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# Epidemiology of comorbidities in chronic obstructive pulmonary disease: clusters, phenotypes and outcomes

*Epidemiologia delle comorbilità nella broncopneumopatia cronica ostruttiva: cluster, fenotipi e outcome*

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## KEYWORDS

COPD;  
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Phenotypes;  
Outcomes.

**Summary** COPD is a complex multisystem disease often accompanied by multiple co-morbidities that contribute to symptoms, exacerbations, hospital admissions and mortality. Individual comorbidities can be grouped into clusters of common human pathology: inflammation/immune response (e.g., ischemic heart disease, metabolic syndrome), thrombosis/hemorrhage (e.g., cerebrovascular diseases, pulmonary embolism), fibrosis/ cell proliferation (e.g., lung cancer and other malignancies) and apoptosis/necrosis (e.g., osteoporosis, skeletal muscle dysfunction). While the prevalence of the co-morbidities has been described in a number of observational studies, there is considerable variability in results; moreover characterization of cluster of co-morbidities with the most clinical significance in terms of morbidity and mortality is still lacking. Pathological mechanisms underlying some of the identified clusters are well known; others need further clarification to identify possible preventative strategies. Treatment of COPD must include management of the underlying co-morbidities for best outcomes.

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## Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous disease that carries a significant morbidity and

mortality as well as economic burden on individuals, families and the society. COPD is currently the fourth leading cause of death worldwide and is projected to be the third leading cause of death by 2020 [1]. Also, COPD is a leading cause of

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hospitalizations in older adults. In the United States, the cost of COPD care was approximately \$ 37.2 billion in 2004 [2]. In Italy, COPD was responsible for 6% of total health care costs in 2008 [3]. Although all these figures are alarming, these figures only represent the “tip of the iceberg”, as COPD rarely occurs in isolation, but often is a part of more complex multisystem syndrome with a large number of associated comorbidities [4].

Our understanding of the natural history of COPD is based on large epidemiological studies that have shown that COPD is largely caused by cigarette smoking, and is characterized by airflow limitation, limited and declining performance status, and is frequently associated with systemic manifestations and complications [5]. COPD progression can vary significantly depending on the predominant phenotype as well as development of systemic complications and comorbidities [6]. Currently, there are gaps in the knowledge of COPD's natural history regarding the exact pathogenesis underlying the different clusters of co-morbidities as well as the extent to which these clusters affect patient outcomes. This review will summarize the comorbidities of COPD using the paradigm of common human pathologic mechanisms to group these comorbidities together.

## What is Comorbidity? Why are Comorbidities Important?

In COPD, comorbid conditions, or comorbidities, may be defined as the other serious diseases and chronic medical conditions that afflict persons who have COPD [7]. Comorbidities differ from systemic consequences of COPD which are thought to be direct consequences of the disease with a cause-and-effect relationship; both however, influence the course of the disease [8]. For example, ischemic heart disease is a common comorbidity in COPD while cor pulmonale is a known systemic consequence. Several factors add to the complexity of studying comorbidities and outcomes in patients with COPD. These include smoking history, aging, polypharmacy and medication interactions, coding inaccuracy of diagnoses, and lack of specific case definitions for some of the comorbidities [9]. Comorbidities play an important role in COPD for several reasons. First, they may share similar pathophysiological mechanisms as COPD. Second, comorbidities have a significant impact on health status, healthcare utilization and all-cause hospital admissions in

COPD patients. Third, mortality due to as associated comorbidities like cardiovascular disease or malignancy can occur earlier than respiratory causes; thus, affecting the overall survival of COPD patients. Fourth, understanding clusters of comorbidities may be useful to phenotype COPD better with diagnostic, therapeutic and prognostic implications.

## Clusters of Comorbidities in COPD

Based on the definition above, several comorbidities have been identified in patients with COPD. The prevalence of these comorbidities in COPD varies significantly between studies based on definitions and methods used (Table 1) [9].

Historically, human diseases have been classified on the basis of their end-organ manifestations, using a traditional clinicopathological approach. The same approach has been used conventionally to group and describe the comorbidities of COPD. Recently, Loscalzo has proposed a novel, holistic method for classifying human diseases based on common human pathologic mechanisms [10]. This approach could be used to group the comorbidities of COPD into different clusters (Table 2) with better understanding of their pathobiology and consequently, their treatment and outcomes.

## Comorbidities classified by organ systems involved

Using the traditional clinicopathological approach and end-organ manifestations of the comorbidities of COPD, they can be grouped as follows.

