PHENOTYPE OF COPD: "FREQUENT EXACERBATOR" AND BIOMARKERS USE IN CLINICAL PRACTICE

Lavinia Davidescu[1], Darius Andrei Davidescu[2], Florica Voiță-Mekeres[3]*, Anca Goman[3], Nicoleta Stefania Motoc[4], Ruxandra Rajnoveanu[4], Milena Adina Man[4]

1. *Department of Pneumology, University of Oradea, Oradea, Romania.*
2. *Department of Morphological Disciplines, University of Oradea, Oradea, Romania.*
3. *Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania.*
4. *Department of Medical Sciences—Pulmonology, Faculty of Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, 400012 Cluj-Napoca, Romania.*

ARTICLE INFO	ABSTRACT
	An actual burden on healthcare systems across the world, chronic obstructive pulmonary disease (COPD) is a prevalent, complicated, diverse disorder that causes rising morbidity, mortality, and healthcare expenses. The radiological, physiological, and cellular phenotypes of COPD, a nosologically complicated illness, are known to be extremely diverse. Precision medicine is a new approach that compares individuals with identical diagnoses but varied prognoses and outcomes by looking at their genetic, biomarker, phenotypic, and psychological features. Understanding the disease's heterogeneity is crucial to successfully phenotyping COPD. We attempted to discuss the development of the classification of COPD, the phenotyping of the illness, the definitions of exacerbations, risk factors, and COPD exacerbations and their impact in this narrative review. Research and therapy efforts should focus on the "high exacerbator phenotype" since it is more likely to have elevated hospital admissions, comorbidities, and death. The frequent exacerbator phenotype of COPD currently lacks confirmed biomarkers that may be used to identify it. While new biomarkers will be discovered and validated in large study COPD populations, adherence to best practice guidelines, diagnosis of clinical "frequent exacerbator phenotype", identification of traditional exacerbator ' risk factors, colonization, and proper management of comorbidities could be the best management of this heterogenous and complex disease.

Introduction

An estimated 3 million people die each year from chronic obstructive pulmonary disease (COPD), which ranks third among all causes of mortality globally. This situation is typical, complicated, and diverse [1]. Celli and Col. defined "complex" as the presence of multiple elements with non-linear relationships between them (e.g., FEV1, exacerbations, symptom perception, comorbidities), such that one element cannot be predicted from another, and "heterogeneous" as the absence of all of these elements in all patients or at all timepoints [2]. The burden of COPD is significant globally in terms of prevalence, mortality, morbidity, and healthcare expenses. Due to risk factors and population aging, COPD is a significant public health issue, and its burden is anticipated to rise over the next few decades. Many risk factors, chief among them exposure to biomass fuel, risky employment, a history of asthma or TB, and exposure to passive smoking, are thought to contribute to the development of the illness. A significant number of COPD patients are nonsmokers [3]. Genetic anomalies, together with the kind and length of toxic exposures, define clinically distinct phenotypes with distinct disease trajectories [1, 2]. Even though the molecular cause of COPD has been researched, a complex web of interactions and other variables affects many of the pathways involved in its development. The fact that not everyone exposed to the disease has air-flow restrictions, however, raises the possibility that some people may be genetically predisposed to the condition. The highly variable phenotypes of COPD, a nosologically complex illness that highlights the interconnections between cellular, physiological, and environmental factors, include a variety of radiological, physiological, and cellular features [4].

Corresponding Author: Florica Voiță-Mekeres; Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania. E-mail: mekeres_florina@yahoo.com.

The pathogenic alterations in all various lung compartments are influenced by inflammation, which is a key characteristic of COPD [2]. Small airways collapsing, parenchymal damage, and goblet cell growth in the bronchial epithelium are all factors in the pathophysiology of COPD, which is primarily characterized by chronic airway and lung inflammation. Mucosal tissue changes, fibrosis, local and systemic inflammation, vascular remodeling, and angiogenesis in the lungs were all major pathogenetic elements relating to lung tissue remodeling in COPD patients that have been studied extensively over the past 20 years. The World Health Organization has decided that "young" patients with COPD refer to the subject's chronological age. Given that lung function peaks between the ages of 20 and 25 and that young individuals may acquire COPD similarly to older patients, GOLD takes young patients with COPD between the ages of 20 and 50 into consideration [5]. The biochemical complexity and clinical variety of COPD have gained growing recognition over the succeeding decades, and its prognosis is quite unpredictable. The effects of COPD are not limited to the respiratory system alone; due to its progressive nature and inflammation as its primary pathology, it can also have an impact on the pulmonary and extrapulmonary systems [6].

