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REVIEW

Analyses of Factors Associated with Acute Exacerbations of Chronic Obstructive Pulmonary Disease: A Review

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Abstract: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is the exacerbation of a range of respiratory symptoms during the stable phase of chronic obstructive pulmonary disease (COPD). AECOPD is thus a dangerous stage and key event in the course of COPD, as its deterioration and frequency seriously affects the quality of life of patients and shortens their survival. Acute exacerbations occur and develop due to many factors such as infection, tobacco smoke inhalation, air pollution, comorbidities, airflow limitation, various biomarkers, history of previous deterioration, natural killer cell abnormalities, immunoglobulin G deficiency, genetics, abnormal muscle and nutritional status, negative psychology, and seasonal temperature changes. There is relatively limited research on the impact of the role of standardized management on the alleviation of AECOPD. However, with the establishment of relevant prevention and management systems and the promotion of artificial intelligence technology and Internet medical approaches, long-term effective and standardized management of COPD patients may help to achieve the quality of life and disease prognosis in COPD patients and reduce the risk of AE.

Keywords: chronic obstructive pulmonary disease, acute exacerbation, related risk factors

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease characterized by high prevalence, disability, and mortality. Acute exacerbation (AE) of chronic obstructive pulmonary disease (AECOPD) is defined as the worsening of a series of respiratory symptoms, such as dyspnea, increased cough, and sputum, in the presence of stable COPD within 14 days of medication adjustments.[1] COPD is one of the four most common diseases globally, with an annual incidence of approximately 12% and a global prevalence of 9%-10% in people ≥40 years of age.[2,3] It became the top three causes of global death in 2016 and was ranked as the fifth leading cause of death in China in the same year. A large epidemiologic survey in 2017 showed that COPD numbered about 300 million people globally, with a prevalence rate of 3.9% in the whole population and became the fourth leading cause of death in America, accounting for 6% of all-cause deaths globally.[4,5] Further, the disease burden is expected to increase in the coming decades.[6,7] Additionally, COPD showed a prevalence of 8.6% and 13.7% in adults over 20 and 40 years old, respectively, based on a 2018 study by the China Pulmonary Health (CPH). The number of individuals with COPD in China is estimated at approximately 100 million.[7] As the population ages and exposure to related risk factors gradually increases, the prevalence of COPD will continue to increase and the age of onset will gradually decrease, causing a major health burden and economic pressure on society and families, rendering COPD one of the major public health problems globally.

The literature suggests that approximately 25% of patients with COPD exhibit declined lung function, attributable to AE.[8] Patients with COPD experience AEs 0.5–3.5 times per year.[9] As a dangerous stage and key event in the course of COPD, AE can worsen disease progression and comorbidities, seriously affecting the patients' quality of life and shortening their survival. Patients with frequent AEs (≥2 times/year) experience a more rapid decline in lung function and have a worse prognosis, and an increased risk of death than those with infrequent AEs (<2 times/year).[10] It has been

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shown that patients with COPD hospitalized for AEs have a mortality rate of 25% and 65% at one year and five years, respectively.[11] Approximately 2%-19% of hospitalized AECOPD patients are ultimately transferred to the Intensive Care Unit (ICU),[12–15] and the ultimate in-hospital mortality rate for such patients is 12–24%,[16–18] with 35% of surviving patients expected to be readmitted to the hospital 3 months after discharge.[19,20] Owing to various factors, such as the large population of people with COPD in China and their widespread distribution, limited awareness of the disease among most patients, and unstandardized diagnosis and treatment of COPD primary medical care, most patients are unable to recognize AE at an early stage and cannot receive timely and effective standardized treatment and management. To this end, China has gradually implemented a hierarchical system for COPD diagnosis and treatment by formulating relevant work plans and promoting health programs to improve the early diagnosis and management of COPD at the primary level.

