Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: February 29, 2024

Citation: Richie, R., C., et al., 2024. Assessing Chronic Obstructive Pulmonary Disease (COPD) Mortality and Morbidity: A Review. Medical Research Archives, [online] 12(2). https://doi.org/10.18103/mra.v12i2.5197

DOI: https://doi.org/10.18103/mra.v12i2.5197

ISSN: 2375-1924

REVIEW ARTICLE

Assessing Chronic Obstructive Pulmonary Disease (COPD) Mortality and Morbidity: A Review

Rodney C Richie, MD, FACP, FCCP, DBIM

Editor-in-Chief *Journal of Insurance Medicine*
3509 Lake Heights Drive, Waco, Texas 76708

rodney.richie@gmail.com

ABSTRACT

From PubMed, referencing articles over the previous 4 years, 146 articles addressing morbidity and mortality of chronic obstructive pulmonary disease (COPD) were reviewed. The major topics covered in this article include the epidemiology of COPD, spirometry with ATS/ERS and GOLD staging, scoring Indices (BODE, ADO, FODEP), trajectories in the development of COPD, pathophysiology of COPD, classification of COPD phenotypes, pharmacotherapy of COPD, causes of Acute Exacerbation of COPD (AECOPD), CT Lung imaging in COPD, and COPD comorbidities. All studies are referenced allowing for greater exploration into given areas of interest (76 ref.).

Keywords: ATS/ERS and COPD spirometry, BODE index, ADO index, FEDOP index, AECOPD, COPD comorbidities, Area Under the Curve of the Receiver Operating Characteristic (AUROC)

Study Design:

146 of 250 sequential relevant articles were reviewed from a PubMed search engine, specifying articles over the preceding four years, to assess most relevant information regarding the Mortality and Morbidity of Chronic Obstructive Pulmonary Disease (COPD). This review was then integrated into relevant areas for reader research, both from an academic and clinical perspective. Each topic was heavily referenced to allow readers to delve further into the summary information provided. Much of the information discussed is familiar to most physicians, but an attempt was made to introduce some new information not commonly known to be relevant to the topic: mortality and mortality of chronic obstructive pulmonary disease (COPD).

Epidemiology

As of 2020, the World Health Organization (WHO) determined that chronic obstructive pulmonary disease (COPD) was the third leading cause of death in the world[1], an observation predicted in 2012 and 2019 by the Global Burden of Disease Study[2-3].

In the United States, the Center for Disease Control (CDC) has measured COPD as the fourth leading cause of death[4].

Surprisingly, despite these numbers, COPD remains both underdiagnosed and misdiagnosed. An analysis of the National Heal and Nutrition Examination Survey (NHANES) demonstrated that that >70% of participants with chronic airway obstruction on spirometry did not have a formal diagnosis of COPD[5].

Çolak Y *et al.*[6] reported that underdiagnosis of COPD is closely related to poor prognosis, even among initially asymptomatic individuals. Compared with persons without diagnosed COPD, the age and sex-adjusted hazard ratio (HR) was significantly elevated: HR 5.0 (95% CI 2.8-8.9) for exacerbations, HR 1.7 (95%CI, 1.3-2.2) for pneumonia, HR 0.7 (95%CI, 0.2-3.0) from respiratory death and HR 1.3 (95%CI, 1.1-1.6) for death from all causes in individuals with undiagnosed asymptomatic COPD. Once an individual with undiagnosed COPD developed symptoms, the HRs worsen: HR 15.1 (95%CI, 11.0-21.8) for exacerbations, HR 2.8 (95%CI, 2.4-3.3) for pneumonia, HR 4.3 (95%CI, 2.8-6.7) for death from respiratory causes, and HR 2.0 (95%CI, 1.8-2.3) for death from all causes.

Although cigarette smoking in developed countries is the major risk factor for development of COPD, in developing countries over half of the COPD patients are non-smokers, particularly women exposed to biomass smoke in poorly ventilated homes (or huts)[7].

Spirometry and ATS/ERS vs. GOLD Staging

Defining persons with COPD is accomplished with tests confirming stable post-bronchodilator airflow obstruction. There are two major systems to accomplish this:

1. American Thoracic Society/European Respiratory Society (ATS/ERS) advocates using a lower limit of normal (LLN) for forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) (i.e., the FEV_1/FVC) < 0.7 below the lower 4th percentile or lower limit of normality (LLN) which decreases with age. LLN uses predicted values and ignores post-bronchodilator use.

2. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: The Obstructive Lung Disease (GOLD) subcommittee uses both post-bronchodilator $FEV_1/FVC < 0.7$ and FEV_1 <80% of predicted value. This definition has also been endorsed by the British National Institute for Health and Clinical Excellence (NICE) and the Canadian Thoracic Society. The major problem of the fixed ratio was clearly highlighted in population studies showing that it carries the risk of over-diagnosis in the elderly non-smokers and under-diagnosis in young smokers. Moreover, the chance of misclassification is expected to be sex dependent, because FEV_1/FVC declines with age faster in males than females.

These spirometric criteria are often described in the medical literature as lower limit of normal (LLN) and fixed ratios (FR). ATS/ERS is considered more sensitive, likely identifying more individuals with milder COPD, but potentially including non-COPD cases. GOLD aims for higher specificity, reducing false positives but possibly missing early-stage COPD.

ATS/ERS has no specific staging system based on lung function, whereas GOLD uses FEV_1% of predicted to stage COPD severity (with hazard ratios)[8].

- Stage 1: ≥80% HR 1.18 (95%CI, 1.00-1.39)
- Stage 2: 50-79% HR 1.43 (95%CI, 1.35-1.51)
- Stage 3: 30-49% HR 1.78 (95%CI, 1.66-1.90)
- Stage 4: <30%).HR 2.13 (95%CI, 1.94-2.34)

While the fixed ratio cutoff is easier to apply, it may result in more false negatives among younger patients who may benefit from early intervention, and more false positives among older patients who may be unnecessarily treated. A prospective cohort study of 95,288 participants in the Copenhagen General Population Study showed that individuals with $FEV_1/FVC <$ LLN but ≥0.7 0 had a median age of 45 years and were at an increased risk of pneumonia, heart failure and all-cause mortality compared to those without airflow obstruction by either definition over a median follow-up of 6 years[9].

1300 participants with COPD aged ≥40 who participated in the Norwegian HUNT Study (1995-1997) to December 31, 2015, were studied to determine the ability of these classifications to predict COPD-related hospitalizations and all-cause mortality. Survival analysis and time-dependent area under receiver operating characteristic curves (AUROC) were used to compare the disclination abilities of the GOLD classification – GOLD 2007, GOLD 2011, and GOLD 2017. In 2011, ABCD groups were introduced by combining severity of airflow limitation with exacerbation history and symptom burden. In 2017, the ABCD groups were updated to include *only* exacerbation history and symptom burden and used severity of airflow limitation separately. The study found that the GOLD 2007 classification (based just on lung function) was better than the GOLS 2011 classification (based on lung function, symptoms burden, and exacerbation history) and the GOLD 2017 classification (based on symptom burden and exacerbation history) in predicting mortality. The GOLD 2017 classification was the worst at predicting COPD hospitalization and all-cause mortality[10].

The revised Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 group ABE classification has undergone major modifications, which can simplify clinical assessment and optimize treatment recommendation for COPD patients. Cheng *et al.*[11] compared the prediction of hospitalization and mortality between this new GOLD group 2023 ABE classification and the earlier 2017 ABCD classification. The risk of hospitalization and mortality was higher in group E than in groups A and B. The time-dependent AUROC and concordance index for predicting mortality was found to be slightly higher in the GOLD 2017 ABCD than in the 2023 ABE groups. The new GOLD 12-subgroup (1A-4E) classification combining the GOLD 1-4 staging and grouping performed similarly discriminate predictive power for mortality to the GOLD 2017 16-subgroup (A1-4D) classification. The authors concluded that all-cause mortality increased gradually from GOLD group A to E. The GOLD 2023 classification based on ABE groups did not predict mortality better than the earlier 2017 ABCD classifications.

In a combined analysis of four U.S. population-based cohorts (mean age 62.8 years) investigating different fixed FEV_1/FVC thresholds as well as the LLN, Bhatt SP *et al.*[12] found that a FEV_1/FVC cutoff of 0.71 was best at discriminating COPD-related hospitalization and mortality, lending support to use of the 0.70 threshold for the identification of individuals at risk for clinically significant COPD.

Two studies based on the data from the Third National Health and Nutrition Examination Survey (NHANES III) showed that FR is a better predictor of long-term mortality than LLN[13-14].

