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# COPD and Traditional Markers of Status of COPD

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**Review Article**

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**Abstract:** Chronic obstructive pulmonary disease (COPD) arises from an interaction between various causal factors, both host factors and environmental exposures. There is increased numbers of neutrophils, macrophages, and T lymphocytes ($CD_8$ more than $CD_4$) in the lungs. Reactive oxygen and nitrogen species are released from inflammatory cells. Many markers of oxidative stress and systemic inflammation are increased in stable COPD. The level of these markers increases further during acute exacerbation. Single global marker in COPD is still a concept and may not be applicable to a complex, multicomponent disorder like COPD. There are various markers in COPD for measurement of the lung function. Forced expiratory volume in 1 second ($FEV_1$) is the usual marker. Additional markers are needed to provide a more comprehensive and clinically meaningful assessment so as to provide a more informed basis for treatment decisions. Markers related to inflammatory processes, structural changes and systemic effects could yield valuable information to complement that provided by $FEV_1$ for airflow limitation. Now there has been a shift in the bio markers from the lung sources toward blood specimens. Increased levels of various inflammatory proteins such as C-reactive protein (CRP), Tumor necrosis factors-α (TNFα) and Interleukin-6 (IL-6) are found in systemic circulation in COPD patients that can be used as markers of status of COPD. Copeptin and procalcitonin have emerged as prognostic biomarkers in acute exacerbation of COPD.
**Keywords:** Chronic obstructive pulmonary disease (COPD), Tumor necrosis factors-α (TNFα), Interleukin-6 (IL-6), C-reactive protein (CRP)

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality throughout the world. It is the fourth leading cause of death. Approximately 2.7 million deaths were reported in 2000 due to COPD. It is ranked twelfth as a burden of disease in a study by the World Bank and WHO in 1990[1]. According to the Global Burden of Disease Study, it results in 1.68 years of living with disability (YLD) per 1,000 population, representing 1.8% of all YLDs, with a greater burden in men than in women (1.93% vs. 1.42%)[2]. Considering the global trends of the present day, increases in the prevalence and mortality of the disease have been predicted in the coming decades.

COPD arises from an interaction between various causal factors, both host factors and environmental exposures. Worldwide, tobacco smoking is the most commonly encountered risk factor[3]. Exposure to smoking from others i.e. passive smoking, termed as environmental tobacco smoke (ETS) exposure, may also play a contributory role especially, in non-smoker individuals including women [4,5]. Alongwith, indoor and outdoor pollutants like exposure to particulate matter, irritants, organic dusts, chemical agents, fumes and motor vehicle emissions have been documented to cause COPD[6]. The smoke from combustion of solid fuels such as dried dung, wood and crop residue used for cooking and heating, especially in villages, sub-urban and slum areas, is an important risk factor for development of COPD in the rural inhabitants especially women[7]. The genetic risk factor that is most documented is a rare hereditary deficiency of alpha-1-antitrypsin ($\alpha_1$-AT)[8].

A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease. Chronic cough is often the first symptom to develop. It is generally productive of sputum but may be intermittent and may not be associated with expectoration. Breathlessness is the hallmark symptom due to which the patients seek

medical attention. It is progressive, persistent and worsens with exercise. Wheezing and chest tightness are nonspecific symptoms that may vary between days, and over the course of a single day. Barrel shaped chest, central cyanosis, pursed-lip breathing, rhonchi and reduced breath sounds are the common examination findings. It is usually a progressive disease and lung function worsens over time, even with the best available care.

The course of COPD is characterized by exacerbation of symptoms[9]. Exacerbations is triggered by infection with bacteria or viruses or by environmental pollutants. There is increased hyperinflation and air trapping, with reduced expiratory flow causing increased dyspnea during an exacerbation. Worsening of ventilation-perfusion ($V_A/Q$) abnormalities occurs resulting in severe hypoxemia.

In COPD, innate and adaptive immune responses to long term exposure to noxious particles and gases, particularly cigarette smoke result in poorly reversible airflow obstruction and an abnormal inflammatory response in the lungs. There is increased numbers of neutrophils, macrophages, and T lymphocytes ($CD_8$ more than $CD_4$) in the lungs. Reactive oxygen and nitrogen species are released from inflammatory cells. They create an imbalance in oxidants and antioxidants of oxidative stress. Many markers of oxidative stress and systemic inflammation are increased in stable COPD[10]. The level of these markers increases further during acute exacerbation[11].

COPD is now labelled as a multisystem disorder due to the presence of systemic inflammatory response. Weight loss, cachexia, osteoporosis, chronic anaemia, cardiovascular disorders and derangement of cognitive function have been observed in these patients alongwith chronic respiratory insufficiency. These have an important influence on the quality of life including limitation of activity, missed work, economic impact, effect on family routines, feelings of depression or anxiety [12].

