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Review Article

The Heterogeneity of COPD: A Comprehensive Review of Clinical Phenotypes

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Abstract

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous condition whose epidemiology and pathophysiology remain incompletely characterized, partly due to challenges in accurately defining and classifying its diverse subtypes. COPD arises from multiple interacting factors, and affected individuals show marked variability in clinical manifestations, disease progression, and response to available therapies, making a uniform treatment approach ineffective. To address this variability, the concept of clinical phenotyping has emerged, aiming to categorize patients into subgroups with shared characteristics that are associated with distinct clinical outcomes. Phenotyping provides a framework for understanding disease heterogeneity and supports the implementation of personalized therapeutic strategies. Broadly, a phenotype refers to any observable characteristic of an organism. In COPD, a clinical phenotype is defined as a single feature or a combination of disease-related attributes that differentiate patients in terms of clinically relevant outcomes such as symptom burden, exacerbation frequency, response to treatment, rate of lung function decline, and mortality. Identification of these phenotypic traits enables prognostic stratification and guides targeted management. Early recognition of COPD subtypes may facilitate timely intervention and improved healthcare delivery. Recent literature has identified several clinically relevant phenotypes, including emphysema-predominant COPD, chronic bronchitis, asthma–COPD overlap, frequent exacerbator phenotype, COPD with bronchiectasis, combined pulmonary fibrosis and emphysema, COPD with obstructive sleep apnoea, tuberculosis-associated COPD, respiratory bronchiolitis with interstitial lung disease, HIV-associated COPD, obesity-related COPD, and COPD in non-smokers etc. Emerging evidence indicates that such phenotypic diversity significantly influences symptoms, exacerbation risk, therapeutic response, lung function decline, and survival.

Keywords: COPD, Clinical phenotypes, Disease heterogeneity.

Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) as a heterogeneous pulmonary disorder characterized by persistent respiratory symptoms such as dyspnoea, chronic cough, and sputum production, resulting from abnormalities of the airways and/or alveoli that lead to sustained, usually progressive, airflow limitation.[1] COPD represents a major global health concern with substantial effects on morbidity, mortality, and quality of life. The disease is marked not only by variable degrees of airflow obstruction but also by significant pulmonary and extra-pulmonary manifestations, reflecting its complex and heterogeneous nature.[2,3]

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This heterogeneity has important implications for both disease understanding and clinical management. COPD does not represent a single pathological entity; rather, it encompasses a spectrum of clinical presentations with differing natural histories and responses to treatment. Consequently, identifying distinct disease phenotypes has become essential for addressing this variability and moving toward individualized patient care. A clinical phenotype refers to a subgroup of patients who share common disease characteristics that are associated with meaningful

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differences in clinical outcomes, including symptom burden, exacerbation frequency, disease progression, and therapeutic response.[4] Recognition of such phenotypes contributes to a better understanding of the epidemiology and underlying mechanisms of COPD.

The global burden of COPD continues to rise, making it one of the leading causes of chronic morbidity worldwide.[5] According to projections by the World Health Organization, COPD is expected to impose an increasing social and economic burden and is predicted to become the third leading cause of death globally by the year 2030.[6] These alarming trends underscore the need for improved disease classification and targeted management strategies.

Despite advances in research, current knowledge of COPD pathogenesis and epidemiology remains constrained by challenges in defining and categorizing the diverse phenotypes that comprise this disorder.[7] COPD is a multifactorial disease influenced by genetic susceptibility, environmental exposures, and host-related factors, resulting in wide inter-individual variability in treatment response.[8,9] In this context, the concept of phenotype—defined as any observable characteristic of an organism arising from the interaction between genetic and environmental factors—provides a useful framework for stratifying patients beyond traditional spirometric classification.[10]

COPD Phenotypes and Their Defining Characteristics

Chronic obstructive pulmonary disease comprises a wide spectrum of clinical presentations. Several distinct phenotypes have been described in the literature, each characterized by specific clinical, functional, radiological, and prognostic features that aid in diagnosis and guide therapeutic decision-making.