### Respiratory

Several respiratory conditions have been found to coexist and complicate the course of patients with COPD. Notable among those are asthma, pneumonia, pulmonary embolism, obstructive sleep apnea and lung cancer.

Traditionally, many have tried to segregate people with obstructive airway diseases into those with asthma or COPD. Nevertheless, evidence suggests that asthma tends to coexist in a proportion of patients with COPD, especially the elderly [11,12]. A recent analysis of the NHANES III database showed that compared to patients who report COPD only, those who report coexisting asthma and COPD have a higher risk of obstruction on spirometry and a higher risk of death during follow-up [13].

**Table 1** Chronic obstructive pulmonary disease and the prevalence of comorbidities (%).

Source	n	Arthritis	Cardiac	HTN	Diabetes	Lipids	Psych	GI	Cancer	Osteoporosis
van Manen and colleagues (1)	1,145	36	13	23	5	—	9	15	6	—
Mapel and colleagues (2)	200	22	65	45	12	—	17	32	18	—
Soriano and colleagues (114)	2,699	28	22	—	—	—	10	26	4	—
Sidney and colleagues (9)	45,966	—	18	18	2	9	—	—	—	—
Walsh and Thomashow (115)	3,000	70	50	52	16	51	38	62	4	32

Table 1 Summary of the studies on prevalence of comorbidities in COPD. Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Chatila WM, Thomashow Bm, Minai OA, Criner GJ, Make BJ. Title: Comorbidities in chronic obstructive pulmonary disease. Journal: Proceedings of the American Thoracic Society 2008 May 1, 5 (4): 549-55. Official Journal of the American Thoracic Society).

Definition of abbreviations:— = no available data; GI = gastrointestinal disturbances; HTN = hypertension.

**Table 2** Clusters of COPD comorbidities based on common human pathologic mechanisms.

1. Inflammation/ Immune response -Asthma, pneumonia, IHD, osteoporosis, skeletal muscle dysfunction, metabolic syndrome
2. Apoptosis/Necrosis/Degeneration-Cardiovascular diseases, malignancies, metabolic syndrome, osteoporosis, skeletal muscle dysfunction
3. Trauma and repair/ Cell proliferation and Neoplasia/ Fibrosis- Malignancies, Musculoskeletal dysfunction
4. Thrombosis/hemorrhage-PE, IHD, cerebrovascular diseases
5. Unknown- Depression, chronic renal failure

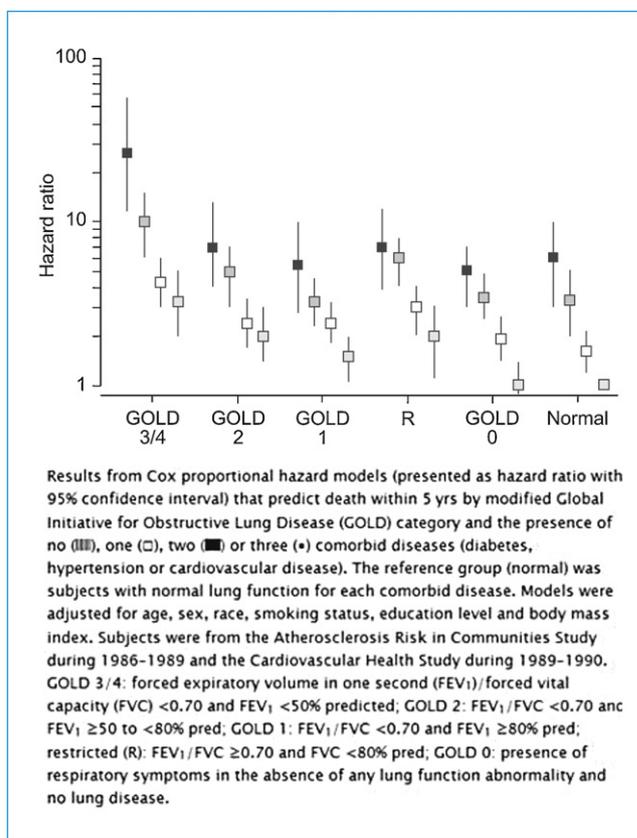
Pneumonia is viewed by some as part of the spectrum of COPD exacerbations; however, there are important differences between the two, and studies have shown that patients with COPD and pneumonia have more abrupt onset of symptoms, more severe illness, longer length of stay, and higher rates of ICU admission and death [14]. Distinguishing COPD exacerbations from pneumonia is important to ensure therapeutic success, although in clinical practice many patients that present to the hospital with new onset pneumonia are unaware of the presence of COPD. For example, in a study that included 707 patients presenting with community-acquired pneumonia, 19% had COPD while in 10% of the cases, pneumonia led to the new diagnosis of COPD [15]. Also, some COPD therapies like salmeterol and fluticasone have been shown to increase the incidence of pneumonia yet decrease the incidence of exacerbations [16].