There are various markers in COPD for measurement of the lung function. Forced expiratory volume in 1 second ($FEV_1$) is the usual marker. However, its measurement correlates poorly with the presence of some symptoms and do not take into account extrapulmonary effects. Single global marker in COPD is still a concept and may not be applicable to a complex, multicomponent disorder like COPD. Additional markers are needed to provide a more comprehensive and clinically meaningful assessment so as to provide a more informed basis for treatment decisions. Markers related to inflammatory processes, structural changes and systemic effects could yield valuable information to complement that provided by $FEV_1$ for airflow limitation [13].

Since COPD is recognised as a systemic disease, there has been a shift in the search of bio marker from the lung sources toward blood specimens[14]. Increased levels of various inflammatory proteins such as C-reactive protein (CRP), Tumor necrosis factors-α (TNFα) and Interleukin-6 (IL-6) are found in systemic circulation in COPD patients[15]. The role of systemic inflammation is being assessed by using CRP as marker in COPD patients widely[16-18].

## CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in the individual patient. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases[20].

Three disorders incorporated in COPD are: emphysema, peripheral airways disease and chronic bronchitis. American Thoracic Society has defined *emphysema* as a condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchioles accompanied by destruction of their walls and without obvious fibrosis. Peripheral airways disease includes inflammation of the terminal and respiratory bronchioles, fibrosis of the airway walls with narrowing and goblet cell metaplasia of the bronchiolar epithelium. Chronic bronchitis is defined by American Thoracic Society as the condition of subjects with chronic or recurrent excess of mucus secretion in the bronchial tree. Chronic was defined as occurring on most days of three months of a year, for at least two successive years, in whom other causes of chronic cough have been excluded[21].

### Epidemiology

COPD is a common problem and its global burden is increasing every year, including both the cost of therapy and the disability associated life years (DALY) attributed to the disease and its sequelae. A large number of cases go unreported and undertreated. Very few people approach medical centers for management in the initial stage of the disease. According to a European study, 75% of COPD cases in general population remain undiagnosed[22].

Various demographics of the studied populations, such as age distribution, smoking habits, gender and socio-economic factors greatly affect the

differences in prevalence found in different studies. Another important factor in prevalence reporting is definition of COPD. Prevalence of mild COPD [$FEV_1$/FVC (Forced vital capacity) < 0.70 and $FEV_1$ > 80% predicted] is 6.9% and that of moderate and severe COPD ($FEV_1$/FVC < 0.70 and $FEV_1$ < 80% predicted) is 6.6% among adults 25-75 years of age (according to American Thoracic Society / European Respiratory Society Standards)[23].

In a recent multicentric study conducted in India, COPD was documented in 4.1% of subjects of age > 35 years, 5.0% among men and 3.2% in women (Male: Female ratio=1.56)[24]. In this study, COPD was defined using the standard criteria for chronic bronchitis i.e. presence of cough with expectoration for more than three months in a year for the past two or more years.

In another study, the 10 year cumulative incidence of COPD in cohort of subjects with respiratory symptoms was estimated at 8.2% and 13.5% respectively according to the British Thoracic Society (BTS) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[25]. The incidence was strongly related to increasing age and smoking.

COPD is currently the fourth leading cause of death in the world, and further increases in the prevalence and mortality of the disease have been predicted in the coming decades. Approximately 2.7 million deaths were reported in 2000 due to it [1]. Mortality data also underestimate it as a cause of death because the disease is more likely to be cited as a contributory than as an underlying cause of death, or may not be cited at all [26]. It is estimated that it will become the third leading cause of death by 2020, with only heart diseases and cerebrovascular diseases accounting for more deaths[1].

**Risk Factors**

Risk factors for COPD include both host factors and environmental exposures. The disease state usually arises from an interaction between the various causal factors, both host and environmental.

***Environmental Factors***

**Tobacco Smoke**

Tobacco smoke is clearly the single most important identifiable etiological factor in COPD. However, only 10-20% of smokers develop clinically significant COPD, while approximately half never develop a clinically significant physiological deficit [27]. This suggests that genetic factors must also modify each individual's risk [28].

Tobacco smoke is a mixture of over 4000 chemical constituents. Mainstream smoke from cigarettes contains nicotine, benzene, polynuclear aromatic hydrocarbons (including benzopyrene), hydrogen cyanide, lead nitrogen oxides, N-nitrosamines, ammonia, and carbon-monoxide [29].

Amongst males, tobacco smoking is responsible for more than 80% of patients [3, 30]. Besides active tobacco smoking, exposure to smoking from others i.e. passive smoking, better termed as environmental tobacco smoke (ETS) exposure, may also play a contributory role especially, in non-smoker individuals including women [4,5].