As a result of advancements in our knowledge of the pathophysiology of COPD at various levels as well as in comprehensive diagnostic and therapeutic strategies, disease management changed from a "one size fits all" to a more individualized approach. In the future, a more accurate description of phenotypes should aid in the development of personalized treatments. A new approach called precision medicine looks at genetic, biomarker, phenotypic, and psychological traits to discriminate between individuals with identical diagnoses. There is a lot of overlap between the phrases precision, customized, and personalized medicine [7]. For a very long time, the field of medicine has been divided into "lumpers" and "splitters"; lumpers often aggregate similar things, while splitters typically use more exact definitions to describe more separate entities [7]. To better comprehend a patient's condition and modify treatment as necessary, it is helpful to recognize the unique phenotypes of each patient. The requirement for a recognizable COPD phenotype is important since the discipline of COPD phenotyping has not yet been sufficiently developed to comprehend the mechanism underlying each clinical presentation. When taken together, this data may enable healthcare professionals to forecast how a patient will respond and the course of their sickness in order to choose an appropriate course of treatment and save costly trial-and-error [1]. Understanding why COPD is a complicated and varied illness is essential to phenotyping COPD successfully.

Phenotypes in COPD Patients

Phenotypes are described as disease features that, either alone or in conjunction with other characteristics, enable researchers to examine variations across COPD patients in terms of several clinically significant parameters that have an impact on treatment. "Phenotype" refers to a set of observable traits that may be used to categorize individuals. These classifications serve to identify groups of individuals that share traits that are related to clinically significant outcomes, such as symptoms, prognosis, and therapeutic response. When examining the pathophysiologic pathways in a condition as diverse as COPD, phenotypic categorization is crucial [8]. Early phenotypes of COPD, such as chronic bronchitis and the emphysematous presentation, or the "blue bloater" and "pink puffer," the latter of which is characterized by emphysema and the wasting of both muscle and fat tissue, have been identified historically. In individuals with a mostly emphysematous appearance, the bronchial obstruction has partially explained the pathophysiology of chronic bronchitis [9]. When a 1959 article titled "Terminology, definitions, and classification of chronic pulmonary emphysema and related conditions" was published in the journal Thorax, the scientific world first became aware of the issues with inadequate phenotyping. Patients that share significant traits indicative of clinical outcomes are grouped into clinical phenotypes. The clinical phenotype of chronic bronchitis, for instance, can result from both chronic irreversible asthma and an airway-predominant neutrophilic inflammatory process, and it may be enriched for a particular endotype, but it is not always descriptive of the underlying pathophysiology or indicative of the outcome of potential treatments [10]. Airflow restriction was the main emphasis of the first GOLD statement, which was released in 2001. It used the GOLD stages 1-4 (mild-to-very-severe COPD) to categorize patients and suggested treatments based on the degree of airflow limitation. Since then, this guide has undergone major updates in 2006, 2011 and 2017 and smaller revisions virtually yearly, making it the most significant resource used in clinical practices throughout the world [11]. The English National Institute for Clinical Excellence (NICE), which published its recommendations in 2004, were the first to advocate a multi-dimensional approach to managing COPD. These recommendations were based on a patient evaluation that considered eight factors, including smoking status, exercise limitation due to breathlessness, the frequency of exacerbations, the presence of respiratory failure, chronic productive cough, body mass index, and mental health. Stage-dependent step ups in treatment health were introduced in GOLD 2007's version [7, 12]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 amended guidelines suggest a therapeutic strategy based on two new factors, symptoms and exacerbations. The ABCD evaluation method was first described in the 2011 GOLD document, which also included a system based on spirometry, patient symptoms (based on the COPD assessment test [CAT] and/or modified Medical Research Council dyspnea scale [mMRC]), and a history of exacerbations in the previous 12 months [13]. The idea of phenotypes re-emerged with the realization that FEV1 was insufficient to identify and categorize COPD patients. The old idea of "blue bloaters" and "pink puffers," which had been abandoned in the past, is now being replaced by a number of distinct phenotypes. The assessment system was improved in the 2017 GOLD version, and the A, B, C, and D groups that defined the pharmacological treatment were based solely on symptoms and exacerbation history, with lung function no longer being included in the classification scheme with maximizing bronchodilation priority [14]. 22.4% of patients fell into group A, 45.3% into group B, 12.6% into group C, and 19.8% fell into group D, according to GOLD 2017. Exacerbation history, hospitalization due to COPD exacerbation, illness duration, CAT, and mMRC Dyspnea Scale were all greater in groups