Pulmonary embolism (PE) is thought to be a common comorbid condition in patients with COPD, although the data is somewhat controversial. In a study of 211 consecutive patients admitted for severe exacerbation of COPD of unknown origin and undergoing spiral CT or ultrasonography, that 25% of patients had PE [17]. In contrast, a more recent study reported a low incidence of PE in 123 consecutive patients admitted for acute exacerbation of COPD: 6.2% of patients with a clinical suspicion of PE, and only 1.3% of those with low suspicion [18].

Finally, although the prevalence of obstructive sleep apnea has not been shown to be significantly different in patients with COPD compared to people without it, patients with concomitant COPD and obstructive sleep apnea have higher pulmonary artery pressures, increased incidence of right heart failure, and more hypoxia and hypercapnia for a similar level of lung function [19]. These patients also have an increased risk of hospital admission for COPD exacerbation and higher mortality than COPD patients without OSA and this risk decreases with use of continuous positive airway pressure [20].

### Cardiovascular and Cerebrovascular

A wide variety of cardiovascular conditions afflict people with COPD including coronary artery disease (CAD), congestive heart failure (CHF), cerebrovascular diseases, arrhythmias and hypertension. Cardiovascular disease is the leading cause of death in patients with mild-to-moderate COPD. In a pooled analysis of two large population-based epidemiological studies by Mannino et al, the prevalence



**Figure 1** Prevalence of different comorbidities across spectrum of GOLD classes of COPD. “Reproduced with permission of the European Respiratory Society. Eur Respir J October 2008 32:962-969; published ahead of print June 25, 2008, doi:10.1183/09031936.00012408” Copyright remains with European Respiratory Society®.

of cardiovascular disease (defined as IHD, heart failure, stroke and/or transient ischemic attack) in COPD patients was found to be 20–22% compared with 9% in subjects without COPD [21]. These increases were particularly amplified in COPD patients with GOLD stage III and IV disease rather than those with mild-to-moderate COPD (Fig. 1) [21].

The main cardiovascular comorbidity in COPD is ischemic heart disease (IHD). Multiple studies have demonstrated that the prevalence and odds of development of IHD in people with COPD is considerably higher compared to controls even when adjusted for known cardiovascular risk factors [22–24]. In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, ‘heart trouble’ was reported in 26% of 2164 COPD patients compared with 11% of 337 smoking controls ( $p < 0.001$ ), with a myocardial infarction reported in 9 versus 3% ( $p < 0.001$ ) [25]. Heart failure is a complex clinical syndrome with many features in common with COPD. There are many causes of heart failure but the most common are IHD and long-standing poorly controlled hypertension, both of which are common in COPD patients. The overall prevalence of heart failure in COPD in the ECLIPSE study was 7%, [25] and increased with the severity of airflow limitation. The prevalence of cardiac arrhythmia in COPD is estimated at around 12% [22], atrial fibrillation being the most common type.

Cerebrovascular diseases are also quite common in people with COPD. Feary and colleagues reported the prevalence of stroke as 9.9% in those with COPD compared with a background prevalence of 3.2% in the rest of the population [26]. In the longitudinal part of the study, COPD was associated with a 2.8-fold increase in the incidence of acute stroke. Despite the reported prevalence and relative importance of stroke, there is a limited data on its symptomatic and functional impact on COPD.

### Metabolic

Metabolic syndrome is a complex disorder recognized clinically by the findings of abdominal obesity, elevated triglycerides, atherogenic dyslipidemia, elevated blood pressure, and high blood glucose and/or insulin resistance. Patients with COPD often have one or more component of the metabolic syndrome and osteoporosis which are at least, in part, independent of treatment with steroids and/or decreased physical activity [27].

Hypertension is consistently one of the most prevalent comorbid diagnoses in COPD. In the pooled analysis of two large population-based cohorts by Mannino et al, prevalence of hypertension of 34% in normal subjects, increasing to 40% in GOLD stage I patients, 44% in GOLD stage II and 51% in GOLD stages III and IV [21]. Hypertension is generally asymptomatic and thus would not be expected to particularly impact on COPD patients. However, it is a key risk factor for atherosclerotic diseases, hemorrhagic stroke and cardiac arrhythmias, and therefore its sequelae may have a profound impact on COPD patients.