**Occupational Exposure**

Exposure to particulate matter, irritants, organic dusts, and sensitizing agents have been documented to cause COPD[6]. Epidemiological and pathological studies have linked exposure to coal mine dust, silica, cadmium, and asbestos[31]. Longitudinal studies show that exposure to cotton and grain dusts may lead to chronic airflow obstruction[32]. Thus, workers employed in coal mining, iron and steel industry, textile, construction or agricultural industries may develop COPD, independently of cigarette smoking.

**Outdoor Air Pollution**

Chief sources of air pollution are burning of fossil fuel from industries and vehicles. Studies have related long term exposure of ambient concentrations of inhalable particles less than 10 nm in diameter ($PM_{10}$) and other pollutants – total suspended sulphates, sulfur dioxide, ozone, nitrogen dioxide with development of COPD [33,34]. Outdoor air pollution is responsible for frequent acute exacerbations and increased mortality in COPD patients.

**Indoor Air Pollution**

The smoke from combustion of solid fuels such as dried dung, wood and crop residue used for cooking and heating, especially in villages, sub-urban and slum areas, is an important cause of pollution of the indoor air. Indoor air pollution in poorly ventilated dwellings has been implicated as a risk factor for development of COPD in the rural inhabitants in general and women in particular [7,35].

**Infections**

A history of severe childhood respiratory infection has been associated with reduced lung function and increased respiratory symptoms in adulthood. However, viral infections may be related to another factor e.g. low birth weight which independently is related to COPD[36].

**Socio-economic Status**

There is evidence that the risk of developing COPD is inversely related to socio-economic status[37].

It is not clear, however, whether this pattern reflects exposures to indoor and outdoor air pollutants, crowding, poor nutrition or other factors that are related to socio-economic status[38, 39].

**Host Factors**

**Genes**

The genetic risk factor that is most documented is a rare hereditary deficiency of $\alpha_1$-AT[8]. It is a glycoprotein and is potent inhibitor of serine protease[40]. It is synthesized in liver. Most of the lung $\alpha_1$-AT is derived from the plasma, although monocytes and macrophages can also manufacture the protein. Chromosome 14 contains a single 12.2 kb gene that encodes the $\alpha_1$-AT protein[41]. The gene for $\alpha_1$-AT is polymorphic with over 70 known alleles, resulting from changes in the amino acid sequence. The $\alpha_1$-AT protein is classified phenotypically by its electrophoretic properties, resulting in the Pi system. The common Pi type is M and the deficient Pi type, which can be clearly distinguished using electrophoresis, is termed Z.

The most common type is PiMM and has been used to establish normal levels at $\alpha_1$-AT within the population. The other phenotypes are much less common and of these SZ and ZZ are associated with severe deficiency and MZ and SS with partial deficiency. The association between emphysema and severe deficiency of the ZZ, SZ and the rarer null phenotype is well-known[42].

**Airway Hyper responsiveness (AHR)**

AHR is not a hallmark of COPD, but nevertheless it has been documented frequently in patients with disease. It has been shown that the risk of developing COPD is significantly increased in patients with AHR compared with those without AHR[43]. But Dutch hypothesis which was introduced in 1961 is still regarded as controversial.

**Dutch Hypothesis**

Orie and coworkers put forward the hypothesis that various forms of airway obstruction such as asthma, chronic bronchitis, and emphysema should not be considered a separate disease but rather as different expressions of one disease entity, a chronic non-specific lung disease. They proposed that in this disease entity, both endogenous (host) and exogenous (environmental) factors play a role in pathogenesis. A hereditary predisposition to develop AHR and allergy was considered to be an important factor in disease susceptibility, but association of AHR with COPD is not clear whether AHR predisposes to COPD or AHR in smokers with COPD is acquired[44].

**Lung Growth**

Lung growth is related to processes occurring during gestation, birth weight, and exposures during childhood[45]. Reduced maximal attained lung function may increase risk for the development of COPD[36].

***Pathogenesis of COPD***

COPD is characterized by chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature. In addition to inflammation, two other processes thought to be important in the pathogenesis of COPD are an imbalance of proteases and antiproteases in the lung, and oxidative stress. Although both these processes may themselves result from ongoing inflammation, they can also arise from genetic or environmental factors.

***Pathology of COPD***

COPD is a group of diseases and pathological changes in patients of COPD are complex and found in the central airways, peripheral airways, lung parenchyma, and pulmonary vasculature[46].

Chronic bronchitis is characterized by changes in central airways – the trachea, bronchi, and bronchioles greater than 2-4 mm in internal diameter. Inflammatory cells infiltrate the surface epithelium of central airways[47 ].Enlarged mucus secreting glands and an increase in the number of goblet cells are associated with mucus hypersecretion.

Peripheral airways disease affects small bronchi and bronchioles that have an internal diameter of less than 2 mm. Chronic inflammation leads to repeated cycles of injury and repair of the airway wall[48]. The repair process results in a structural remodelling of the airway wall, with increasing collagen content and scar tissue formation that narrows the lumen and produces fixed airways obstruction[49].