C and D than they were in groups A and B. Less FEV1 (% expected) and more severe airflow limits were seen in the more symptomatic individuals (B and D). Like CAT, the mMRC dyspnea score was greater in individuals who presented with more symptoms. In comparison to groups B (A and B), groups C and D had older patients, longer disease durations, higher mMRC Dyspnea Scale and CAT scores, lower FEV1, and more severe airflow restriction [4]. A further improvement was reported in the 2019 paper, and Groups A, B, C, and D are now solely utilized to guide the first therapy. Dyspnea symptoms and exacerbations are recommended for follow-up, each with a unique therapy protocol [12]. Even with this new categorization, COPD's heterogeneity may not be sufficiently reflected [12]. In order to avoid exacerbations, the Global Initiative for Chronic Obstructive Lung Diseases advises using double- and triple-inhaled combination therapy that contains glucocorticoids (ICS), long-acting 2-agonists (LABA), and long-acting muscarinic receptor antagonists (LAMA). Despite receiving triple inhaled medication (ICS plus LABA plus LAMA), it is observed that 30 to 40% of patients still have moderate or severe exacerbations [15]. In individuals who have frequent exacerbations with an eosinophilic inflammatory profile, inhaled corticosteroids (ICS) are useful for lowering the risk of exacerbation and alleviating symptoms, but they are ineffective, if at all, in patients who experience rare exacerbations without eosinophilic inflammation [16]. These patients have few alternatives for further, supplemental treatments: Former smokers who have a chronic bronchitis phenotype and a forced expiratory volume in one second (FEV1) that is less than 50% of their anticipated value are advised to take azithromycin, according to GOLD [16]. Despite the fact that COPD patients have inflammation, there is no particular anti-inflammatory medication for COPD [16]. According to the length of these processes, two different types of inflammatory responses—acute and chronic—have been identified. Inflammation is a broad range of physiological processes that an organism engages in in response to a foreign stimulus, including human pathogens like viruses, bacteria, and inorganic particles. Cytokines, which are released by the immune cells enlisted at the inflammation site and are categorized according to their function as pro-inflammatory, anti-inflammatory, or chemotactic, play a significant role in both situations [17]. Numerous lung functions and the development of COPD are significantly impacted by oxidative stress (OS). These side effects include apoptosis, modification of the extracellular matrix, damage to the alveolar epithelium, mitochondrial respiration, membrane lipid peroxidation (LPO), mucus hypersecretion, and oxidative inactivation of surfactants and antiproteases [18]. When a number of reactive species and free radicals overwhelm the antioxidants (fudosteine, erdosteine, carbocysteine, and N-acetyl-L-cysteine) available, oxidative stress (OS) occurs. The onset and evolution of inflammation, as well as host defense and physiological signaling pathways, depend on reactive nitrogen species, reactive oxygen species (ROS), and their counterbalancing antioxidants [19]. One recent study used CT to assess a group of COPD patients and identified two pathological phenotypes: One had long-term respiratory symptoms, greater influence on SGRQ score, positive bronchodilator responsiveness, exacerbation, cardiovascular disease, and diabetes mellitus were associated with COPD patients who had thickened airway walls, while the others had lower BMI, greater influence on BODE index, rapid progression, mortality, low bone mineral density, and lung cancer were associated with COPD without thickening of the airway walls, with implications for the therapeutic approach.

Exacerbations

COPD exacerbations interrupt the disease's normal course. A scaled definition of exacerbations was adopted by Anthosen in 1987: Type 1 was defined by increased dyspnea, sputum volume, and sputum purulence; type 2 was when two of these symptoms were present; and type 3 was when one of the three major symptoms was present along with at least one of the following: an upper respiratory infection within the previous five days, fever without other explanation, increased wheezing or coughing, or an increase in respiratory rate or heart rate by 20% compared to baseline. An initial rise in airway inflammation, which leads to airway edema, mucus production, and bronchoconstriction, is what defines exacerbations. Similar to a "stroke of the lungs," an acute exacerbation is a significant incident that sets off a catastrophic cascade that may be fatal and overpowering [20]. The term "exacerbation" was first used by RODRIGUEZ-ROISIN in 2000 to describe a condition that is "acute in onset, a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variations, and necessitates a change in regular medication in a patient with underlying COPD" [21]. Exacerbations of COPD are linked to a quicker drop in FEV1, a worse quality of life (HRQL), hospitalizations, a higher risk of cardiovascular disease (CVD), a higher chance of developing further exacerbations, and a higher death rate [20]. Despite therapy, a study of the time course indicated that 14% of patients were still not entirely recovered by 5 weeks and in a small group, symptoms never returned to the baseline level, even though half of the patients treated in the community recovered to their baseline symptoms by 7 days. Exacerbations of COPD worsen the condition and increase mortality (of those admitted to the hospital for the first time due to an exacerbation, > 20% pass away within a year of being released) [22]. A single exacerbation can significantly lower a patient's overall score on the St. George's Respiratory Questionnaire (HRQL), with some patients' HRQL continuing to decline six months after the exacerbation. Additionally, the GOLD guidelines emphasize the importance of exacerbations when deciding on a course of therapy using the new ABCD disease risk stratification tool. The GOLD yearly report, which is based on an assessment of the best available research, is the COPD guideline that is most frequently followed in clinical practice. The new definition of 2023 defined COPD exacerbations as "worsening of respiratory symptoms associated with local and systemic inflammation," thus placing the major role of inflammation at the center of the definition [1]. GOLD's definition of exacerbation included acute worsening of respiratory symptoms that necessitated additional therapy.