Type II diabetes is more prevalent in moderate-to-very severe COPD than in the general population, with an overall prevalence of 12.7% [21]. Although, some nondiabetic patients have hyperglycemia induced by systemic corticosteroids, many more have truly overt diabetes.

Studies on dyslipidemia in COPD are limited and have generally relied on questionnaire or diagnostic codes to determine frequency [9]. Therefore, it is unknown if dyslipidemia is another independent factor that could explain the increased risk of cardiovascular morbidity and mortality in COPD. There is no evidence that management of dyslipidemia in COPD should be different to that recommended for the general population, particularly in terms of lifestyle and diet modifications. However, there is a growing body of evidence that statin therapy is beneficial in COPD patients, beyond important effects on cardiovascular risk reduction [28].

Osteoporosis and osteopenia are more prevalent in COPD than control subjects at 40–70% depending on the study population, and are related to disease severity, CT-quantified emphysema score, arterial stiffness, systemic inflammatory markers, BMI and physical activity [29]. Males in their mid to late 60s with a smoking history of greater than 60 pack-years have a prevalence rate of vertebral fractures similar to, and possibly greater than, postmenopausal women greater than or equal to 65 years old [30]. Systemic steroids remain the most common cause of drug-related osteoporosis; the role of inhaled corticosteroids in the development of osteoporosis is still a matter of controversy. Skeletal muscle dysfunction is also quite common in COPD [29] for many reasons including periods of relative inactivity, use of systemic glucocorticoids, malnutrition, and possibly systemic inflammation and

oxidative stress. COPD patients with suspected or known skeletal dysfunction benefit highly from pulmonary rehabilitation programs.

### Malignant

Lung cancer is an important cause of mortality in COPD. Depending on studies, lung cancer has been found to be the cause of death in 7 to 38% cases [9]. Although smoking causes COPD and lung cancer, airways obstruction has a greater risk on developing lung cancer than status or degree of smoking [31]. Moreover, the risk of developing lung cancer has been shown to be proportional to the severity of airways obstruction. Compared with smokers with normal lung function, hazard ratios for developing lung cancer for patients with mild to moderate and severe COPD ranged between 1.4 and 2.7 and 2.8 and 4.4, respectively [32]. The risk of lung cancer was 3.5-fold higher for women than men at similar levels of FEV1 [31].

COPD patients are also at increased risk of extrapulmonary malignancies, although there is limited research in this area. In one study, COPD was also associated with an increased risk of death from extrapulmonary cancer, with a hazard ratio of 1.43; the relationship was significant for moderate COPD (HR, 1.70), but not for severe COPD (HR, 1.38), nor for patients with mild COPD (HR, 1.22) [33].

### Miscellaneous

Chronic renal failure (CRF) is another comorbidity of COPD that needs more research. In a cohort of 365 patients, the prevalence of concealed (with normal GFR) and overt CRF in patients with COPD was 20.8% and 22.2%, respectively compared to 10.0% and 13.4%, respectively in controls [34]. Diabetes, hypoalbuminemia, and musculoskeletal diseases were significant correlates of concealed CRF while body mass index (BMI) and diabetes were significantly associated with overt CRF. Although there may not be a direct renal therapy applicable for CRF coexisting with COPD, there may be an underlying comorbidity such as hypertension or diabetes which could be managed more appropriately. CRF may also affect the ability to compensate for hypercapnic respiratory failure [29].

Symptomatic gastroesophageal reflux disease (GERD) occurs in up to 30–60% of COPD patients [35] many more asymptomatic are detected by esophageal manometry. There are reasons why reflux may be more prevalent in COPD, including a low lying diaphragm from hyperinflation, coughing and increased use of abdominal muscles for ventilation [29]. Data from the ECLIPSE study identified a history of heartburn or reflux as an independent predictor of frequent COPD exacerbations [36].

Depression is a common comorbidity of most symptomatic chronic diseases that has great implications; prevalence may be higher in COPD than other chronic diseases [37]. Data from the ECLIPSE study showed around a quarter of COPD patients had depression as defined by the score on a validated questionnaire compared with 12% of control subjects [38]. It is widely acknowledged that depression is under-recognized in COPD and screening questionnaires may be a useful adjunct to a clinical diagnosis, upon which management should be based. Systemic pulmonary rehabilitation, pharmacological antidepressants and psychotherapeutic strategies may all be

beneficial, but more work is required to optimize the management pathway of these individuals.