Emphysema is characterized by abnormal, permanent enlargement of the airspaces, distal to terminal bronchioles accompanied by destruction of their walls and without obvious fibrosis[21]. Protease-antiproteases imbalance and oxidative stress contribute to parenchymal destruction in emphysema[50,51]. Centriacinar emphysema is more common in the upper zones of the upper and lower lobes, whereas panacinar emphysema may be found anywhere in the lungs but is more prominent at the bases and may be associated with $\alpha_1$-AT deficiency[52]. Periacinar (distal acinar) emphysema occurs less commonly and occurs extensively in a subpleural position and may be associated with pneumothorax. There may be bullae in emphysema, which are localized areas of emphysema that have over distended. Loss of airway attachments, loss of lung elastic recoil and compression by enlarged airspaces in emphysema lead to airflow limitation[53].

Pulmonary vascular changes in COPD are characterized by a thickening of the vessel wall that

begins early in the disease. Thickening of the intima is the first structural change, followed by an increase in smooth muscle and the infiltration of the vessel wall by inflammatory cells[54,55].

***Diagnosis of COPD***

The diagnosis is suspected on the basis of symptoms and signs and supported by spirometry.

**Assessment of symptoms**

A diagnosis of COPD should be considered in any patient who has a risk factor (generally smoking) and who presents with chronic cough, chronic sputum production, dyspnea that is progressive or persistent and worsens on exercise and during respiratory infections[20].

**Physical examination**

Though an important part of patient care, a physical examination is rarely diagnostic is COPD. Physical signs of airflow limitation are rarely present until significant impairment of lung function has occurred[56]. Chest examination may reveal hyper inflated chest, reduced crico-sternal distance, obliteration of cardiac dullness, downward displaced upper border of liver dullness, use of accessory muscles, purse lip breathing, wheeze or uniformly diminished intensity of breath sounds[57].

**Spirometry**

The obstruction in forced expiratory airflow is the most important disturbance of respiratory function in COPD[58]. Because earliest changes in COPD affect the alveolar walls and small airways, the tests of small airway function may be abnormal and changes are not reflected in conventional spirometric measurements [21]. By the time most patients present clinically, conventional spirometry is abnormal.

The presence of a postbronchodilator $FEV_1$ < 80% of the predicted value in combination with an $FEV_1$ / FVC < 70% confirms the presence of airflow limitation that is not fully reversible[20] Spirometry contributes to the assessment of the severity of COPD and predicts prognosis in COPD[20, 59].

Bronchodilator reversibility testing is useful help to rule out a diagnosis of asthma. Change in $FEV_1$ should be considered significant only if it exceeds 200 ml and improvement of 12% over baseline $FEV_1$ both after use of short acting bronchodilators[60]. Significant reversibility is the hallmark of asthma.

**Stages of COPD**

**Stage I: Mild COPD**

Characterized by mild airflow limitation ($FEV_1$/FVC < 0.70; $FEV_1 \geq 80$ % predicted). Symptoms of chronic cough and sputum production may be present, but not always. At this stage, the individual is usually unaware that his or her lung function is abnormal.

**Stage II: Moderate COPD**

Characterized by worsening airflow limitation ($FEV_1$/FVC < 0.70; 50% ≤ $FEV_1$ < 80% predicted), with shortness of breath typically developing on exertion and cough and sputum production sometimes also present. This is the stage at which patients typically seek medical attention because of chronic respiratory symptoms or an exacerbation of their disease.

**Stage III: Severe COPD**

Characterized by further worsening of airflow limitation ($FEV_1$/FVC < 0.70; 30% ≤ $FEV_1$< 50% predicted), greater shortness of breath, reduced exercise capacity, fatigue, and repeated exacerbations that almost always have an impact on patient's quality of life.

**Stage IV: Very Severe COPD**

Characterized by severe airflow limitation ($FEV_1$/FVC < 0.70; $FEV_1$ < 30% predicted or $FEV_1$ < 50% predicted plus the presence of chronic respiratory failure)[20].

**Acute Exacerbation of COPD**

COPD is often associated with exacerbations of symptoms[9,61,62]. An exacerbation of COPD is defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD [63,64]

Exacerbations are categorized in terms of either clinical presentation (number of symptoms) and/or health-care resources utilization[62,63]. The impact of exacerbations is significant and a patient's symptoms and lung function may both take several weeks to recover to the baseline values[65]

**Etiology**

COPD exacerbations have been associated with a number of etiological factors, including infection and pollution episodes. COPD exacerbations are frequently triggered by upper respiratory tract infections, and these are commoner in the winter months, when there are more respiratory viral infections in the community. It is also possible that patients are more susceptible to exacerbations in the winter months, as lung function in COPD patients shows small but significant decrease with reduction in outdoor temperature during the winter months[66]. COPD patients have also been found to have more hospital admissions during times of more environmental pollution[67].