Emphysema Phenotype

The emphysema–hyperinflation phenotype is characterized predominantly by exertional dyspnoea and reduced exercise tolerance, often accompanied by clinical and physiological evidence of lung hyperinflation. Patients with this phenotype frequently exhibit a lower body mass index compared to other COPD subtypes.[11] The diagnosis is supported by functional evidence of hyperinflation, radiological demonstration of emphysema on high-resolution computed tomography (HRCT), and/or reduced gas transfer as assessed by a decreased diffusing capacity for carbon monoxide (DLCO/VA), corrected for haemoglobin levels.

Isolated emphysema is not independently associated with an increased risk of exacerbations unless it coexists with chronic bronchitis.[8] Two principal morphological patterns of emphysema are recognized in COPD. Panlobular emphysema is typically associated with α_1-antitrypsin deficiency and, less commonly, smoking, and is characterized by uniform alveolar enlargement with predominant involvement of the lower lung zones. In contrast, centrilobular emphysema, most commonly related to cigarette smoking, demonstrates patchy destruction of the respiratory bronchioles with preferential involvement of the upper lobes.[12,13] Histopathological studies have shown that centrilobular lesions are often supplied by abnormal bronchioles lined with altered epithelium, along with airway wall thickening and luminal narrowing.[14] Paraseptal emphysema, however, has not been consistently associated with increased symptom burden or significant impairment in lung function.

Impaired diffusing capacity has been identified as an independent predictor of radiological emphysema severity, resting hypoxaemia, exercise-induced oxygen decrease, SpO2, and overall functional limitation.[4] In an Indian study by Singh *et al.*,[15] emphysema was the most common phenotype, accounting for 45% of cases, followed by asthma–COPD overlap and chronic bronchitis (20% each), while 15% of patients had COPD with bronchiectasis. Upper-lobe predominant emphysema represents an important anatomical phenotype with a strong genetic basis and is particularly relevant due to its favourable response to surgical lung volume reduction procedures.[16]

Chronic Bronchitis Phenotype

Chronic bronchitis is a well-recognized phenotype of COPD, traditionally defined by the presence of productive cough for at least three months in two consecutive years.[17] Patients with COPD and chronic bronchitis experience frequent exacerbations, a faster decline in lung function, poorer health-related quality of life, and a trend toward increased mortality as compared with those without chronic bronchitic symptoms.[18,19]

Despite its strong association with COPD, chronic bronchitis is also prevalent in the general population, with reported rates ranging from 3.4 to 22%.[20] Long-term observational data from Pelkonen *et al.*,[21] who followed 1,711 Finnish men over three decades, demonstrated a markedly higher incidence of chronic bronchitis among continuous smokers (42%), compared with ex-smokers (26%) and never-smokers (22%). Objective cough monitoring studies have further confirmed that current smokers with COPD have higher cough frequency, followed by ex-smokers with COPD and healthy smokers.[22]

In a phenotype-based analysis by Singh *et al.*,[15] chronic bronchitis accounted for 37% of cases characterized by sputum production exceeding three months per year, followed by emphysema (29.6%), COPD with bronchiectasis (22%), and asthma–COPD overlap (11.1%). Notably, nearly half of patients with emphysema in this cohort had moderate-to-severe dyspnoea, corresponding to mMRC grades 2 and 3.