The 2023 edition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) for the treatment of COPD states that the goal of AE treatment is to minimize its negative effects and prevent its recurrence. Early prevention, timely detection, and aggressive interventional treatment can significantly reduce the readmission and death disability rates of patients with COPD, significantly shorten their lost life years, and substantially increase their quality of life after hospital discharge. Therefore, understanding the risk factors that may cause AE and strengthening the prevention of AE can improve the outcomes of COPD treatment and reduce the occurrence of adverse events during the course of the patients' illnesses.

Risk Factors
Infection
Bacterial infection
Bacterial infections are generally considered to be an important factor in the exacerbation of COPD, and bacteria can be isolated from sputum specimens of 40−60% of patients with AECOPD.[21,22] The occurrence of AE involves a variety of bacterial pathogens, with common bacterial pathogens including Haemophilus influenza, Moraxella catarrhalis, streptococcus pneumonia, pseudomonas aeruginosa, etc.[21] However, there are differences in the prevalence of bacteria among different countries, with Pseudomonas aeruginosa, Klebsiella pneumoniae, and Haemophilus influenzae being more common in China,[23] and Haemophilus influenza, Pseudomonas aeruginosa, and moraxella catarrhalis being more common in Australia and other countries.[24] The bacterial infection leads to neutrophil and interleukin-8 (IL-8) production and increased production of matrix metalloproteinases (MMPs) by neutrophils and macrophages, which promote disease progression by participating in the pulmonary inflammatory response, airway remodeling, and development of emphysema.[25–28]

The strains colonizing the airways in the stable phase of COPD highly overlap with those isolated in the acute phase. However, strain population changes in the acute phase are more strongly associated with the degree of respiratory infection and systemic inflammatory response than those in the stable phase.[29] Although bacterial infections are associated with poor clinical outcomes in cases of COPD, there is a quantitative relationship between levels of airway inflammatory markers.[30] A microbiota homeostasis generated by the balance of bacterial migration and elimination already exists in the lungs; however, during AE, there is ciliary dysfunction in the lungs, increased mucus secretion, and enhanced bacterial migration, and the original airway flora balance is disrupted, leading to bacterial proliferation beyond the clearance capacity of the respiratory tract.[31] Based on this, it may be hypothesized that AE triggers a homeostatic imbalance in which the microflora attacks the host's respiratory and systemic immune systems. This therefore suggests that bacterial infections are unidirectionally associated with AE. However, regardless of the direction of the association, most clinical studies still find traces of bacterial infection in samples from respiratory secretions or tissues of patients in acute exacerbation.[24,32,33]

Viral Infection
Advances in detection technology have shown that viral infections are more closely associated with AE than bacterial infections.[34–37] Additionally, 40−80% of AE cases with high-frequency hospitalization are attributed to viral infections.[38] Common viruses isolated from the secretion specimens of patients with AE include rhinovirus, coronavirus, influenza virus, parainfluenza virus, adenovirus, and respiratory syncytial virus,[21] with rhinovirus, influenza virus, and respiratory

syncytial virus being the most common.[39] In addition, there are geographical differences in the prevalence of respiratory viruses; for example, small RNA viruses are most common in the West, while the influenza viruses are most common in the East (Asia).[40]

Among these respiratory viruses, rhinoviruses are thought to play an important role in the occurrence of AE.[41,42] When the body is infected with rhinovirus, the production of interferons and neutrophils is reduced, leading to the occurrence of viral AE, which eventually aggravates the physical changes and symptoms in the patient's body.[43] In addition, the impact of the 2019 novel coronavirus (2019-nCoV) pandemic on patients with COPD cannot be ignored. The 2019-nCoV promotes viral binding to the angiotensin-converting enzyme 2 (ACE-2) receptors and cell entry by carrying envelope burst proteins. As mRNA expression of ACE-2 receptors is increased in patients with COPD, the 2019-nCoV and other coronaviruses have a deleterious effect on respiratory health and pose a significant threat to patients with COPD.[44]