**Manifestations**

Exacerbations of COPD are of major global importance. They have a profound and long lasting effect on patients, resulting in poor health status; they may accelerate the progression of the disease; and they account for a large proportion of the increasing healthcare expenditure on COPD. Exacerbations accelerate the progressive decline in lung function in COPD patients, making their prevention even more important [68]. In general, exacerbation frequency increases with disease severity, as represented by airflow obstruction, but the relationship between exacerbation frequency and $FEV_1$ is not particularly close and new evidence indicates a possible role for extrapulmonary factors in the genesis of exacerbation [69].

Over time COPD exacerbations become more frequent and more severe, and this is associated with increasing functional impairment. Thus, it is the patients with more severe COPD who are prone to more severe exacerbations and are more likely to need hospital admission, especially in the winter months when respiratory viral infections are common[70]. Risk factors for exacerbation relapses include low pre-treatment $FEV_1$, a need to increase bronchodilator or corticosteroid use, previous exacerbations (more than three in the last 2 yrs), prior use of antibiotics and the presence of comorbid conditions (congestive heart failure, coronary artery disease, chronic renal or liver failure) [71,72]. Patients with exacerbations are at increased risk of dying compared with patients who do not exacerbate or those who do so but do not require hospital admission[73].

Early data from the cohort studies by Fletcher et al suggested that exacerbations have no effect on lung function decline in COPD[74]. However, recent evidence suggests that exacerbations may have an important effect on COPD disease progression. One recent study suggested that among smokers exacerbations are associated with more lung function decline[75]. In another study, in which patients were divided into frequent and infrequent exacerbators, the patients with histories of frequent exacerbation had faster $FEV_1$ decline than patients who had infrequent exacerbations [68]. Further calculations suggested that the contribution of exacerbation to lung function decline was of the order of 25%, and thus cigarette smoking is still the most important factor in COPD disease progression.

**Airway inflammation in COPD Exacerbation:**

COPD exacerbations are associated with airway inflammation, though there has been little information available on the nature of inflammatory markers, especially when studied close to an exacerbation, because performing bronchial biopsy during exacerbation is difficult in patients with moderate to severe COPD[76]. The relationship of airway inflammatory changes to symptoms and physiologic changes at exacerbation is also an important factor to consider.

In one study, in which biopsies were performed at exacerbation in patients with chronic bronchitis, increased airway eosinophilia was found, though the patients studied had only mild COPD [77]. At exacerbation there were more modest increases observed in neutrophils, T -lymphocytes, and cells positive for TNF-α. Sputum induction allows study of these patients at exacerbation, and sputum induction is safe and well-tolerated with COPD patients [78]. In the East London study, inflammatory markers in induced sputum were related to symptoms and physiologic variables at baseline and exacerbation in patients who had moderate-to-severe COPD[76]. There was a relationship between exacerbation frequency and sputum cytokines; baseline measurements of sputum from patients who suffered frequent exacerbations had more IL-6 and IL-8 than did sputum from patients who suffered infrequent exacerbations, although there was no relationship between cytokines and baseline lung function.

**Systemic inflammation in COPD Exacerbation:**

The presence of systemic inflammation in COPD has been linked with a variety of complications including weight loss, cachexia, osteoporosis, and cardiovascular diseases [12,79]. Moreover, data from Dahl *et al.* suggest that individuals with increased systemic inflammatory markers such as fibrinogen experience an accelerated decline in lung function and are at increased risk of COPD hospitalisations in the future [80]. The relationship between COPD, systemic inflammation, and cardiovascular diseases may be especially germane as over half of patients with COPD die from cardiovascular causes [81]. Indeed, airflow limitation doubles the risk of cardiovascular mortality independent of smoking [79]. Moreover, during periods of exacerbation, plasma levels of fibrinogen and serum levels of IL-6 increase significantly, which may further contribute to increased cardiovascular morbidity and mortality in patients with COPD[82].

**The Need for New Marker in COPD**

Reflecting the multicomponent nature of the disease, there is extensive heterogeneity among patients with COPD in terms of clinical presentation, disease severity and rate of disease progression. It is increasingly apparent that a single marker is unlikely to be predictive of clinical outcome in all patients with COPD, given the diverse range of pathological mechanisms involved. Furthermore, with the variable clinical presentation of COPD, a single outcome is unlikely to provide a full assessment of the impact of

COPD across all patients. Despite this limitation, staging and prognosis of COPD is currently determined solely on the basis of lung function measurements, principally $FEV_1$. In effect, $FEV_1$ has been used as a global marker for all the pathophysiological changes in COPD, even though a number of the changes are extrapulmonary. The ability of therapies to prevent the progression of COPD is thus judged in terms of effects on a single marker that is relevant to only some of the pathophysiological processes in COPD and so is unlikely to provide an accurate assessment of the overall clinical effect.