Exacerbations have a significant role in the natural course of COPD as a risk factor for the disease's development and loss of lung function. A COPD exacerbation is described as "an event in the natural evolution of COPD, characterized by aggravation compared to the basal status of dyspnea, cough, and/or expectoration, which determines the modification of the treatment

scheme" by the ATS/ERS consensus. Acute COPD exacerbations continue to be a significant aspect of the disease, despite the fact that COPD is a progressive condition characterized by ongoing symptoms and, in certain patients, a steady deterioration in lung function and quality of life [21]. It is easier to manage "unstable" COPD (in patients who have frequent or severe exacerbations and a rapid loss in pulmonary function) than "stable" COPD, which is characterized as when symptoms are well-managed and pulmonary decline is limited. Exacerbations can occur more frequently in some individuals than others, and the majority of patients don't worsen at the same rate year after year. They can also range in intensity, from mild, self-limited episodes to severe symptoms that could necessitate hospitalization or even result in death. Its complicated nature with varied effects on the airways, pulmonary vasculature, lung parenchyma, and the dynamic impact of acute exacerbations are only a few of the elements that might explain this. Most often, bacterial or viral infections are the cause of these episodes of an abrupt rise in respiratory symptoms [23]. Respiratory viruses can cause COPD exacerbations, much like bacterial infections do. Viruses such as the coronavirus, influenza virus, and rhinovirus may cause exacerbations [18].

How Much Worse?

Another factor in how things are getting worse is the degree of exacerbations: how much worse? The most widely used grading method is an event-based evaluation for moderate to severe exacerbations, which has included any increases in inhaled medicine in mild exacerbations, systemic corticosteroids only in moderate exacerbations, and only hospital admissions or fatalities in the severe group [21]. Patients all around the world are using quite different drugs from their usual therapy; thus, what marks a change in routine medication is a problem with symptoms or treatment characterized as COPD exacerbations [22]. The Spanish Guidelines for Management of COPD (GesEPOC) categorized COPD patients as non-exacerbators, asthma-COPD overlapped, and exacerbators with emphysema or chronic bronchitis based on risk stratification and clinical manifestations [24]. Using multiple thresholds mostly derived from the median exacerbation frequency in several cohorts, which had two or more mild to severe exacerbations throughout one year [25], the particular phenotype of frequent exacerbators in COPD patients has been determined. According to the ECLIPSE research, COPD patients who have repeated exacerbations have a unique phenotype that may be recognized based on a history of exacerbations. The frequency of exacerbations varies greatly amongst individuals, although the percentage of patients who have two or more episodes in back-to-back years is quite low [1]. Researchers found in the SPIROMICS research that the frequency of exacerbations varies greatly over time and that the status of a frequent exacerbator—defined as having at least two exacerbations annually—is markedly rare [26]. As a result, the frequent exacerbator phenotype is typically described using this cut-off, and this description is now reflected in the GOLD. The GOLD supports the use of inhaled corticosteroids (ICS) for patients who are "frequent exacerbators" based on a threshold of 2 moderate or 1 severe AECOPDs in the previous 12 months, and the Canadian recommendations adopt a similar criteria for the frequent exacerbator phenotype [25]. The intensity and frequency of COPD exacerbations might vary greatly. In the ECLIPSE trial, the prevalence of frequent exacerbators was reported to be 22% in GOLD 2, 33% in GOLD 3, and 47% in GOLD 4 COPD. In a post-hoc analysis of POET-COPD, the prevalence was found to be 41.4% for GOLD 1-2 and 58.6% for GOLD 3 and 4 COPD. According to the 2017 version of GesEPOC, patients were categorized as either low-risk or high-risk depending on whether they had dyspnea that was graded 0 to 1 on the mMRC scale and had an exacerbation within the previous year (without admission). Patients who did not meet any of these criteria were classified as high-risk. GesEPOC modified the categorization by phenotypes in its most recent iteration in 2021. Maintaining the idea of low-risk or high-risk individuals, three phenotypes have been identified for the latter: non-exacerbator, non-eosinophilic exacerbator, and eosinophilic exacerbator [3]. Individuals with COPD were divided into non-exacerbators, asthma-COPD-overlapping individuals, and exacerbators with emphysema or chronic bronchitis in the GesEPOC. In recent research, 16% of exacerbation-naive patients with COPD who were monitored for three years had new exacerbations, 5% had frequent exacerbations (2 occurrences per year), and 5% had no more exacerbations [4].

Risk of Future Exacerbations

When beginning treatment and at follow-up/annual reviews, it is important to take into account a number of variables that may predict the likelihood of future exacerbations, including smoking, a history of exacerbations, blood eosinophil counts above 20, chronic bronchitis, comorbid conditions, and severe airflow restriction [22]. Although it is yet unknown why some COPD patients suffer more frequent exacerbations than others, exacerbations often increase in frequency and severity as the underlying COPD worsens [21]. In comparison to people who do not experience acute exacerbations, those who are more likely to experience exacerbations are older, have worse FEV1, have lower levels of daily physical activity, spend more time sitting down during the day, have more comorbid conditions, score higher on the dyspnea scale, are more likely to experience anxiety and depression, and have more evidence of small airway abnormality on computed tomography [21]. Exacerbations of COPD can take many different forms, and many phenotypes have been described, each with a unique biological foundation, prognosis, and therapeutic response. The severity of airflow restriction as determined by FEV1 and exacerbation frequency are closely correlated. In a recent study from Norway, the incidence ratios for utilization-defined acute exacerbations of COPD were 2.45, 3.43, and 5.67 with GOLD spirometry stages II, III, and IV, respectively. In a similar manner, in an analysis of the Copenhagen General Population Study, the risk of exacerbations was compared to people with GOLD 1, was 17-fold for GOLD 4, five-fold for GOLD 3, and was two-fold for GOLD 2 [22]. The SGRQ would show a larger short-term loss in quality of life in patients with frequent exacerbations than in those with infrequent exacerbations. We therefore hypothesized that patients with frequent exacerbations would experience a higher drop in FEV1 and body mass index (BMI) than those with less