The COPDGene study reported a chronic bronchitis prevalence of 26.2% among GOLD stage 1–4 patients using the classical definition; however, this increased to 39% when cough and sputum symptoms were assessed using the

St George's Respiratory Questionnaire.[23] Radiologically, chronic bronchitis has been linked to more pronounced airway disease, with early CT-based studies demonstrating significantly greater bronchial wall thickness and higher wall area percentages in patients with chronic bronchitis compared to those without.[24]

Asthma–COPD Overlap (ACO) Phenotype

Asthma–COPD overlap refers to a phenotype in which patients demonstrate persistent airflow limitation characteristic of COPD along with clinical, functional, or inflammatory features suggestive of asthma.[25] Epidemiological estimates suggest that approximately 10 to 20% of individuals with COPD exhibit asthmatic traits. ACO is not a single disease entity but encompasses several subgroups, including patients with chronic asthma who develop fixed airflow obstruction, smokers with asthma and predominant neutrophilic inflammation, and COPD patients with eosinophilic airway inflammation.[26]

Clinically, individuals with ACO tend to experience greater symptom burden, more frequent exacerbations, increased hospitalization rates, and poorer quality of life compared to patients with COPD alone. Interestingly, despite higher morbidity, ACO has been associated with lower mortality when compared with other high-risk COPD phenotypes, such as frequent exacerbators with emphysema or chronic bronchitis.[27]

Given the heterogeneity and diagnostic challenges associated with ACO, attention has increasingly focused on blood eosinophil counts as a practical biomarker. Elevated blood eosinophil levels have been shown to predict a favourable response to inhaled corticosteroids, particularly in reducing exacerbation frequency among COPD patients.[28] In a study by Chandravanshi *et al.*,[29] 20% of patients met criteria for ACO, with significant associations observed with advancing age, male sex, and longer smoking duration among asthmatics, while age remained the primary associated factor among COPD patients.

Frequent Exacerbator Phenotype

Acute exacerbations of COPD contribute significantly to accelerated lung function decline, deterioration in quality of life, and increased healthcare utilization. A previous history of exacerbations remains the most reliable predictor of future events, forming the basis for identification of the frequent exacerbator phenotype, which is incorporated into the GOLD treatment framework.[30]

Gupta *et al.*[31] categorized COPD patients into frequent exacerbators, defined as those experiencing two or more exacerbations in the preceding year, and infrequent exacerbators with fewer than two episodes annually. Patients in the frequent exacerbator group demonstrated a higher prevalence of productive cough and dyspnoea, lower body mass index, increased airway bacterial colonization, impaired arterial oxygenation, and significantly reduced spirometric and gas transfer parameters, including FEV_1, FVC, DLCO, and KCO. These findings highlight the frequent exacerbator phenotype as a distinct clinical entity characterized by specific physiological, microbiological, and functional attributes that confer heightened vulnerability to recurrent exacerbations.[32]

Rapid Decliner Phenotype

Cluster-based phenotyping studies have identified a subset of patients with COPD who experience a rapid decline in lung function over time. These individuals are often relatively younger, have fewer cardiovascular comorbidities, and demonstrate poor nutritional status, compromised overall health, and increased mortality risk.[33] Although the precise mechanisms underlying this rapid decline remain unclear, early recognition of this phenotype is crucial. Such patients may benefit from prompt referral to specialized centers for intensified disease-modifying interventions and consideration for advanced therapies, including lung transplantation.

Combined Pulmonary Fibrosis and Emphysema (CPFE) Phenotype

Emphysema and pulmonary fibrosis exert contrasting physiological effects on lung mechanics. Emphysema is characterized by reduced elastic recoil, increased lung compliance, hyperinflation, and diminished expiratory flow rates, whereas pulmonary fibrosis leads to increased elastic recoil, reduced compliance, and decreased lung volumes with relatively preserved or even elevated expiratory flow at comparable lung volumes. Despite these opposing features, both pathological processes frequently coexist, particularly in smokers, though this overlap is often underrecognized in routine clinical practice.