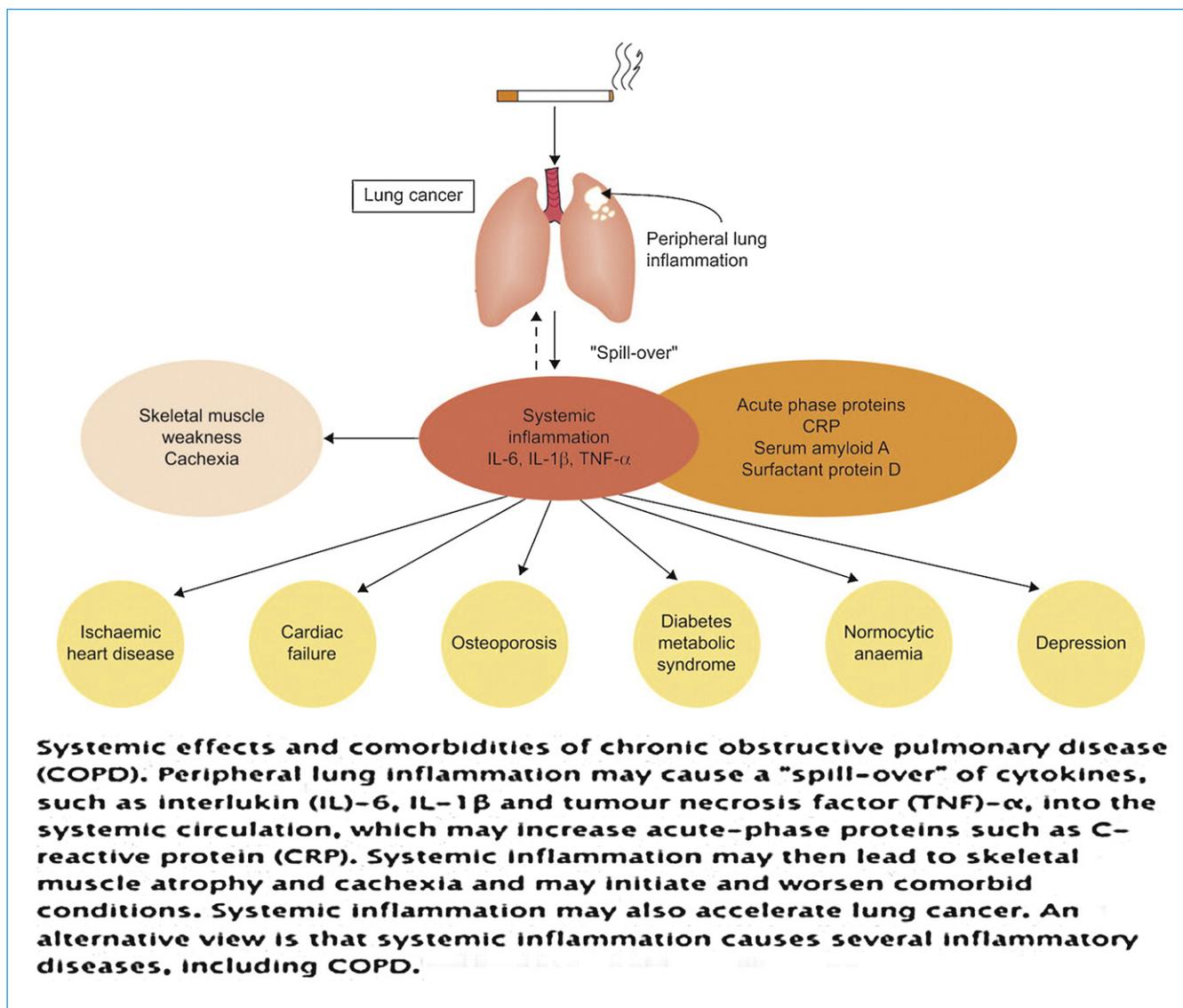
### Comorbidities Classified by Pathophysiological Mechanisms Involved

Although the association between COPD and its comorbidities is quite strong, the pathophysiological link is not as well understood. The mechanisms that have been proposed are very interrelated. As mentioned previously, these may potentially be used to cluster the comorbidities as summarized in Table 2.