COPD is defined by fixed spirometric ratio, FEV_1/FVC <0.70 after inhaled bronchodilators. However, the implications of variable obstruction in which the prebronchodilator FEV_1/FVC ratio is less than 0.70 but increases to 0.70 or more after inhaled bronchodilators, had not been determined. Buhr *et al.*[15] recorded FEV_1/FVC ratio before and after bronchodilators in 778 SPIROMICS participants followed for up to 3 years. At baseline, 175 had a ratio of <0.70 before testing which normalized post-bronchodilator, with the remainder having normal pre- and post-test values. During the follow-up, the group with variable obstruction were 6 times more likely to develop obstruction on post-bronchodilator testing and had more small airways disease and emphysema on their initial CT scan (95%CI, 4.6-8.3; p<0.001). These findings support consideration of expanding spirometric criteria defining COPD to include pre-bronchodilator obstruction.

Scoring indexes for mortality in COPD: BODE, ADO, and FODEP

Although FEV_1 is often used to grade the severity of COPD, persons with COPD have systemic manifestations that are not reflected by the FEV_1. In an evaluation of 207 persons with COPD, four factors predicted the risk of death in this cohort: the body-mass index (**B**), the degree of airflow obstruction (**O**) and dyspnea (**D**), and exercise capacity (**E**) measured by the 6-minute-walk test. These variables were used to construct the BODE index, a multidimensional 10-point scale [a calculator is on-line at BODE index for COPD] in which higher scores indicate a higher risk of death. This index was prospectively validated

in a cohort of 625 persons, with death from any cause and from respiratory causes as the outcome variables. Persons with higher BODE scores were at higher risk for death; the hazard ration for death from any cause per one-point increase in the BODE score was 1.32 (95%CI, 1.26-1.42; p<0.001). The C statistic for the ability of the BODE Index to predict the risk of death was larger than that for the FEV_1 (0.74 vs 0.65).

Computation of the BODE Index				
Variable	1	2	3	4
B – BMI	>21	<21		
O – FEV_1% predicted	≥65	64-50	49-34	<34
D – Distance walked in 6 min (m)	≥350	349-250	249-150	<150
E – MMBC Dyspnea Scale	0-1	2	3	4

The BODE index predicted mortality better than obstruction as a single measure[16]. In an evaluation comparing the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging, the BODE Index as found to be superior in predicting mortality[17].

The **ADO** (**A**ge, **D**yspnea, and **O**bstruction) Index was found to be a predictor of 3-year mortality in 10 cohorts including more than 13,000 patients[18]. In a large cohort of more than 3000 persons with more than 1200 deaths, the ADO index was the best predictor of mortality, followed by the BODE index[19].

The fat-free mass index (FFMI) has been shown to be better than BMI for assessing the nutritional status of patients with COPD. The BMI does not reflect the status of skeletal muscle in patients with COPD. Compared with BMI, FFMI seems to be more related to muscle atrophy, exercise capacity, and quality of life. FFMI was also found to be a predictor of overall mortality in subjects with normal BMI[20-21]. Thus, replacing BMI with FFMI could more accurately reflect the nutritional status of COPD patients[22].

Inspiratory muscle strength is commonly reduced in COPD patients, and the degree of reduction is related to the severity of disease. Inspiratory muscle strength, as assessed by MIP, has been shown to be an independent predictor of survival in COPD patients. The BODE index does not include any indicator of respiratory muscle function[23].

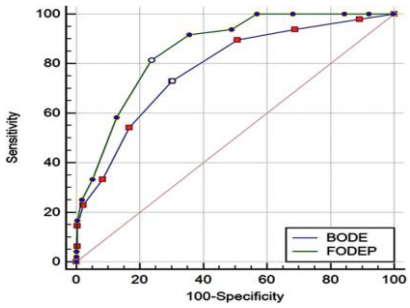
To address these issues, Xu et al.[24] constructed a new index they labeled FODEP from 326 patients followed up to 59 months or death (which occurred in 14.7%). The following modifications were made to the BODE index: 1) the reclassification of lung function according to the GOLD guidelines, 2) the substitution of the FFI for BMI, and 3) the additional of maximal inspiratory pressure (MIP). The FODEP index scores range from 0 to 15. Airflow limitation is based on GOLD guidelines, with the threshold for FEV_1% ranging from 0 to 3. The value of FFMI ranged from 0 (FFEMI ≥21.7 kg/m^2 for males and FFMI ≥18.2 kg/m^2 for females) to 3 (FFMI ≤16.6 kg/m^2 for males or FFMI ≤14.5 kg/m^2 for females). A MIP >60 cmH_20 was considered normal, and the value of MIP was 0 when MIP was >60 cmH_20; otherwise, it was three. The ranges of mMRC and 6MWT were the same as in the BODE index.