Patients with combined pulmonary fibrosis and emphysema exhibit distinctive pulmonary function profiles and clinical outcomes that differ from those seen in isolated emphysema or fibrosis. Traditional diagnostic approaches may underestimate this coexistence, as spirometric abnormalities can be partially masked by opposing physiological effects. The widespread use of high-resolution computed tomography (HRCT) has markedly improved detection of CPFE, allowing more accurate phenotypic classification and prognostication.[34,35]

Physical Frailty Phenotype

Frailty represents a multidimensional syndrome characterized by diminished physiological reserve and increased susceptibility to adverse health outcomes. Although commonly associated with aging, frailty is not solely age-dependent and is frequently observed in patients with chronic respiratory diseases, particularly COPD. Two widely used frameworks for assessing frailty include the fried frailty phenotype—defined by the presence of three or more criteria such as generalised weakness, slowness, low physical activity, fatigue, sedentary lifestyle, and unintentional weight loss—and the frailty deficit index, which quantifies cumulative health deficits identified during comprehensive geriatric assessment.

Frailty has a strong and clinically relevant association with COPD severity. It may be present in up to half of COPD patients, especially among older individuals, and is linked to worse airflow limitation, increased symptom burden, and higher exacerbation frequency. Importantly, frailty is a potentially reversible condition, with pulmonary rehabilitation shown to improve functional capacity and reduce frailty risk.[36-38] Dutta *et al.*[39] demonstrated a significant inverse relationship between six-minute walk distance and frailty risk, highlighting exercise capacity as a key modifiable factor. Additionally, patients classified under GOLD group B have been shown to carry a disproportionately higher risk of frailty, suggesting an opportunity for early intervention before irreversible musculoskeletal and cardiovascular deconditioning develops.[37]

Emotional Frailty Phenotype

Emotional frailty is often an underappreciated phenotype in COPD, with substantial implications for clinical outcomes. This phenotype encompasses psychological and emotional disturbances such as anxiety, depression, and fear of breathlessness, which independently contribute to increased morbidity, mortality, hospital admissions, prolonged hospital stays, and readmission rates.

The development of emotional frailty in COPD is multifactorial, arising from interactions between disease severity, symptom perception, individual coping mechanisms, emotional intelligence, psychosocial support systems, personality traits, and biological changes induced by chronic illness and comorbid conditions. Recognition of this phenotype is essential, as targeted psychological and behavioural interventions may significantly improve overall disease management and patient-centered outcomes.[40]

COPD with Bronchiectasis Phenotype

Bronchiectasis is defined by irreversible and progressive dilation of the bronchi resulting from chronic airway injury and impaired host defence mechanisms. It is not a standalone disease but rather a manifestation of various underlying conditions. With increasing use of HRCT, COPD has been increasingly recognized as both a contributing factor and a comorbid condition associated with bronchiectasis.[41] Since 2014, bronchiectasis has been acknowledged as a significant comorbidity of COPD in the GOLD guidelines, with subsequent updates emphasizing its impact on disease progression and prognosis.[42]

COPD-associated bronchiectasis is characterized by persistent neutrophilic inflammation, chronic airway infection, and frequent radiological detection of bronchial dilatation. Patients with this phenotype typically exhibit greater expectoration, more frequent exacerbations, poorer lung function, and higher rates of bacterial colonization.[43,44] These features have direct therapeutic implications, including the potential role of airway clearance techniques and long-term antimicrobial strategies.

Diaz *et al.*[45] highlighted the emerging clinical relevance of the COPD–bronchiectasis overlap, demonstrating that smoking-related increases in bronchial–arterial diameter ratios may be driven by reductions in vascular calibre. Quantitative CT parameters such as bronchial wall thickness, wall area percentage, and bronchial–arterial ratios may serve as objective tools for identifying bronchiectasis in smokers.