#### Inflammation/Immune Response

Systemic inflammation appears to play a central role in the pathogenesis of COPD and its comorbid conditions. [27]. However, the origin of systemic inflammation in COPD

is unknown, and several potential mechanisms have been proposed [39]. Some authors believe that systemic inflammation in COPD may result from "spill-over" of mediators, cytokines, or activated inflammatory cells from the lung into the systemic circulation, although others argue that inflammation may arise in non-pulmonary tissues [8]. Patients with COPD have been observed to have increases in circulating levels of cytokines (IL-6, IL-8, TNF- $\alpha$ ), acute phase reactants (CRP, adhesion molecules, fibrinogen, serum amyloid A) and circulating activated inflammatory cells, particularly neutrophils [8]. Cigarette smoking appears to be the common inciting factor for the inflammatory cascade in many patients with COPD and its comorbidities, Figure 2 [40]. However, not all smokers develop COPD; moreover inflammation from cigarette smoking exposure seems to persist after cessation of smoking. These observations have given way to the hypothesis that COPD is an autoimmune condition [41]. There is now evidence that both innate and adaptive immune



**Figure 2** Role of systemic inflammation in development of comorbidities of COPD (40). Reproduced with permission of the European Respiratory Society. Eur Respir J May 2009 33:1165-1185.

response is impaired in COPD. Also, there are many potential mechanisms that can boost an acquired immune response in COPD [42].

Systemic inflammation in COPD is known to contribute significantly to the development of cardiovascular diseases, particularly atherosclerosis via endothelial dysfunction [27]. Systemic inflammation may also explain why patients with COPD have an increased risk of developing diabetes: some aspects of inflammation can predict the development of diabetes and glucose disorders while fibrinogen, circulating white blood cell count and lower serum albumin predict the development of type 2 diabetes [43]. Post-menopausal osteoporosis is related to high serum levels of TNF- $\alpha$  and IL-6, and osteopenia found in COPD is also associated with an increase in circulating TNF- $\alpha$  [27]. Systemic inflammation may also lead to lack of response to nutritional supplementation resulting in muscle wasting and skeletal muscle dysfunction [44]. There is also increasing recent evidence that chronic infections act as a source of inflammation in COPD and contribute to exacerbations [45]. The immune response part of the inflammatory cascade in COPD could potentially explain some of the other comorbidities in COPD, particularly asthma, and the metabolic syndrome [42].

#### **Degeneration/Apoptosis/Necrosis**

COPD has often been considered a degenerative disease of ageing similar to other chronic diseases. Aging is commonly characterized as a progressive, generalized impairment of function resulting in an increasing vulnerability to environmental challenge and a growing risk of disease. Cellular degeneration is highly complex, involving multiple mechanisms at different levels including DNA damage, oxidative stress and telomere shortening. Current theoretical understanding suggests that cells tend to accumulate damage as they age. Such damage is intrinsically random in nature, but its rate of accumulation is regulated by genetic mechanisms for maintenance and repair. As cell defects accumulate, the effects on the body as a whole are eventually revealed as age-related frailty, disability and chronic diseases [46,47]. Recently, a number of antiaging molecules have been identified, and evaluation of these molecules in patients with COPD might identify several new molecular targets for the treatment of COPD [48].

Aging of the population increases the prevalence of chronic diseases including cardiovascular disease, cancer, diabetes, and osteoporosis all of which are known comorbidities of chronic obstructive pulmonary disease (COPD) [49]. A single common pathway of cellular degeneration may explain part of the development of all these syndromes as they often develop in parallel or closely spaced in time.

#### **Trauma and Repair: Oxidative Stress and protease/antiprotease imbalance/Cellular proliferation/Neoplasia/Fibrosis**

Another potential mechanism in COPD pathogenesis is trauma with poor repair. Cellular trauma seems to be mediated by at least two mechanisms namely oxidative stress and protease/antiprotease imbalance. Repair subsequently occurs via fibrosis and/or cellular proliferation; both of these are relatively understudied in COPD.

Oxidative stress, defined as oxidant-antioxidant imbalance metabolism is over-activated in COPD. The major external source of oxidants is components of cigarette smoke. Bronchial inflammation involving phagocytes, such as neutrophils and macrophages, adds an internal production of oxidants. Antioxidants such as the glutathione system and the haemoxygenase (HO)-1 pathway which counteract oxidative stress are also impaired in COPD [50].

There is also considerable protease-antiprotease imbalance in COPD [51]. Proteases are cleavage proteins produced by various cells within the airways. Their activity is regulated by the production and release of antiproteases, such as  $\alpha$ 1-antitrypsin, secretory leukoprotease inhibitor and tissue inhibitor of metalloproteinases (TIMPs). Cigarette smoke inhibits the activity of antiproteases leading to a protease-antiprotease imbalance identical to what is seen in alpha-1 antitrypsin deficiency. Consequently, there is tissue damage that can lead to local and systemic inflammation.