FODEP index				
Variables	0	1	2	3
FEV_1%	≥80	79-50	49-30	<30
6MWT (m)	≥350	349-250	249-150	≤149
Modified MRC	0-1	2	3	4
FFMI kg/m^2 for males	≥21.7	21.6-19.8	19.7-16.7	≤16.6
FFMI kg/m^2 for females	≥18.2	18.1-16.8	16.7-14.6	≤14.5
MIP cmH_20	>60			≤60

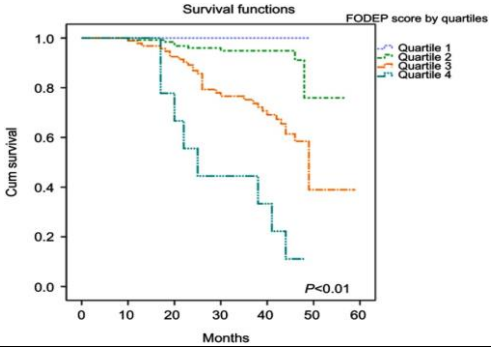
Multivariate Cox analysis revealed that the following factors were significantly associated with mortality:

- FFMI (p=0.001)
- FEV_1% (p<0.001)
- mMRC score (p=0.025)
- 6MWT distance in meters (p=0.001)
- MIP (p-0.001)

The receiver operating curves area under the curves (AUROC) were 0.86 (95% CI, 0.817-0.896) for the FODEP index and 0.778 (95% CI, 0.729-0.822) for the BODE index.



Patients were categorized into quartiles according to their FODEP scores: 0-4, 5-8, 9-12, and 13-15. The Kaplan-Meier cure is presented below.



This study showed that the FODEP index, consisting of FFMI, FEV_1%, the mMRC score, the 6MWT distance (in meters) and MIP is a significant and independent predictor of mortality, with every one-point increase in the FODEP index score associated with a 1.55-fold increased risk of death.

PRISm

Smokers *without* airflow obstruction but with chronic respiratory symptoms were also found to experience significant respiratory morbidity[25]. A subset of these smokers with $FEV_1/FVC \geq 0.7$ but FEV_1 <80% predicted were labeled preserved ratio impaired spirometry (PRISm), which has become a focus of research in several observational cohorts. A recent longitudinal analysis of participants in the Rotterdam Study showed that a third of participants with PRISm transitioned to COPD over 4.5 years of follow-up, and that the presence of PRISm and COPD GOLD 2-4 were both significant predictors of all-cause mortality[26].

However, there are good reasons to be skeptical about the stability of this subgroup of people as outlined in the 10-year follow-up data from the COPDGene study which showed that around half of the PRISm patients changed their group classification when tested at subsequent visits. Whether this

reflects biology or measurement error is unclear[27-28].

Trajectories in Development of COPD

Multiple birth-cohort studies have identified lung function trajectories from birth or childhood to early adulthood that may reflect influence of potentially modifiable factors such as preterm birth, smoke exposure, recurrent infections, and persistent asthma during childhood, which could be the focus of interventions to maximize lung growth and reduce the risk of COPD in older age. Divo *et al.*[29] examined the comorbidities and mortality risk in adults younger than 50 years of age with COPD compared to the more common older group with COPD (age>50). Compared to an age-balanced control group without airflow obstruction, the younger COPD group had a nine-fold increased mortality risk ($p<0.0001$). Comorbidities differed between the younger and older group with COPD, with tuberculosis, substance use, and bipolar disorders being distinct comorbidities associated with increased mortality risk in the younger COPD group.

Pathophysiology of COPD

Multiple birth-cohort studies have identified lung function trajectories from birth or childhood to early adulthood that may reflect the influence of potentially modifiable factors such as preterm birth, smoke exposure, recurrent pulmonary infections, and persistent asthma during childhood, which could be the focus of interventions to maximize lung growth and reduce the risk of COPD in older age. This new understanding of lung function trajectories has motivated researchers to study the early pathophysiologic changes in COPD with the ultimate goal of identifying patients with early disease who may derive greater benefit from intervention[30].