HIV-Associated COPD Phenotype

In contrast to many opportunistic pulmonary infections associated with HIV, HIV-related emphysema appears to be increasingly prevalent despite effective antiretroviral therapy. This is likely attributable to prolonged survival, cumulative exposure to smoking, and chronic HIV-related immune activation. Large cohort studies involving HIV-infected veterans have demonstrated a significantly higher prevalence of COPD compared to HIV-negative populations, even after adjusting for traditional risk factors.[46]

Reported prevalence rates of HIV-associated emphysema in industrialized countries range from 15 to 42%, far exceeding those observed in the general population. HIV infection remains an independent risk factor for COPD even with the use of highly active antiretroviral therapy (HAART). Mechanistic studies suggest that HIV-mediated macrophage infection leads to increased expression of matrix metalloproteinases, resulting in alveolar wall destruction.[47] In addition, infiltration of $CD8^+$ T lymphocytes and excessive interferon-γ production may contribute to progressive airway and parenchymal damage.[48] Given the irreversible nature of COPD, its presence may significantly compromise long-term outcomes in HIV-positive individuals, particularly in resource-limited settings, underscoring the need for heightened clinical awareness.[49]

Tuberculosis-Associated COPD (TOPD) Phenotype

A history of previous pulmonary tuberculosis has emerged as an important risk factor for subsequent development of chronic airflow obstruction. Allwood *et al.*[50] introduced the term tuberculosis-associated obstructive pulmonary disease (TOPD) to describe this phenotype. Aggarwal *et al.*[51] reported that nearly one-third of COPD patients in a tertiary care setting had a previous history of pulmonary tuberculosis, with a significantly higher odds of prior TB compared to controls. Patients with TOPD were younger, had lower cumulative smoking exposure, and experienced more frequent hospitalizations, despite similar degrees of airflow limitation.

Further characterization demonstrated that TOPD constitutes a clinically distinct entity with variable disease severity, ranging from mild to very severe airflow obstruction.[52] A significant negative correlation was observed between disease duration and severity, suggesting progressive functional deterioration over time. These findings emphasize the importance of recognizing TOPD as a separate phenotype with unique clinical implications.

COPD with Obstructive Sleep Apnoea Phenotype (Overlap Syndrome)

Obstructive sleep apnoea (OSA) and COPD are among the most prevalent chronic respiratory disorders, and their coexistence—termed the overlap syndrome by Flenley—occurs frequently, even by chance alone.[53] The likelihood of OSA varies across COPD phenotypes. Patients with predominant emphysema, characterized by lower BMI and increased lung volumes, appear relatively protected against OSA, whereas those with chronic bronchitis, higher BMI, and peripheral oedema are at increased risk.

Both COPD and OSA share common pathophysiological pathways, including intermittent hypoxia and systemic inflammation, which increase cardiovascular morbidity. Pulmonary hypertension is particularly common in patients with overlap syndrome, further worsening prognosis.[53]

Non-Smoker COPD Phenotype

Non-smoker COPD represents a distinct and increasingly recognized phenotype, accounting for approximately 25 to 45% of COPD cases globally. Unlike traditional smoking-related COPD, this phenotype is driven by alternative environmental exposures and host-related factors. Biomass fuel combustion and ambient air pollution are major contributors, mainly in low- and middle-income countries.

Non-smoker COPD predominantly affects women, presents at a younger age, and is often associated with higher BMI compared to smoker-related COPD. Radiological and pathological studies have demonstrated distinct patterns, with greater involvement of small airways, fewer neutrophils in sputum, and a slower rate of lung function decline.[54,55] Chronic bronchitis and bronchiectasis-like features are commonly observed in this group.

Obese COPD Phenotype

The association between obesity and COPD remains complex and incompletely understood. Adipose tissue acts as an active endocrine organ, secreting numerous pro-inflammatory mediators including leptin, adiponectin, resisting, tumour necrosis factor-α, and interleukins such as IL-6 and IL-8.[56] Dysregulation of these adipokines contributes to chronic low-grade systemic inflammation, which may adversely affect lung function.

Elevated levels of C-reactive protein, a marker of systemic inflammation, have been inversely correlated with FEV_1 and FVC in obese individuals with COPD.[57] Garcia-Aymerich *et al.*[58] identified a "systemic" COPD subtype characterized by obesity and heightened inflammatory activity, with increased expression of inflammatory cytokines and mediators among overweight and obese patients.