Cellular damage and aberrant repair may explain some of the comorbidities of COPD. Oxidative stress and protease-antiprotease imbalance both result in systemic inflammation with its successive consequences as described above. Oxidative stress is also thought to contribute significantly to corticosteroid resistance in COPD with many resultant implications in COPD comorbidities [52]. Skeletal muscle in COPD is thought to be partly a result of oxidative stress [40]. Also, cellular trauma and aberrant repair mechanisms are thought to be the etiology of various pulmonary [53] and extrapulmonary cancers seen in COPD.

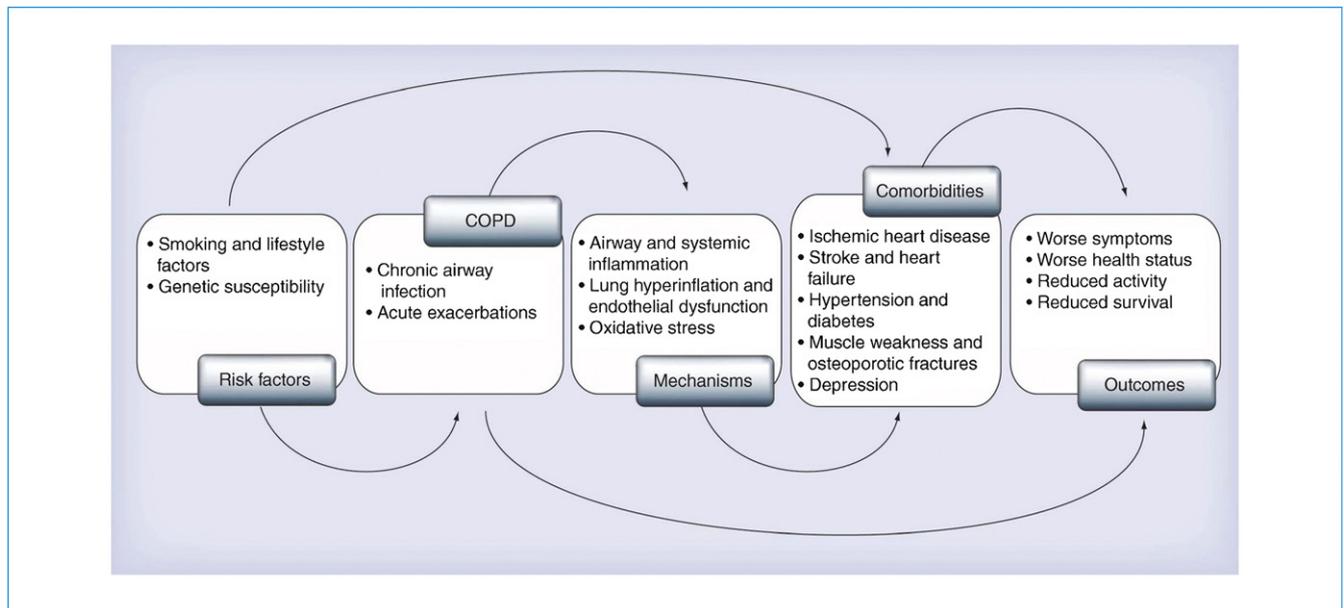
#### **Thrombosis/Hemorrhage**

There is now some evidence to consider COPD as a prothrombotic state. Fibrinogen levels are higher in stable COPD patients than in healthy controls [54]. It is further elevated during acute exacerbations of COPD, probably due to systemic inflammation [55]. Fibrin clots in COPD patients are denser than in healthy subjects and therefore more resistant to lysis, although statin therapy may ameliorate this [56]. Platelet activation has been shown to be increased in stable COPD as detected by platelet-monocyte aggregates and further increased during exacerbations [57]. Moreover, there is evidence of endothelial dysfunction in COPD [27] which could predispose to both thrombogenesis and/or hemorrhage.

Prothrombotic state in COPD could explain several of the comorbidities including venothromboembolic diseases, cerebrovascular conditions and ischemic heart diseases. For example, the elevated fibrinogen levels would explain the increased incidence of ischemic heart disease. Moreover, incidence of acute coronary syndrome is known to be significantly higher immediately after a COPD exacerbation [58], and this correlates to even higher fibrinogen levels [55]. The increased platelet activation could explain the increased incidence of venothromboembolic diseases too.