In the healthy lung, the small airway cells secrete dimeric immunoglobulin (IgA) into the mucosal lumen from the polymeric IG receptor (pIgR). Cleavage of pIgR at the luminal surface liberates secretory IgA (SIgA), still bound to a portion of pIgR called the secretory component. SigA helps to prevent bacterial invasion of respiratory epithelium. Smoking reduces pIgR expression, leading to localized SIgA deficiency in small airways. In the absence of SIgA, bacteria can invade respiratory epithelial cells. The resulting nuclear factor-κB activation initiates and sustains airway inflammation. Differences in lung microbial community structures may also help explain why not all smokers develop COPD, but which specific microbes drive disease progression and when they do so are important unanswered questions. These findings suggest that bacterial invasion may be a trigger leading to airway remodeling[31].

A history of respiratory exacerbations was associated with higher mortality in GOLD 1-2 and GOLD 3-4, quantitative emphysema in GOLD 1-2 and airway wall thickness in PRISM and GOLD 3-4[32]. Studies have shown that systemic inflammation persists despite smoking cessation[33] and increases during exacerbations[34].

Classification of COPD phenotypes[35]:

Widely accepted COPD phenotypes	Emerging COPD phenotypes
	Pulmonary cachexia phenotype
Chronic Bronchitic	Overlap COPD and bronchiectasis
Emphysematous	Upper lobe-predominant Emphysema Phenotype
Asthma-COPD-Overlap	The fast decliner phenotype
Frequent exacerbator	The comorbidities or systemic phenotype
Rare exacerbator	α1-Antitrypsin Deficiency
	No smoking COPD

The use of analytic approaches, like cluster analysis, has advanced the study of phenotypes. They facilitate the identification of unique groups of related variables to recognize features that might relate to both underlying diseases biologically and clinically significant outcomes. The COPDGene study was a multicenter observational study designed to identify genetic factors with COPD. Subjects of that study underwent inspiratory, whole-lung volumetric multidetector computed tomography (CT) with measurements of total lung emphysema percentage. Using the data of that trial, Han and collaborators were able to determine that both bronchial wall thickness and total lung emphysema percentage were predictive factors of COPD exacerbation frequency in a continuous way independently of severity of airflow limitation[36].

It has also been noted that there is a mixed COPD-asthma (ACO) phenotype which is more prevalent in the biomass exposure subgroup, that can affect a total of more than 60 million patients globally[37]. The reported prevalence of asthma history among COPD subjects varied from 15% to 50% in individual studies, with an overall pooled prevalence of 27%. ACO represents a distinct clinical phenotype with more frequent exacerbations, hospitalization, worse health-related quality of life, and higher healthcare costs than either disease alone[38].

Gender Differences in COPD:

According to a systematic review, the annual decline in FEV_1 was faster in female smokers compared with male smokers even though females smoked less[39]. This has been attributed to the greater prevalence of airway hyperresponsiveness in women, which is a significant predictor of lung function decline and results in increased susceptibility to harmful effects of smoking among women. However, other studies have found that survival in women is better vs men with COPD[40].

Pharmacotherapy of COPD

Eosinophilic inflammation in COPD has been a topic of study for many years. It has been recognized that eosinophils may be involved in the inflammatory response in COPD. Under certain circumstances, inflammatory cues promote eosinophil recruitment to the lungs, where secretion of a variety of chemokines, cytokines and cytotoxic granular products contributes to inflammation[41-42]. Eosinophil

numbers in the blood of patients with COPD and asthma are similar and are predictive of risk of exacerbations and response to ICS during stable disease and to oral corticosteroids during disease exacerbations.

The GOLD 2023 update includes the replacement of the ABCD initial assessment tool which had remained unchanged since its introduction in 2011, with a new ABE model. Group E, which merges the previous Group C and Group D, comprises patients with a history of either two or more moderate exacerbations or any severe exacerbation (defined as one requiring hospitalization) in the previous year, irrespective of symptom burden. The initial treatment recommended for patients in Group E is dual bronchodilation with long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs), regardless of the intensity of dyspnea or quality of life scores. For patients in Group E who are at high risk of exacerbations based on blood eosinophils of ≥300 cells/μL, initial treatment with triple therapy (inhaled corticosteroids (ICS) + LABA + LAMA) is recommended. Triple therapy is the only pharmacological intervention that has been demonstrated to improve survival for patients with COPD. Patients who continue to experience exacerbations despite being on maximal LABA/LAMA inhaled therapy are also recommended to be escalated to triple therapy[43].