In addition to common respiratory viral infections, human immunodeficiency virus (HIV) infections increase the risk of AE by accelerating lung aging and promoting chronic lung inflammation, oxidative stress, immune activation, and alteration of lung microbiota.[45,46] HIV attacks the human immune system by targeting CD4+T lymphocytes, resulting in decreased immune function and a significant increase in the risk of respiratory tract infections. One study found that HIV carriers and patients with COPD and low CD4+ T lymphocyte counts had >4-fold higher risk of AE compared to patients not infected with HIV.[47]

Respiratory symptoms, length of hospital stay, and systemic symptoms were also significantly worse in patients with AE and viral infections, compared to those without viral infection.[36,48] Some viruses are still detectable in patients with stable COPD, owing to the presence of lung microbiota. However, the detection rates of viruses and bacteria in patients with AECOPD was significantly higher than those in the stable phase.[49] This finding demonstrates the important role of viral infections in the development of AE. Acute viral infections increase airway reactivity and airway epithelial damage, causing the development of airway inflammatory edema, thus worsening airflow obstruction, which, in turn, leads to systemic inflammation.[50–52]

In most cases of AECOPD, mixed viral and bacterial infections occur more frequently than single viral or bacterial infections. Approximately 73% of patients with viral infections develop secondary bacterial infections within 14 days of the onset of worsening symptoms, suggesting that bacterial infections may be more important in the later stages of viral-induced deterioration.[53] The percentage of bacterial and viral detection was positively correlated with the levels of hypersensitive C-reactive proteins (CRP), leukocytes, and other biological markers.[35,54] Therefore, clinical practitioners' can determine the AE status of patients with COPD by testing the levels of the corresponding biomarkers.

Tobacco Smoke Inhalation

Tobacco smoke inhalation is widely recognized as an essential factor in the development and progression of AECOPD. GOLD 2023 shows that smoking is a major risk factor for COPD, accounting for more than 70% of the total factors in high-income countries, whereas in lower-middle-income countries, smoking accounts for 30−40% of the total factors. A CPH Study states that the incidence of COPD is 13.7% in smokers, 10.9% in former smokers, and 6.2% in never-smokers,[7] and significantly higher in smokers compared to non-smokers. Tobacco smoke is the main risk factor for frequent exacerbations in patients with COPD and can enhance the risk of hospital visits or readmissions due to AE.[55,56] Research at the Nantong University demonstrated that active smokers with AE had more severe clinical symptoms, impaired lung function, and worse follow-up treatment outcomes, compared to non-smokers.[57] Most AE patients with a smoking history of >30 pack-years use non-invasive ventilation (NIV), which increased during hospitalization.[58] Notably, smoking cessation significantly reduced COPD readmission rates.[59]

Tobacco smoke causes immune deficiency, impairs immune homeostasis and defense mechanisms, and has a reverse effect on the antimicrobial signaling cascade, which influences inflammatory response to microorganisms.[60] Another study showed that tobacco smoke affects intrapulmonary mechanical barriers (such as intraepithelial cells and cilia) by decreasing the frequency of ciliary oscillations and inducing squamous metaplasia, leading to a decrease in the number of ciliated cells and an increase in the number of cup cells and submucosal glands, causing excessive mucus production and favoring the growth of microbial pathogens,[61,62] which indirectly proves the correlation between tobacco smoke inhalation and AE.

Air Pollution

Outdoor Air Pollution

Air pollution is also a crucial risk factor in the course of COPD.[7,63–65] The prevalence of COPD in an PM2.5 exposed group was significantly increased by two-fold compared to that in the general and never-smoking populations.[7] Additionally, there was a positive correlation between airborne fine particulate matter concentrations and COPD incidence, hospitalizations, and mortality.[66–68] A study that selected air samples from seven randomized areas in the Guangdong Province of China found that particulate matter concentrations were negatively associated with some lung function indicators (FEV1, FVC, and FEV1/FVC).[69] In addition, increased PM2.5 exposure was associated with increased COPD hospitalizations and mortality;[67] for every 10 μg/m^3 increase in PM2.5, patients with COPD had a 2.5% increased risk of emergency department visits and hospitalizations for AE.[66] Several regional studies in China reported that airborne pollutants may increase the occurrence of AE.[70–74] Part of this theory suggests that air pollutants can trigger AE by damaging the airway epithelium and macrophages, thereby affecting ciliary clearance, or by inducing alveolar inflammation and disturbing respiratory homeostasis.[71,74,75] It is evident that the influence of outdoor air pollution in the development and deterioration of COPD should not be underestimated.[67,76–78]