Vascular Phenotype of COPD

Pulmonary hypertension is a recognized complication of advanced COPD and is associated with poor prognosis, particularly when accompanied by right ventricular dysfunction. While mild to moderate pulmonary hypertension is common in severe COPD, severe pulmonary hypertension is relatively rare and often linked to additional comorbidities.[59]

Recent evidence, however, has identified a distinct pulmonary vascular phenotype defined by severe pulmonary hypertension in patients with only mild to moderate airflow limitation and minimal emphysema.[60] These patients exhibit marked vascular pruning, severely reduced diffusing capacity, profound hypoxemia, and a high prevalence of right heart failure. This phenotype resembles the so-called "vanishing capillary syndrome" observed in smoking-related pulmonary vasculopathy and may involve alternative pathogenic pathways, including molecular mechanisms such as hypoxia-inducible factor-2 signaling.[61] Recognition of this subgroup is critical, as these patients may benefit from pulmonary hypertension–specific therapies.

Indian Evidence on COPD Phenotypic Heterogeneity

Indian studies evaluating COPD phenotypes remain limited. Singh *et al.*[15] analysed 100 COPD patients and reported emphysema as the most prevalent phenotype, followed by COPD with bronchiectasis, asthma–COPD overlap, and chronic bronchitis. Male predominance was observed across all phenotypes, with emphysema most commonly affecting individuals aged 56 to 65 years. Underweight status was frequently noted in emphysema, whereas obesity was more prevalent in chronic bronchitis. Biomass exposure was strongly associated with bronchiectasis and chronic bronchitis phenotypes. Emphysema patients demonstrated the highest exacerbation frequency, poorest exercise capacity, and lowest FEV_1 values. Pulmonary arterial hypertension was most frequently observed in emphysema, followed by chronic bronchitis and overlap phenotypes.

These findings reinforce the substantial heterogeneity within COPD and highlight the need for accurate phenotypic identification. Recognition of distinct clinical, functional, radiological, and inflammatory patterns can facilitate personalized management strategies, improve therapeutic outcomes, and ultimately enhance survival in patients with COPD.

Conclusion

Chronic obstructive pulmonary disease mostly impacts individuals in the fifth and sixth decades of life, with a male predominance and a strong association with smoking exposure. Among the various clinical phenotypes, emphysema was identified as the most prevalent, followed by chronic bronchitis and asthma–COPD overlap (ACO). Underweight status was most frequently observed in patients with the emphysema phenotype, whereas chronic bronchitis showed the strongest correlation with cumulative smoking exposure measured in pack-years. Patients with emphysema and chronic bronchitis experienced a higher frequency of exacerbations during the course of the disease. Emphysema phenotype

was also associated with more severe airflow limitation and significantly reduced diffusing capacity, while patients with ACO demonstrated greater airway inflammation, reflected by elevated exhaled nitric oxide levels. Pulmonary hypertension was observed more commonly in patients with emphysema compared to other phenotypes.

Overall, the studies highlight the marked heterogeneity inherent in COPD. The disease does not represent a single uniform entity; rather, patients differ substantially in their clinical presentation, functional impairment, radiological findings, and inflammatory profiles. Consequently, a uniform treatment strategy is inadequate. Each phenotype reflects a distinct underlying pathophysiological process, necessitating a tailored therapeutic approach. For instance, patients with eosinophilic airway inflammation benefit from inhaled corticosteroids, whereas those with coexisting bronchiectasis require additional interventions such as prolonged antibiotic therapy, mucolytics, vaccination, and airway clearance physiotherapy. Accurate identification and understanding of COPD phenotypes can therefore facilitate personalized management, optimize treatment outcomes, and ultimately improve survival and quality of life in patients with COPD.

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