A significant proportion of COPD subjects in ECLIPSE (37.4%) had peripheral blood eosinophil counts persistently ≥2% (or the alternative blood eosinophil cut-off level in absolute numbers ≥150μL^{-1}) over 3 years. These patients also had better clinical characteristics at baseline, including higher FEV_1 and lower SGRQ and mMRC scores. There was an increased rate of emphysema progression in subjects with eosinophil counts persistently <2%. This finding is biologically reasonable as lower eosinophil numbers in this group implicate other immune cell types in disease pathophysiology, such as neutrophils which are known to cause emphysema[44].

Corticosteroid benefit has been shown in the cohort of COPD patients with significant eosinophilia, and inhaled corticosteroids have been demonstrated to reduce inflammation and cardiovascular mortality[45]. However, prospective work has shown minimal benefit of inhaled corticosteroids on all-cause mortality[46].

A secondary analysis of IMPACT modeled eosinophil count as a continuous variable and showed no difference in exacerbation reduction between the LAMA/LABA/ICS and LAMA/LABA arms at eosinophil counts <100 cells/μL but progressively greater treatment effects in the ICS-containing regimens with higher eosinophil levels[47].

The eosinophilic inflammatory response in patients with COPD (and asthma) has been designated type 2 inflammation, with increased levels of IL-5, IL-4, IL-13 associated with increased eosinophil counts in sputum, bronchial tree, and blood. Cytokines and immune cells are commonly elevated in patients with type 2 inflammation that include IL-5, IL-4, IL-13, type 2 innate lymphoid cells, and Th2 cells. A patient with COPD currently on LAMA/LABA dual therapy who continues to experience symptoms and has an eosinophil count of 300 cells/μL should be given ICS. For patients who continue to have uncontrolled symptoms and exacerbations, dupilumab, a fully human monoclonal

antibody, blocks the shared receptor component for interleukin-4 and interleukin-13, key drivers of type-2 inflammation. In a 939-patient randomization with 468 receiving dupilumab and 471 receiving placebos, the annualized rate of moderate or severe exacerbations was 0.78 (95%CI, 0.64-0.86) with dupilumab and 1.10 (95%CI, 0.93-1.30) with placebo (rate ratio, 0.70 (95%CI, 0.58-86; p<0.001). There was significant improvement in FEV_1 and SGRQ scores as well[48].

It has been documented that **eosinopenia** (≤2%) is associated with higher in-hospital mortality in AECOPD, as revealed in the DECAF (Dyspnea, Eosinopenia, Consolidation, Acidemia, and atrial Fibrillation) Score. The DECAF AUROC for mortality of 0.85 (95%CI, 0.82-0.89)[49-50].

Roflumilast, a phosphodiesterase-4 inhibitor, has been shown to reduce exacerbations and is indicated for patients with recurrent exacerbations, FEV_1<50% predicted, and the chronic bronchitis phenotype[51]. Recent concerns about the adverse psychological side effects, including depression and suicide, have been raised and the FDA now has a black-box warning about these risks and urges physicians to discuss the risks vs. benefits of taking this medication.

Azithromycin has been shown to reduce exacerbations when given prophylactically to patients with COPD and an increased risk of exacerbation. Subsequent research showed little treatment effect. Known side effects of azithromycin include QTc prolongation and hearing loss, both of which should be monitored regularly in patients on this medication. Antibiotic resistance is another potential concern among active smokers, supporting its use in former smokers only[52].

Causes of Acute Exacerbations in COPD (AECOPD)

COPD's underlying pathophysiologic mechanisms are highly complex and involve a multitude of diverse factors including chronic inflammation, increased levels of oxidative stress resulting in DNA damage, cytokines repressing DNA repair mechanisms, and changes of the pulmonary microbiota. Causative factors include inhalation of tobacco and biomass/smog. There are multiple genetic factors that have been associated with COPD, in particular single nucleotide variants identified by GWAS studies[53]. Mounting evidence indicates that single nucleotide polymorphisms in RNAs that are *not* translated into protein also play a role in the development of COPD[54].

Small non-coding microRNAS (miRNAs) that are 21-23 nucleotides in length have an impact on the development and progression of COPD. Tissue-based miRNA signatures as well as circulating miRNA profiles in COPD have previously been reported[55-56]. MiRNA profiles of COPD patients have also been used to predict lung cancer development[57-58].