There is another risk in relying solely upon the $FEV_1$ as a marker of COPD. Bronchodilators are central to current strategies for managing COPD, and $FEV_1$ is a reliable marker of a principal clinical effect of these therapies. It is possible that new agents that act by mechanisms other than bronchodilation might have little or no effect on $FEV_1$, but significantly improve clinical outcomes such as mortality and hospitalisation. For example, pulmonary rehabilitation has been shown to improve exerce tolerance and symptoms of COPD including breathlessness and muscle fatigue, without modifying $FEV_1$ or other lung function parameters [83].

The limitations of relying on a single marker to describe the progression of a multicomponent disease are compounded by a number of other considerations that, taken together, highlight the need for new and additional markers in COPD. For example, the use of $FEV_1$ to assess treatment efficacy seems paradoxical, since COPD is diagnosed on the basis of low $FEV_1$ that is poorly responsive to bronchodilator therapy. In other words, new treatments for COPD are required to modify a marker in a population that has been selected on the basis of the unresponsiveness of that same marker to established COPD therapies. Given this paradox, it is perhaps unsurprising that many trials of bronchodilators and anti-inflammatory agents have shown only marginal efficacy in terms of improvements in $FEV_1$[84-87].

It is important to remember that $FEV_1$ is a marker, and not a clinical outcome, of COPD. Whilst it has been shown to correlate with mortality and health status, these correlations are weak, and it is not until it falls to 50% of the predicted level that mortality begins to rise substantially. Furthermore, in patients where the percentage of predicted $FEV_1$ has fallen to very low levels, this measure has little predictive value [88]. Evidence suggests that other measures may be better indicators of disease progression than $FEV_1$.

The concept of a single global marker has the attraction of simplicity and convenience, but may not be appropriate to a complex, multicomponent disorder, such as COPD. Additional markers and outcomes are needed to provide a more comprehensive and clinically meaningful assessment and so provide a more informed basis for treatment decisions. In particular, markers related to inflammatory processes, structural changes and systemic effects could yield valuable information to complement that provided by $FEV_1$ for airflow limitation. Given that COPD is a progressive disorder, it may be that certain markers and outcomes are more relevant and useful at particular disease stages.

There has been a shift in the focus of biomarker discovery away from lung sources and toward blood specimens[14]. Serum or plasma biomarkers are attractive because blood is readily available and their measurement can be easily standardized. More recent publications have further fuelled the excitement by showing that certain blood-based biomarkers such as CRP, IL-6, pulmonary activation-regulated chemokine[89], and inhibitors of plasminogen activators relate to lung function and even to hard clinical outcomes such as exacerbations, morbidity, and mortality [90]. Of these blood-based biomarkers, CRP has shown the greatest promise. There are now at least two major epidemiologic cohort studies that have separately demonstrated that raised blood CRP levels are associated with major outcomes of interest in COPD, including reduced lung function, hospitalization, and mortality, independent of the effects of smoking [91]. CRP levels also relate to poor health status and increased risk of exacerbations [92].

Joppa *et al*. Studied the degree of systemic inflammation reflected by circulatory levels of CRP, TNF-α, and IL-6 in COPD patients with and without pulmonary hypertension. A total of 43 patients were taken into the Cross-sectional study. Pulmonary hypertension was present in 19 patients and was absent in 24 patients. In patients with pulmonary hypertension, serum CRP and TNF-α levels were significantly higher than in those patients without hypertension (median 3.6 mg/l vs 1.8 mg/l ($p = 0.034$); and median 4.2 pg/ml vs 3.1 pg/ml ($p = 0.042$) [15].

De Torres *et al*. found the relationship between CRP levels and factors known to predict outcome in stable COPD patients. They studied 130 stable COPD patients with: spirometry, lung volumes, $PaO_2$, dyspnoea, 6 minute walk distance (6MWD), body mass index, free fat mass index, BODE index, health related quality of life, smoking status, the presence of cardiovascular risk factors or disease, corticosteroids use and number of exacerbations in the previous year. CRP levels were measured in these patients and in 65 control and using univariate and multivariate analysis evaluated any possible association with the predictors of outcomes.CRP levels were higher in COPD patients than in controls (4.1 vs. 1.8 $mg \cdot L^{-1}$ respectively, $p<0.001$). Correlation was found with the following

variables: $FEV_1$ (-0.23, p=0.008), $FEV_1$% (-0.20, p=0.03), FVC (-0.24, p=0.006), FVC% (-0.24,p=0.006), GOLD stage (0.17, p=0.04), BODE (0.17, p=0.05), IC/TLC (-0.20, p=0.04), $PaO_2$ (-0.40, p<0.001) and 6MWD (-0.30, p=0.001). Using multivariate analysis, $PaO_2$ and 6MWD manifested the strongest negative association with CRP levels. CRP levels in stable COPD patients were best correlated with $PaO_2$ and 6MWD [92].