Indoor Air Pollution

Household biomass exposure was correlated with an increased risk of COPD, with an additive effect and no significant sex differences.[79] In recent years, the prevalence of COPD in females has gradually become equal to that of males, with 80% of non-smoking COPD patients being female.[80,81] Exposure to household biomass in real life is common in the female population. Particulate matter, CO, SO_2, NO_2, and other components of biomass fumes have irritating effects on the respiratory tract and are strongly oxidizing. This can cause destructive changes in the airway and alveolar structure, inducing cupped cell hyperplasia of the airway mucosa and excessive secretion of airway mucus, resulting in persistent airway hyperreactivity and respiratory inflammation.[82,83] The clinical signs of AE from biomass smoke were slightly different from those of tobacco smoke. Patients with COPD under former exposure have a less emphysematous phenotype and more often present with a small airway disease phenotype and more clinical symptoms such as cough, sputum, and shortness of breath, often with comorbidities such as bronchial asthma or allergic rhinitis, which aggravates clinical symptoms in patients with AE.[83–85]

Comorbidities

More than 80% of patients are estimated to have at least one chronic comorbidity, which can affect patient quality of life and disease prognosis, increase the risk of AE, and reduce patient survival.[86–89] The Charlson Comorbidity Index (CCI) was first proposed in 1987, and current research suggests that CCI can be an independent risk factor for AE or death.[90] Patients with COPD had lower survival rates and higher CCI scores, and patients with CCI scores ≥5 (patients with ≥4 comorbidities) had five or more times the mortality rate than did patients without comorbidities.[91] A randomized controlled trial of elderly patients with COPD after hospital discharge also found that the risk of death, length of stay, and readmission increased in COPD populations with a higher CCI.[92] In addition, the number of comorbidities was significantly associated with the risk of readmission in patients with COPD; that is, each additional comorbidity was associated with a 47% higher risk of readmission.[93]

COPD comorbidities mainly involve the cardiovascular system, respiratory system, mental status, or endocrine metabolism, and include ischemic heart disease, coronary artery disease, heart failure, pulmonary hypertension, dyslipidemia, lung cancer, pulmonary fibrosis, anxiety and depression disorders, osteoporosis, malnutrition, and diabetes.[89,94] Among them, cardiovascular disease is more common and at a higher risk than other systemic diseases.[87]

Severe pulmonary hypertension is a complication of advanced COPD. Long-term pulmonary hypertension can stimulate proliferation of the vascular smooth muscle layer, leading to thickening of the pulmonary artery, which is currently being evaluated as a marker of pulmonary vascular disease.[95] The mechanism of AE caused by pulmonary artery thickening may be related to cardiac systolic and diastolic dysfunction, a pulmonary parenchymal disease with the absence of a capillary bed, etc.[96] The ratio of pulmonary artery diameter to aortic diameter (PA: A) correlates with right ventricular hypertrophy, right ventricular enlargement, and reduced right ventricular function; thus, cardiac-pulmonary

interactions are critical during acute exacerbations.[97] Most studies have shown a significant increase in AE risk when the PA: A ratio exceeds a threshold of 1.[98] Pulmonary artery thickening (PA: A>1) is closely associated with AE and predicts the development of AECOPD.[96,97]

Chronic Bronchitis (CB) is also a more common comorbidity. A previous study showed a significant increase in annual AE rates and hospital admissions in COPD patients with combined CB and a higher probability of combined CB in patients with GOLD grade 2–4.[99] CB is strongly associated with annual AE rates, adverse events, and accelerated disease progression in patients with COPD.