frequent exacerbations [26]. In comparison to individuals who experienced 1 or fewer moderate-to-severe AECOPD incidents, frequent exacerbators reported statistically significant deterioration in SGRQ symptom ratings [27]. There are currently no validated biomarkers to assist identify the COPD phenotype of frequent exacerbators, and having a history of two moderate or severe prior exacerbations is the strongest predictor of exacerbations [1]. The probability of an exacerbation is inversely connected with the FEV1 classification of disease severity but strongly correlated with a history of exacerbations. Depending on the populations examined, frequent exacerbator phenotypes range from 13% to 47% representation, and the proportion rises as the degree of airway restriction increases. Frequent exacerbations result in a much higher chance of developing depressive symptoms, a deterioration in lung function, a worse quality of life, less physical activity, higher healthcare costs, and an up to threefold increase in mortality [28].

The GOLD ABCD assessment method, which integrates exacerbation history as well as symptom load to guide pharmacologic care, illustrates the importance of preventing exacerbations in the management of COPD. Patients with COPD who experience two or more exacerbations a year are considered "exacerbators". The interval between these exacerbations should be at least 4 weeks following the preceding exacerbation's conclusion of therapy, or 6 weeks in situations where no medication was administered at the time of the exacerbation's commencement. To be able to discern between the current incident and earlier treatment failures, this is required [8]. Exacerbations in COPD are not sporadic occurrences but occur in a high-risk window for recurrent exacerbations in the eight weeks after an initial exacerbation, which could be a therapeutic window for healthcare providers to perform preventative interventions. These appointments should center on areas like treatment regimen, inhaler technique, and measurement of symptoms [22].

Inhaled corticosteroids (ICS) are advised for patients who are "frequent exacerbators" based on a threshold of 2 moderate AECOPDs or 1 severe AECOPD in the prior 12 months, and the Canadian recommendations adopt a similar criteria for the frequent exacerbator phenotype [29]. The prognosis of COPD still depends, however, on the detection and tracking of exacerbations. As a result, a systemic biomarker that reflects the frequency of exacerbations in a COPD patient would be very helpful in forecasting the risk of exacerbations, either on its own or in conjunction with clinical outcomes [30]. Even though evidence-based recommendations can standardize and enhance care for many patients, the margins of advantage may not be very large [25]. According to current recommendations, a well-resourced healthcare system, and reasonably priced pharmaceuticals, patients in medium- and high-income nations may be given the finest treatments available [30]. Different COPD phenotypes might define their consequences for outcomes and day-to-day management, which could assist in individualizing care [28]. In the so-called non-proportional Venn diagram of COPD, some researchers have made recent efforts to quantify the various "faces" or phenotypes of the disease [6]. Cluster analysis has been used in a number of earlier research to identify various patient subgroups and determine their relationships to clinically significant outcomes, including mortality or projected mortality scores, hospital admissions, or frequency of exacerbations [7].

Frequent Exacerbator Phenotype

Different COPD phenotypes might define their consequences for outcomes and day-to-day management, which could assist in individualizing care [26]. In the so-called non-proportional Venn diagram of COPD, some researchers have made recent efforts to quantify the various "faces" or phenotypes of the disease [5]. In a number of earlier research, cluster analysis was used to define various patient subgroups and discover relationships between those categories and clinically significant outcomes, including death or projected mortality scores, hospital admissions, or frequency of exacerbations [26].

A significant portion of the COPD population, or 22%, has the frequent exacerbator phenotype, which is now recognized as a distinct clinical subgroup, is associated with worse clinical outcomes, and is stable across disease severities. This phenotype is defined as the occurrence of 2 COPD acute exacerbations within 1 year. These frequently occurring exacerbators should receive special attention in terms of research and care since they are more likely to result in higher hospital admissions, many comorbidities, and increased mortality [15, 31, 32]. The quality of life and life expectancy of COPD patients are seriously threatened by frequent exacerbations, making them a unique disease subgroup that demands improved diagnostic and treatment tools [31]. With a large increase in health care expenses and these costs increasing with the frequency and severity of exacerbations, hospitalizations for exacerbations of COPD have been projected to have an in-patient fatality of 10%, and the 4-year fatality following an exacerbation can be as high as 45% [26].