Karadag *et al.* confirmed CRP as a valid biomarker of low-grade systemic inflammation in stable COPD patients. Sixty percent of the patients had severe or very severe and 40% had moderate COPD. Serum CRP was found to be significantly higher in stable COPD patients than in control subjects (p<0.001)[93].

De Torres *et al*. studied the association of CRP levels with survival in patients with moderate to very severe COPD in comparison with other well-known prognostic parameters of the disease. In 218 stable patients with COPD, they measured baseline serum CRP level, BODE (body mass index, obstruction, dyspnea, and exercise capacity) index and its components, arterial oxygenation ($PaO_2$), inspiratory capacity (IC) to total lung capacity (TLC) ratio, and Charlson comorbidity score. They followed up the patients over time and evaluated the strength of the association between the variables and all-cause mortality. During the follow-up time (median, 36 months; 25th to 75th percentiles, 24 to 50 months), 54 patients (25%) died. CRP levels were similar between survivors and the deceased (median, 3.8 mg/L; 95% confidence interval, 1.9 to 8.1; vs median, 4.5 mg/L; 95% confidence interval, 2.1 to 11.5; p=0.22) and was not significantly associated with survival. In this population of patients with clinically moderate to very severe COPD, the CRP level was not associated with survival compared with other prognostic clinical tools such as the BODE index, modified Medical Research Council scale, 6MWD, percentage of predicted $FEV_1$, IC/TLC ratio < 0.25, and $PaO_2$[94].

Broekhuizen *et al.* investigated the discriminative value of high sensitivity CRP in COPD with respect to markers of local and systemic impairment, disability, and handicap and concluded that high sensitivity CRP is a marker for impaired energy metabolism, functional capacity, and distress due to respiratory symptoms in COPD. Regression analysis also showed that, when adjusted for $FEV_1$, age and sex, CRP was a significant predictor for body mass index (p=0.044) and fat mass index (p=0.016) [95].

Pinto-Plata *et al*. compared the CRP levels in patients with COPD, control smokers (S) and non-smokers (NS) and found that serum CRP levels were significantly higher in patients with COPD (5.03 (1.51) mg/l) than in controls (adjusted odds ratio 9.51; 95% confidence interval 2.97 to 30.45) but were similar in the two control groups (S: 2.02 (1.04) mg/l; NS: 2.24 (1.04) mg/l). CRP levels were raised in COPD patients without clinically relevant IHD and independent of cigarette smoking, and reduced in patients with COPD using inhalational corticosteroids. So, CRP may be a systemic marker of the inflammatory process that occurs in patients with COPD [96].

Hurst *et al.* assessed the use of 36 plasma biomarkers in 90 paired baseline and exacerbation plasma samples from 90 patients with COPD to confirm exacerbation and predicting exacerbation severity and found that to confirm the diagnosis of exacerbation, the most selective biomarker was CRP. However, this was neither sufficiently sensitive nor specific alone (area under the receiver operating characteristic curve [AUC], 0.73; 95% confidence interval, 0.66–0.80). The combination of CRP with any one increased major exacerbation symptom recorded by the patient on that day (dyspnea, sputum volume, or sputum purulence) significantly increased the AUC to 0.88 (95% confidence interval, 0.82–0.93; p < 0.0001). There were no significant relationships between biomarker concentrations and clinical indices of exacerbation severity. They concluded that plasma CRP concentration, in the presence of a major exacerbation symptom, is useful in the confirmation of COPD exacerbation[90]**.**

Dahl *et al***.** evaluated whether increased serum CRP in individuals with airway obstruction predicts future hospitalization and death from COPD. They performed a cohort study with a median of 8-yr follow-up of 1,302 individuals with airway obstruction selected from the ongoing Copenhagen City Heart Study and measured serum CRP at baseline, and recorded COPD admissions and deaths as outcomes. During follow-up, 185 (14%) individuals were hospitalized due to COPD and 83 (6%) died of COPD. Incidences of COPD hospitalization and COPD death were increased in individuals with baseline CRP > 3 mg/L versus ≤ 3 mg/L (log rank: p < 0.001). After adjusting for sex, age, $FEV_1$% predicted, tobacco consumption, and IHD, the hazard ratios for hospitalization and death due to COPD were increased at 1.4 (95% confidence interval, 1.0–2.0) and 2.2 (1.2–3.9) in individuals with baseline CRP > 3 mg/L versus ≤ 3 mg/L. After close matching for $FEV_1$% predicted and adjusting for potential confounders, baseline CRP was, on average, increased by 1.2 mg/L (analysis of variance: p = 0.002) and 4.1 mg/L (p = 0.001) in those who were subsequently hospitalized or died of COPD, respectively. The absolute 10-yr risks for COPD hospitalization and death in individuals with CRP above 3 mg/L were 54 and 57%, respectively, among those older than 70 yr with a tobacco consumption above 15 g/d and an $FEV_1$%

predicted of less than 50.So, they concluded that CRP is a strong and independent predictor of future COPD outcomes in individuals with airway obstruction [97]**.**