#### **Unknown**

The pathogenesis behind many comorbidities of COPD has not clearly been elucidated and merits further research. Chronic depression associated with COPD has been thought to result from direct damage to the white matter in the brain from vascular endothelial dysfunction but there are no definitive studies to support this hypothesis [59]. Similarly, chronic



**Figure 3** Complex Pathway Linking Chronic Obstructive Pulmonary Disease and Its Key Comorbidities (29). Taken from: Expert Review of Respiratory Medicine, October 2011, Vol. 5, Pages 647-662.

renal failure could be attributed to increased atherosclerosis but this needs further studies.

### How do Phenotypes of Comorbidity relate to worse Outcomes?

The presence of both COPD and other comorbidities is associated with poor health outcomes. The inter-relationship between COPD, its comorbidities and outcomes is summarized in Figure 3 [29].

COPD patients are more likely to die from a comorbid disease than COPD itself. The data from the Towards a Revolution for COPD Health (TORCH) study demonstrated this nicely (Table 3) [60]. Of the 911 deaths in patients with

**Table 3** Causes of mortality in COPD in the TORCH study (60). Adapted by permission from BMJ Publishing Group Limited. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee, McGarvey, LP, et al, Thorax 62(5), 411–415 (2007).

Classification of cause-specific mortality (n = 911)			
System	%	Subcategory	%
Cardiovascular	26	Congestive heart failure	3
		Myocardial infarction	3
		Stroke	4
		Sudden death	16
Respiratory	35	COPD	27
		Pneumonia	8
		Other	<1
Cancer	21	Lung	14
		Other	7
Other cause	10		
Unknown cause	8		

well-characterized COPD, only 40% of the deaths were definitely or probably related to COPD. The remainder was mostly unrelated to COPD (50%) or unknown (9%).

Comorbidities are a common cause, or a contributing cause, to many of the hospitalizations in COPD patients. In the Lung Health Study 12.8% of the 5,887 smokers were hospitalized, with 42% of the hospitalizations secondary to cardiovascular events or pulmonary complications [61]. In a study of over 45,000 patients with COPD, heart failure was the leading cause of hospitalization, followed by myocardial infarction and stroke [62]. Kinnunen and colleagues found that comorbidities had an impact on the duration of COPD hospitalizations, and reported a mean length of stay of 7.7 days without any comorbidity compared with 10.5 days if a concurrent disease was present [63].

Comorbidities also influence outcomes of COPD exacerbations. A study evaluated, hospital mortality, length of stay, and death and readmission at 90 days after index admission for a COPD exacerbation [64]. Prevalence of co-morbidities was associated with worse outcomes for all four measures. Hospital mortality risk was increased with cor pulmonale, left ventricular failure, neurological conditions and non-respiratory malignancies whilst 90 day death was also increased by lung cancer and arrhythmias. Ischemic and other heart diseases were important factors in readmission.

Finally, the economic burden of comorbidities in COPD is significant. An analysis of Maryland Medicare database [65] for example, showed that compared with the controls Medicaid COPD patients had higher comorbidity burden and were more likely to have myocardial infarction, congestive heart failure, cerebrovascular disease, peptic ulcer, mild liver disease, hypertension, sleep apnea, tobacco use, and edema. COPD patients on average had 24% more medical claims (81.4 vs. 65.4,  $p < 0.001$ ) and were 33% more expensive than controls (\$7603 vs. \$5732,  $p < 0.001$ ). Hypertension, tobacco use, and edema were associated with

incremental medical utilization and cost in COPD patients; depression was associated with incremental medical utilization but not cost.

## Conclusion

Chronic obstructive pulmonary disease is a complex and a heterogeneous disease. The vast majority of patients have other comorbidities. Pulmonary and extra-pulmonary comorbidities share pathophysiological links and have a profound impact on morbidity and mortality. The comorbidities can be clustered into identifiable groups based on determinants of common human pathology that could help to create better phenotypes of patients with COPD. Regardless, understanding the relationships between COPD and its comorbidities from a cellular to a population level would enable future intervention that ultimately will result in improved outcomes.

## Declaration of conflict of interest

Drs. Aryal and Diaz-Guzman have no conflicts of interest to disclose.

Dr Mannino has the following disclosures: DM has served on advisory boards for Boehringer Ingelheim, Pfizer, GlaxoSmithKline, Sepracor, Astra-Zeneca, Novartis and Ortho Biotech and has received research grants from Astra-Zeneca, GlaxoSmithKline, Novartis and Pfizer.

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