Unexpectedly, PPM (potentially pathogenic microorganisms) are typically present in the airways of COPD patients who experience regular flare-ups without an eosinophilic pro-file, and the application of ICS in these patients might raise the possibility of isolation of Pseudomonas aeruginosa (PA), bacterial exacerbations, or pneumonia. Further medical choices for these people are scarce. For individuals with a chronic bronchitis phenotype and a forced expiratory volume in one second (FEV1) that is less than 50% of their expected value, GOLD advises either the oral PDE4 inhibitor roflumilast or zithromax therapy. In fact, a number of clinical studies have shown that roflumilast enhances lung function and lowers the frequency of exacerbations in COPD patients, especially in those with a chronic bronchitis phenotype. Despite the fact that COPD patients have inflammation, there is no particular anti-inflammatory medication available for COPD [23].

It is also well known that the airway microbiome exhibits differential characteristics between various inflammatory endotypes and, more intriguingly, demonstrates a striking connection with patient mortality, even in the stable phase of COPD. Furthermore, despite variations among cohorts, recent studies have found a correlation between the makeup of the upper airway (sputum) microbiome during clinical stability and the frequency of exacerbations. One hypothesis is that a person's encounter with exacerbation events on a regular basis may help to destabilize the lungs' microbiome, leading frequent

exacerbators to have more dysbiosis than less frequent exacerbators [31]. Additionally, cluster studies have demonstrated the ability to separate patient subgroups based on their clinical and prognostic characteristics. Because the various clinical phenotypes of COPD would have diverse biological pathways connecting the comorbidities, the multimorbidity network of a patient with COPD would alter based on such phenotypes [31]. Significant comorbidities may have an effect on mortality and morbidity as well [8]. The prognosis of COPD is severely worsened, and extensive care is required in around 80% of people with the disease [23] due to co-occurring chronic illnesses and comorbidities.

In the first year following a COPD diagnosis, German real-world COPD patients had a high death rate (almost 20%) and a high number of comorbidities (mean 5.3) [33]. A specific frequent-exacerbator profile was discovered by the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort research. No matter how severe the condition was, this patient was more prone to exacerbations. They may be identified by a prior history of two or more exacerbations in the year before. Younger patients with severe COPD and a low likelihood of cardiovascular comorbidities and older people with moderate respiratory disease and a high prevalence of comorbidities, obesity, and inflammatory markers could be identified as two major clinical phenotypes with a consistent poor prognosis across multiple studies by a systematic review [4]. Even among those with low cardiovascular risk, the risk of cardiovascular events was higher overall during and in the 30 days after exacerbations of chronic obstructive pulmonary disease, emphasizing the need for exacerbation prevention and monitoring for cardiovascular events after exacerbations [33]. An extensive assessment for co-existing bronchiectasis, GORD, and sinus disease should be conducted in patients with "frequent exacerbations with emphysema" and "exacerbators with chronic bronchitis."

In individuals with severe COPD, the prevalence of bronchiectasis ranges from 4 to 72%. To continue managing this group, a high-resolution CT (HRCT) with expiratory pictures is essential. The HRCT detects mucus plugging, assesses the amount and location of bronchiectasis, and confirms its presence. In the event of an exacerbation, antibiotic treatment regimens for patients with confirmed bronchiectasis should be continued for a further 14 days and referred to physiotherapy and airway clearance education. Patients with recurring exacerbations in COPD-Bronchiectasis Overlap should also be examined because long-term macrolide treatment dramatically lowers the frequency of exacerbations [25]. Approximately 50% of people have bacterial illnesses, according to a 2020 comprehensive evaluation; however, 20% may have concurrent bacterial and viral infections [17]. The importance of bacterial pathogens such as Moraxella catarrhalis, Streptococcus pneumoniae, and Haemophilus influenzae has been well documented, and their prevalence supports the need for empirical antibiotic therapy in patients who have symptoms suggestive of an infective exacerbation. Numerous recent investigations have focused on the role that viruses play in AECOPD [22]. The frequent exacerbator phenotype of COPD still lacks validated biomarkers; thus, doctors may be able to identify at-risk COPD patients and implement effective preventative treatments with the aid of the discovery of simple, readily accessible systemic biomarkers linked to frequent exacerbations [6].

Biomarkers

Precision medicine is based on the idea that by differentiating between endotypes, we may focus medicines on patients who are most likely to benefit from them and potentially prevent iatrogenic side effects from unneeded therapy. The use of bioinformatics to identify patients with genetic predispositions or biomarkers has become a paradigm shift in medicine [5]. For the development of precision medicine techniques, a deeper comprehension of this alarming phenotype and the investigation of a novel biomarker for improved diagnosis are essential [31]. Therefore, a systemic biomarker that reflects the frequency of exacerbations in a COPD patient would be very helpful in predicting exacerbation risk, either on its own or in conjunction with clinical outcomes. For successful risk assessment and to provide individualized treatment for COPD, biomarkers are required [19]. The three categories of biomarkers—diagnostic, predictive, and prognostic—can be broadly categorized as laboratory, radiological, anatomical, physiological, or other measurable parameters that help distinguish one disease from others and may be used to predict how a disease will progress and/or how well a treatment will work [34].

An objective measurement that is easily accessible, reproducible, and externally verified and that indicates or confirms an exacerbation when linked to symptoms would be the ideal exacerbation biomarker. If recommendations recommend against using systemic corticosteroids for a patient who is aggravating and has low eosinophils, the trend to profile patients and their exacerbations for targeted treatment methods would lead to fewer documented episodes. The ideal exacerbation biomarker would be a readily available, repeatable, and externally verified objective test that, when linked to symptoms, either suggests or confirms an exacerbation [21].

