been shown to improve lung function [93]. One of the key components of pulmonary rehabilitation is exercise training, encompassing both endurance and strength training. This is the best intervention currently available for treating skeletal muscle dysfunction in COPD [91, 94]. Most recent guidance suggests that the benefits of pulmonary rehabilitation can be seen even in those in the early stage of the disease. The role of pulmonary rehabilitation following an acute exacerbation must also

be emphasised as there is abundant evidence that it improves exercise tolerance, symptom burden and lowers readmission rates [94].

Neuromuscular electrical stimulation has been proposed as an alternative option to improve muscle strength and exercise capacity, especially in those who are unable to engage in traditional pulmonary rehabilitation [91]. A 2016 trial found that neuromuscular electrical stimulation improved exercise capacity in severe COPD by enhancing quadriceps function and mass, with the maximal effect at 6 weeks [95].

Pulmonary hyperinflation in individuals with COPD leads to a reduction in the pressure-generating capacity of the inspiratory muscles, which is felt to contribute to exercise intolerance and dyspnoea. There has been keen interest in the role of inspiratory muscle training (IMT), which involves using a device to add resistance when breathing to strengthen the diaphragm and intercostal muscles. The current consensus is that IMT improves the strength of inspiratory muscles; however, it has not consistently demonstrated improvements in dyspnoea or exercise capacity. There may be a role in those unable to complete a traditional pulmonary rehabilitation programme [94, 96].

Other comorbidities

Gastro-oesophageal reflux

Gastro-oesophageal reflux disease (GORD) has a high prevalence in the general population and has a number of implications when it coexists with COPD. GORD is an important risk factor for exacerbations, with an estimated 1.7 times increased risk of exacerbations in those who report reflux symptoms [97]. One study found that this increased risk only occurred in patients not prescribed proton pump inhibitor (PPI) therapy, indicating a potential role for these medications in preventing exacerbations [98]. One further small study suggested that PPIs reduced the risk of COPD exacerbations in patients without GORD; however, given the limited trial data available they are not routinely recommended [99].

Diabetes

Diabetes is the third most prevalent comorbidity associated with COPD [2]. Cohort studies have shown that moderate-to-severe COPD increased the risk of diabetes, with studies hypothesising that the systemic inflammation associated with COPD plays a key role in the development of insulin resistance in these patients [100]. ICS use is associated with a modest increase in the risk of the development and progression of diabetes, with the risks most pronounced at the higher doses [101].

Anxiety and depression

Individuals with COPD have higher rates of anxiety and depression compared with the general population and compared with individuals with other chronic health conditions. Comorbid depression and anxiety are associated with higher rates of acute exacerbations and higher rates of rehospitalisation [102]. One study noted that during acute admissions, patients with anxiety have worse dyspnoea scores, despite less severe physiological parameters [103]. Depression is common in this patient cohort and has been shown to have a negative prognostic impact [11].

There is no consensus on the most appropriate screening tool for anxiety or depression in patients with COPD. The Anxiety Inventory for Respiratory Disease (AIR) and Brief Assessment Schedule Depression Cards (BASDEC) are screening tools that have been designed for patients with COPD [102]. However, given ambiguity over their utility in clinical practice, GOLD does not advocate for their routine use [41].

Treatment approaches for anxiety and depression should follow a biopsychosocial model and can broadly be divided into pharmacological interventions and psychological interventions. There is no evidence that depression or anxiety should be treated any differently in the presence of COPD [41]. Psychological interventions include relaxation therapies, cognitive behavioural therapy and self-management strategies. Randomised controlled trial data has shown that pulmonary rehabilitation is effective at improving symptoms of anxiety and depression, underlining its importance in the management of all patients with COPD [104].

Frailty

COPD is a disease of advanced age, and therefore, comorbid cognitive impairment and frailty are common findings. Frailty is a complex syndrome characterised by loss of physiological reserve and an increased vulnerability to adverse health outcomes. A meta-analysis found that frailty and pre-frailty were predictors for all-cause mortality in patients with COPD, even after adjustments for confounding factors [105]. A European Respiratory Society statement emphasises the importance of a multidisciplinary approach in the management of frailty in patients with COPD. The statement recommends assessment using the

Comprehensive Geriatric Assessment model and treatment strategies that encompass rehabilitation, nutrition, minimising polypharmacy, and psychological and social support [106].

Conclusion

This review outlines the multitude of comorbidities associated with COPD. Tobacco smoking and advanced age are well established risk factors for both COPD and many of these comorbidities; however, the association probably extends beyond this. There is growing recognition of the role of systemic inflammation in the pathophysiology of these disease processes. COPD is truly a multisystem disease; the additive effect of these comorbidities has a detrimental effect on patients with COPD in terms of mortality, exacerbation frequency, symptom burden and overall quality of life.

The diagnosis of comorbid disease in the presence of COPD is challenging due to overlapping symptoms, and difficulties interpreting routine diagnostic tests in the presence of coexistent COPD. It is important to remember that the presence of COPD does not significantly alter the management strategy of most common comorbid diseases. It is essential therefore that clinicians have a high index of suspicion to ensure early diagnosis and management.

Self-evaluation questions

1. Which of the following are recognised comorbidities in COPD:
    a) Osteoporosis
    b) Diabetes
    c) ACS
    d) Frailty
    e) All of the above
2. Multimorbidity in COPD is not associated with which of the following:
    a) Increased quality of life
    b) Increased exacerbations
    c) Increased mortality
    d) Reduced exercise tolerance
    e) Reduced lung function
3. COPD exacerbations are increased in the presence of which of the following:
    a) Arrhythmia
    b) GORD
    c) Anxiety
    d) Osteoporosis
    e) All of the above
4. The interpretation of which of the following investigation(s) can be impaired in multimorbid COPD:
    a) Pulmonary function tests
    b) Echocardiogram
    c) Bone densitometry scan (DEXA)
    d) Overnight oximetry
    e) All of the above

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Suggested answers

1. e.
2. a.
3. e.
4. e.