Less knowledge has been gathered on factors underlying the marked variance in survival after a diagnosis of COPD. These genome-wide miRNA signatures have potential for automated, affordable, chip-based detection that could become readily available. Mirra D *et al.*[59] had 480 subjects who survived the 54-month follow-up period. They identified two blood-born microRNAs (miR-150-5p and mir-320b) that were highly predictive for survival

of COPD patients. Overexpression of these miRNAs in lung tissue and blood in the lung suppress the proliferation of immune cells. The suppression of factors in COPD to a prolonged survival includes suppressing the development of lung cancer, which is a common cause of death in COPD patients. The effects of these miRNAs on survival may be twofold. First in blood cells by a possible reduction of tissue destruction via suppression of inflammatory cascades, secondly via suppression of the development of lung cancer and other cancers associated with COPD.

Using bacterial 16s ribosomal RNA sequencing, 102 patients hospitalized with acute COPD exacerbations who were demonstrated to have infections with *Staphylococcus* species (which are pathogens in the lungs) had a 7-fold increase in the risk of 1-year mortality compared to hospitalized COPD patients without these organisms. Similarly, those who lost *Veillonella* species (which are commensals in the airway) in their sputum had a 13-fold increase in the risk of 1-year mortality. Importantly, those who demonstrated *Staphylococcus* but no *Veillonella* in their sputum had an 85-fold increase in the risk for 1-year mortality compared to those who retained *Veillonella* in their sputum[60].

Given the close link between bacterial infections and COPD exacerbations, impairments in humoral immunity could explain the susceptibility to exacerbations in certain individuals. Indeed, immunoglobulin deficiency is not uncommon in COPD patients, with one out of four patients with moderate to severe disease being IgG deficient. Recent studies in the MACRO and Simvastatin for the Prevention of Exacerbations in COPD exacerbations (STATCOPE) cohorts have demonstrated that serum IgG (defined when serum total IgG levels were below the lower limit of normal for adults -- <7.0 g/L) can be used to identify patients at high risk for developing exacerbations (a prognostic biomarker)[61]. Specifically, IgG1 and IgG2 subclass deficiencies were most significantly associated with exacerbations and hospitalizations. Approximately 1 in 5 COPD patients had one or more IgG subclass deficiencies[62].

One small observational trial of eight COPD patient with Ig deficiencies receiving IVIG noted a reduction in the annual exacerbation rate from 4 to 0.5[63]. Another retrospective study of COPD patients who had received IVIG therapy reported a decrease in exacerbations from 4.7 to 0.6 per year[64].

CT Lung Imaging in COPD

To determine whether airway mucus plugs identified on chest CT were associated with increased all-cause mortality, assessment of plugs were defined as occluding 2- to 10-mm lumen diameters in medium to large-sized airways affecting 0, 1 to 2, or 3 or more lung segments[65].

- Mortality rate was 34% (95%CI 32-35.8%) with mucus occlusion in 1 segment.
- Mortality rate was 47% (95%CI 43-49%) with mucus occlusion in 2 segments.
- Mortality rate was 54% (95%CI 51-57%) with mucus occlusion in 3 segments.

A promising method of using CT Lung to identify those at greatest risk for disease progression comes from an analytic technique designed to identify small airway abnormalities. Parametric response mapping

(PRM) is an image processing technique that uses dynamic image registration of paired inspiratory and expiratory CTs to classify areas of the lung as normal, emphysematous, or nonemphysematous air trapping (referred to as functional small airways disease [fSAD]). In ever-smokers with no or mild-to-moderate airflow obstruction, PRM fSAD was more strongly associated than PRM emphysema with FEV_1 decline over 5 years of follow-up. Importantly, the PRM metrics have been validated with human lung tissue removed from patients with advanced COPD at the time of lung transplantation to show that PRM fSAD correlates with loss of terminal bronchioles as well as narrowing, thickening, and obstruction of the surviving terminal bronchioles. These results support the hypothesis that loss of small airways occurs prior to detectable emphysema or a significant decline in airway function and that these changes can be identified using clinical CT Lung with appropriate image processing techniques. As such, PRM fSAD may be a good biomarker to study and identify early COPD[66-67].