In a sample of COPD patients, ex-smokers with normal lung function, and healthy non-smokers chosen from the ECLIPSE cohort, biomarker repeatability was evaluated at baseline and three months, with CRP demonstrating substantial variability. The most repeatable biomarker, fibrinogen, had weak correlations with 6-min walking distance, exacerbation rate, BODE (body mass index, airflow obstruction, dyspnea, exercise capacity) index, and MRC dyspnea score. CRP, fibrinogen, interleukin-6, and surfactant protein-D were significantly higher in those with exacerbations within 30 days of the 3-month visit compared to those who did not worsen [21]. Several inflammatory markers appear to represent longer-term disease activity.

In COPD, more than 100 distinct mediators, including many cytokines and chemokines, are produced, amplifying and sustaining lung inflammation. Neutrophil counts, C-reactive protein (CRP), tumor necrosis factor- α, interleukin (IL) 6 and IL-8, and fibrinogen are a few of the biomarkers suggested in stable and worsened COPD patients [35]. Although it is not a

good indicator of the risk of AECOPD, only fibrinogen has been recognized as a viable biomarker for use in clinical studies due to its repeatability and connection with factors of COPD severity and prognosis [6].

Eosinophilic Airway Inflammation

About 15 to 40% of COPD patients experience eosinophilic airway irritation, which is accompanied by increases in sputum eosinophils during exacerbations. Low eosinophil counts (2%) were linked to a higher risk of pneumonia when treated with ICS, and eosinophil levels may connect with patient responses to medicines and outcomes [1]. Sputum eosinophils need time to induce, and some patients were unable to provide sufficient samples. Given that there is some association between both tests within the same person, both in stable COPD patients and during exacerbations, detecting blood eosinophils is more practical and appears to be a proxy biomarker for sputum eosinophils. Blood eosinophil levels are also made available as a biomarker for predicting whether using an ICS will reduce the exacerbation rate [2]. A subset of patients who appear to be at higher risk of exacerbations and more likely to benefit from short-course corticosteroids appear to be identified by elevated blood eosinophil levels of 3% or 300 cells/mm3, but this characteristic varies and may be visible both when the patient is clinically stable and during an exacerbation [30]. The evidence that is currently available demonstrates that patients who are least likely to benefit from ICS may be identified by having a blood eosinophil level below 100/L, and individuals who are most likely to benefit from ICS can be identified by having a blood eosinophil count above 300/L [30].

Although it may not always be correlated with eosinophil levels present in the airways or lung parenchyma, high lung eosinophil levels may signify a unique host endotype with a Th2 phenotype that is responsive to corticosteroids [1]. Regardless of the severity of their COPD, about a third of people have eosinophilic COPD. The blood eosinophil count cut-off for eosinophilic COPD was greater than 150 cells/L (2%), according to research [36]. Because different studies have produced different results, the stability of BEC is still debatable. Inflammatory biomarkers were measured in peripheral blood throughout a three-year period of ECLIPSE research. In contrast to 16% of COPD patients who exhibited persistent systemic inflammation as shown by elevated levels of the tested markers, 30% of COPD patients at baseline did not exhibit any signs of systemic inflammation [21]. A number of biomarkers have been discovered that characterize particular clinical characteristics during exacerbations. Blood eosinophil counts of 300 cells/L, sputum eosinophil counts of 300 cells/L, and bacterial or viral airway colonization are all linked to an increased risk of exacerbations [36].

Neutrophilic Airway Inflammation

Because neutrophils are the most prevalent inflammatory cells in blood and sputum and because neutrophil proteases can mimic many of the characteristics of COPD in disease models like emphysema and mucus hypersecretion, COPD is primarily classified as a neutrophilic inflammatory disorder [19]. In the ECLIPSE research, elevated blood neutrophil levels were similarly linked to a high mortality and a frequent exacerbation phenotype [21]. Neutrophils primarily kill germs through phagocytosis, which is their primary function. Due to chemotactic factors, neutrophils move from the peripheral blood circulation toward inflammatory stimuli, where they get activated and release reactive oxygen species (ROS), lactoferrin, and proteinases [19]. The lung is essential for establishing immune defenses against all substances inhaled, including infections and particulate matter, because it serves as the body's interface with the outside world. Key innate immune response sentinels that control the phagocytic response to these infections are alveolar macrophages [36]. The majority of AECOPD cases are associated with infections, but up to 30% of cases are also caused by hidden heart ischemia, pulmonary thromboembolism, exposure to allergens or toxic compounds from the environment, and infections [26]. Through the breakdown of airway elastin, among other processes, excessive neutrophilic inflammation is connected to an increased frequency of exacerbations and rapid decreases in lung function. As shown by a decreased alpha diversity, frequent exacerbators have a more dysbiotic sputum microbiome [31]. Patients with COPD and healthy controls have been shown to have different microbial communities in their respiratory and gastrointestinal tracts, opening up a new avenue for research into potential biomarkers that could help further categorize patients with COPD, particularly those who exhibit the frequent exacerbators phenotype [31].