In addition, patients with chronic diseases are prone to electrolyte disorders, and hyponatremia is a common electrolyte disorder in patients with AECOPD.[100,101] Hyponatremia causes a decrease in the body's serum osmolality, which leads to the development of pulmonary edema and pleural effusion by modulation of the transient receptor potential ion channel 4, further exacerbating COPD.[102,103] Most studies have concluded that the severity of hyponatremia severity is associated with longer hospital stays, higher mortality rates, higher readmission rates, and increased need for post-discharge care in patients with AECOPD, and can be used as a predictor of the occurrence of an adverse clinical outcome in AECOPD.[104–106]

Airflow Limitation

The primary pathophysiological alteration observed in individuals with COPD is the restriction of airflow. This is primarily caused by inflammation in the small airways, the accumulation of mucus, and the development of fibrous tissue, all of which contribute to an increase in resistance within the small airways. In cases of emphysema, the normal ability of alveoli to exert a pulling force on the small airways is diminished, along with a significant reduction in the elastic retraction force of the alveoli. Consequently, this leads to obstructive ventilation dysfunction, resulting in persistent limitations in expiratory flow, the retention of carbon dioxide within the lungs, and an adverse impact on the body's metabolic processes and gas exchange function, particularly during AE.[107] The FEV1%Pred, which serves as a lung function indicator, is frequently employed to assess the extent of airflow limitation in individuals diagnosed with COPD. Based on the decline in FEV1%Pred, the GOLD Grades categorize patients into four distinct grades. Research conducted in Japan revealed that COPD patients experiencing AE exhibited more severe FEV1 impairment, higher GOLD Grades, and elevated modified Medical Research Council (mMRC) scores compared to those without AE.[108] The presence of high airflow limitation and low FEV1 has been found to potentially elevate the likelihood of recurrent AE. FEV1 can serve as an independent prognostic factor for AE, as well as being associated with predicting adverse clinical outcomes such as mortality and the need for mechanical ventilation in individuals with COPD. Furthermore, additional research has indicated a positive correlation between the frequency of AE and the decline in FEV1, suggesting a mutually causal relationship between airflow limitation and AE.[109,110] Hence, in the diagnosis and management of COPD, consistent utilization of bronchodilators and regular monitoring of pulmonary function indicators assume paramount significance.

Biomarkers
Abnormal Levels of Eosinophils

It is well known that an important part of the inflammatory response in COPD is the activation and aggregation of neutrophils, however, in recent years several studies have shown that eosinophilic inflammation also plays an essential role. A total of 10%-40% of COPD patients with have eosinophilic airflow limitation.[111] Since induced sputum is highly correlated with the proportion of eosinophils in the peripheral blood, increased blood eosinophils may be somewhat predictive of sputum eosinophils.[111,112] Studies have shown that lung function is worsens and the risk of AEs is increased when sputum and peripheral blood eosinophils levels are elevated.[112–114] The risk of AE is increased 1.85-fold when the percentage of peripheral blood eosinophils is more than 2%, the risk of AE is higher in patients with moderate to severe COPD with blood eosinophil counts ≥150 cells/μL, and the risk of AE is increased 3.21-fold with blood eosinophil counts ≥340 cells/μL.[111,113,115,116] There is a degree of eosinophilic airflow limitation in any period of COPD.[117,118] High level of eosinophils in the stable phase may predict an increased risk of progression,[113] however, the proportion of eosinophils in AE is more than 30 times higher than that in the stable phase.[119] Eosinophils regulate type 2 immune

response, and when eosinophils are recruited, they can mediate a stronger inflammatory response, activating the secretion of various cytokines and cytotoxic granules that can cause airway damage.[120] Eosinophilis has also been associated with a variety of disorders such as metaplastic, infectious, and rheumatologic disorders, which may also contribute to the development of AEs and increased readmission rate.