CT Lung provides visual information that can be used to investigate structural and underlying pathophysiologic changes in COPD patients but is prone to inter- (and intra-) reader variability, limiting its application to broad clinical and experimental settings. Radiomics has been proposed to explore the correlation among medical images by extracting high-throughput quantitative features from radiographic images. Heretofore, this has resulted toward crude quantification of emphysema and more recently targeting the airway component of COPD, which includes direct airway parameter measurements and quantification of air trapping as functional manifestations of small airway disease[68].

Recently, the performance of deep learning (DL) has been intensively demonstrated. A convolutional neural network (CNN) which uses a trainable filter bank with an extensive weight-sharing scheme can quickly outperform prior attempts at using CT Lung imaging to reflect lung function and mortality. These deep learning-based approaches have had impressive results for CT analysis in COPD. In a study by González *et al.*[69] a chest CT-based deep radiomics approach with a CNN was used to predict survival in COPD patients. With deep radiomics approach reflecting morphologic alterations, essential information related to phenotypic heterogeneity and pathophysiology may be learned from radiographic images and used to improve medical decision making in COPD patients. The AUROC for 3-year survival was 0.89 (95%CI 0.79-0.99) and the 5-year survival was 0.84 (95%CI, 0.79-0.89).

COPD Comorbidities:

COPD and cardiac comorbidities are frequently associated. They share common risk factors, pathophysiological processes, signs and symptoms, and act synergistically as negative prognostic factors. From an epidemiological point of view, patients with COPD are particularly vulnerable to cardiac disease. Mortality due to cardiac disease in patient with moderate COPD is higher than mortality related to respiratory failure[70].

Labaki *et al.*[71] stratified current and former tobacco cigarette users enrolled in Genetic Epidemiology of Chronic Obstructive

Pulmonary Disease (COPDGene) into normal spirometry, PRISm (Preserved Ratio Impaired Spirometry), Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1-2 COPD, and GOLD 3-4 COPD. Over 10.1-year median follow-up, 2,299 deaths occurred among 10,132 participants. Death from cardiovascular disease (CVD) was most frequent in PRISm (31% of deaths). Lung cancer deaths were most frequent in GOLD 1-2 (18% of deaths vs. 9-11% in other groups). Respiratory deaths outpaced competing causes of death in GOLD 3-4, particularly when BODE index ≥7. St. George's Respiratory Questionnaire score ≥25 was associated with higher mortality in all groups:

- Hazard ratio (HR), 1.40 (95%CI, 1.05-1.87) in PRISm
- HR, 1.80 (95%CI, 1.49-2.17) in GOLD 1-2
- HR, 1.65 (95%CI, 1.26-2.17 in GOLD

Systemic inflammation is associated with accelerated decline in lung function[72], and a two-to-four-fold risk of CVD, diabetes, lung cancer, and pneumonia[73].

While smoking remains an important shared risk factor for both COPD and CVD, it is becoming more widely accepted that responses to smoking are not the sole reason for the association of the two diseases. COPD is no longer "just a disease of the lungs" but is now described as the pulmonary component of systematic endothelial disease whereby a range of "inflammageing" processes simultaneously affect multiple organs giving rise to a state multimorbidity, without any clear indication as to which disease came first[74].

A meta-analysis of observational studies supports more than a two-fold increase in the odds of having any CVD in persons with COPD relative to COPD-free patients [odds ratio (OR) 2.46, 95%CI 2.02-3.00; p<0.0001], and the ORs in the range 2-5 for ischemic heart disease, arrhythmias, heart failure, and disease of the arterial circulation. Additionally, patient with COPD reported hypertension more often (OR 1.33, 95%CI, 1.13-1.56; p=0.0007) and diabetes (OR 1.36, 95%CI, 1.21-1.53; p<0.0001)[75].

The observation that arterial stiffness is more pronounced in patients with COPD compared to controls matched for age and smoking status has led to the hypothesis that COPD is associated with elastin degradation both in the lung (where it results in emphysema) and in the vasculature – systemic elastin degradation – where it results in increased arterial stiffness. Arterial stiffness is considered a surrogate indicator of coronary, cerebrovascular and peripheral arterial disease and is assessed by measuring aortic pulse wave velocity. This measure is strongly associated with cardiovascular mortality in the general population and is of potential interest as a predictive marker of CVD risk in COPD[76].

Conclusions:

COPD is not confined to lung dysfunction but is a systemic disorder, with the basic pathophysiology being chronic inflammation and on-going destruction of the lung as well as development of multiple comorbid conditions.

Conflict of Interest:

None

Acknowledgements

None

Funding:

None

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