In COPD, elevated peripheral neutrophil counts are a sign of systemic inflammation, which has been linked to disease stage and comorbidities. It has also been shown that neutrophil activation markers, such as neutrophil elastase (NE), myeloperoxidase, and neutrophil extracellular traps in sputum and bronchoalveolar lavage, correlate with disease stage and neutrophil activation [19]. Inflammatory alterations in COPD are also characterized by an unbalanced proteolytic equilibrium between proteases (such as matrix metalloproteinase-9) and antiproteases (such as tissue inhibitors of metalloprotease) and an elevated level of oxidative stress. As a result, there may be more goblet cells, more mucus is produced, fibrosis develops, and lung tissue is destroyed. The secretory leukocyte protease inhibitor (SLPI) and 16-kDa club (Klara) cell secretory protein (CC16) can both be produced by the airway epithelium. Both inflammatory and microbiological features are present in SLPI. Evaluation of the protease/antiprotease balance may benefit from measuring MMP-9, TIMP-1, the ratio of these biomarkers, as well as SLPI. CC16 analysis of serum samples may be utilized to determine whether oxidative stress is present [23].

Bacterial Infections

About 50% of COPD exacerbations are brought on by bacterial infections. Currently, procalcitonin and C-reactive protein (CRP) are employed as indicators to start antibiotic therapy. In COPD acute exacerbations, eosinopenia is a valuable guide for when to begin antibiotic treatment [37]. While eosinophils mediate a predominately TH2 response, which previous groups have suggested may limit acute phase response, CRP is a crucial acute phase protein that is most significantly connected with

bacterial infections. Procalcitonin (PCT) assays are now widely available as a result of recent advancements in laboratory testing, and using these levels as a screening tool for a bacterial component of COPD exacerbations could result in a reduction in the use of antibiotics. According to some studies, greater amounts of apolipoprotein-AII, C-reactive protein, and macrophage inflammatory protein-4 are associated with greater relative dangers of lung injury, whereas greater degrees of the soluble vascular cell adhesion molecule and decreased amounts of myeloperoxidase predict resistance [38].

Patients with COPD have more CD8+ T cells in their airways than healthy people. These cells are thought to contribute to the pathophysiology and progression of severe COPD through inflammation, the breakdown of the alveolar wall, and small airway fibrosis [23].

NLR, PLR and EBR

Other markers seen in standard blood analysis, such as the NLR, the platelet/lymphocyte ratio (PLR), and the eosinophil/basophil ratio (EBR), have been suggested for use as indicators of the risk and severity of ECOPD as well as prognostic indicators of hospital mortality from ECOPD in recent research [6, 39].

The ratios of neutrophils, platelets, and lymphocytes are useful tools for indirectly assessing both inflammatory states and cell-mediated immunity since inflammation causes an increase in neutrophil and platelet counts along with a drop in lymphocyte counts. New inflammatory markers of prognostic importance in a variety of inflammatory disorders include hematological indexes of inflammation such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Their values are greater in COPD patients than in the general population, according to several studies, and they become even higher after a COPD exacerbation. The highest increased values have been reported in the presence of bacteremia, and higher values have been noted in acute vs. chronic situations. Higher NLR values have also been observed in acute as opposed to chronic diseases, with the presence of bacteremia being associated with the highest values [39].

The NLR upon admission is strongly related to the likelihood of a number of adverse outcomes while receiving hospital care, including short-term mortality up to 90 days in AECOPD, according to a new systematic review and meta-analysis. In order to determine the potential clinical value of the NLR, either alone or as a component of a composite prediction model, in early risk stratification and therapy decisions in patients with AECOPD, additional prospective studies examining other biomarkers over longer follow-up periods are required [24, 29].

Oxidative str

The proinflammatory transcription factor nuclear factor-B (NF-B), as well as signaling molecules like Ras/Rac, p38 mitogen-activated protein kinase (MAPK), Jun-N-terminal kinase (JNK), PI3 kinase, and protein tyrosine phosphatases, are all activated by oxidative stress. These intracellular signaling pathways then result in the production and release of these inflammatory mediators. Particularly in airway epithelial cells and macrophages, the expression and activation of NF-B are enhanced in COPD, and ROS is the activator. The inactivation of 1-antitrypsin by oxidative stress improves elastolysis and boosts neutrophil elastase activity, as well as activating transforming growth factor (TGF)-β signaling, upregulating matrix metalloproteinase (MMP)-9 expression, degrading elastin fibers, and breaking down elastin fibers [34].

Conclusion

The future accuracy of risk classification and patient treatment recommendations could be greatly improved by the discovery of novel biomarkers. While new biomarkers will be found and validated in sizable study COPD populations, adhering to best practice recommendations, diagnosing clinical "frequent exacerbator phenotypes," finding traditional exacerbator 'risk factors, colonization, and proper management of comorbidities may be the best ways to treat this heterogeneous and complex disease.

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