Bircan *et al***.** investigated the value of CRP as a marker of COPD exacerbations or specifically bacterial exacerbations and evaluated a correlation between raised CRP levels and other markers of inflammation in patients with an acute exacerbation (AECOPD). In this retrospective study patients were categorized according to the nature of sputum as mucoid or purulent and to the findings on chest radiographs as with pneumonia (PCOPD) or without pneumonia. Stable COPD (SCOPD) patients and a group of asymptomatic nonsmokers were also included in the study. All COPD patients (SCOPD: 30; AECOPD: 51; PCOPD: 32) and control subjects (30) were male. The mean CRP levels and WBC counts of the groups were PCOPD: 108.1 ± 61.8 mg/l and 13.7 ± 6.8 × $10^9$/l; AECOPD: 36.8 ± 43.9 mg/l and 11.4 ± 4.8 × $10^9$/l; SCOPD: 3.9 ± 1.4 mg/l and 7.9 ± 1.9 × $10^9$/l; control: 2.1 ± 0.9 mg/l and 7.7 ± 1.1 × $10^9$/l. The mean CRP level of AECOPD was statistically different from those of PCOPD and SCOPD ($p = 0.0001$, $p = 0.002$, respectively). The sensitivity and specificity of CRP to determine an acute exacerbation were 72.5 and 100%, respectively. Among the patients with AECOPD, 25 had purulent sputum and a mean CRP level of 46.4 ± 48.6 mg/l, which is significantly higher than the CRP level (28.0 ± 44.5 mg/l) of the 18 patients with mucoid expectoration ($p = 0.015$). Among the mucoid-expectorating subgroup, the patients with leukocytosis had significantly higher CRP levels than the patients without leukocytosis ($p = 0.034$). Therefore a high serum CRP value may indicate an infectious exacerbation in COPD patients and it correlates with sputum purulence and increased serum WBC counts[98].

Dev *et al*. evaluated the value of C-reactive protein measurements in exacerbations of COPD. They measured CRP levels in 50 patients who were admitted to hospital with clinical evidence of exacerbation [PaO2=7·3 ± 1·3 (sd) kPa, baseline $FEV_1$=0·8 ± 0·4 (sd) 1]. These patients all had serial measurement of CRP, peripheral white cell count, body temperature, peak expiratory flow rate, Karnofsky performance status and chest X-ray, in addition to serial sputum bacteriological analysis carried out in a specialized laboratory. CRP was elevated ( > 10 mg/l) in all patients (n=29) with proven infection [103 ± 98 (sd) mg/l]. Levels were markedly elevated in patients infected with Streptococcus pneumoniae (mean 156 mg/l); there was also a rapid fall in the CRP with therapy. TLC fell with therapy, giving a correlation with CRP level (r=0·44, p<0·01). Since CRP elevation was observed in patients having exacerbation with proven infections and also in those where infection was not proven, it is possible that, while it is a marker for COPD exacerbation, it is not necessarily a marker of bacterial infection per se. However, it was evident from their study that it was of value in the assessment of exacerbations of COPD, where routine bacterial culture of sputum is often unreliable, and thus the measurement of serum CRP may provide an additional objective indicator of infection[19].

Stolz *et al*. evaluated the role of Copeptin, CRP, and Procalcitonin as prognostic biomarkers in acute exacerbation of COPD and found that plasma levels of all three biomarkers were elevated during the acute exacerbation ($p < 0.001$), but levels at 14 days and 6 months were similar (p = not significant). CRP was significantly higher in patients presenting with Anthonisen type I exacerbation ($p = 0.003$). In contrast to CRP and procalcitonin, copeptin on hospital admission was associated with a prolonged hospital stay ($p = 0.002$) and long-term clinical failure ($p < 0.0001$). Only copeptin was predictive for long-term clinical failure independent of age, comorbidity, hypoxemia, and lung functional impairment in multivariate analysis ($p = 0.005$). The combination of copeptin and previous hospitalization for COPD increased the risk of poor outcome ($p < 0.0001$). Long-term clinical failure was observed in 11% of cases with copeptin < 40 pmol/L and no history of hospitalization, as compared to 73% of patients with copeptin ≥ 40 pmol/L and a history of hospitalization ($p < 0.0001$). Thus, they suggested copeptin as a prognostic marker for short-term and long-term prognoses in patients with AECOPD requiring hospitalization[99].

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