Moreover, a low eosinophil status predicts a decline in lung function and an increased risk of mortality due to critical illness. It was positively correlated with the length of hospitalization and mortality within 12 months in patients with AECOPD.[121] In contrast to eosinophilia, low levels of eosinophilia indicate that the body is susceptible to infection and should be treated with antibiotics to prevent infection.[122]

Vitamin D (VitD) Deficiency

Several studies have confirmed the prevalence of low serum VitD levels in patients; that is, the higher the severity of COPD, the lower the serum VitD levels.[123,124] The risk of disease deterioration is three times higher in COPD patients with VitD deficiency than in those without.[123] Although Vit D supplementation does not increase the risk of upper respiratory tract infections, it has a protective effect against severe exacerbations in patients.[125] Low vitamin D levels increase the risk of frequent respiratory infections, and reduced levels of VitD, an immunomodulatory effector in the body, can affect the body's immune capacity, increase airway smooth muscle hyperplasia, and aggravate airflow limitation.[123,126,127]

High Fibrinogen Levels

Fibrinogen (FIB) is the primary plasma protein produced by hepatocytes and serves as an acute-phase reactant in the human body, with its expression being upregulated in response to inflammatory mediators. In patients with COPD, the occurrence of airflow limitation, thromboembolism, emphysema, and atherosclerosis are more prevalent when FIB levels exceed 4g/L.[128,129] Several studies have demonstrated a negative correlation between FIB level and FEV1, as well as a positive correlation with AE rate, readmission rate, exercise tolerance, and COPD mortality. This suggests that FIB level can serve as a biomarker for predicting the failure of NIV in COPD patients.[129–132] Furthermore, a meta-analysis consisting of 45 studies further supports the notion that higher FIB concentration is associated with greater severity of COPD.[133] Mannino et al conducted a study on the relationship between FIB level and mortality, revealing that COPD mortality significantly increased when FIB levels reached or exceeded 4.03g/L.[134] Another consistent study also indicated that elevated level of FIB (≥3.5g/L) was linked to increased rates of readmission within one year and higher mortality rates within three years.[131] Currently, FIB is recognized as one of the most diverse inflammatory biomarkers in the progression of COPD.[129,135–137] It possesses the potential to predict individuals at a heightened risk of COPD exacerbation and mortality, while also offering a less invasive means of measurement. Consequently, the Food and Drug Administration (FDA) has acknowledged FIB as a valuable tool in the management of COPD.[137]

Hyperuricemia

Uric acid (UA) is a byproduct of purine metabolism that can generate reactive oxygen free radicals in the human body. Consequently, UA serves as a potential indicator of oxidative stress.[138] Hyperuricemia has been linked to systemic inflammation and cardiovascular incidents. Hypoxia caused by exacerbation of COPD can stimulate increased UA synthesis.[139] Moreover, increased blood UA level can impair renal function, disrupt the prognosis of hypercapnic AECOPD patients, and increase the risk of cardiovascular events, and exacerbate the burden of comorbidities in AECOPD patients.[140] According to the study's findings, individuals with stage GOLD 3–4 and hypoxemia had greater levels of serum UA than patients with stage GOLD 1–2 and non-hypoxemia.[141,142] Furthermore, it was observed that there existed a positive correlation between the elevation of serum UA level and the deterioration of lung function, an increased susceptibility to adverse clinical events (AE), and the serum UA level upon admission could be utilized as a standalone prognostic indicator for mortality within a 30-day timeframe.[143,144] Consequently, given its accessibility and affordability, serum UA can be regarded as a valuable biomarker for assessing the severity of COPD in the clinic.

Previous Deterioration History

A history of disease progression is one of the most influential risk factors for future exacerbation, readmission, and death.[145] The higher the risk of AE, the more frequent the deterioration and increased mortality of patients. Therefore, a history of previous deterioration can be an important independent predictor of frequent COPD deterioration.[146–150] In a follow-up trial study of 73,106 patients selected for the first hospitalization for COPD, the risk of re-AE was found to increase approximately three times after experiencing a second exacerbation compared to the first exacerbation population; when patients experienced a tenth severe exacerbation, the risk of re-AE increased to 24 times. Mortality after the second exacerbation was 1.9 times higher compared to after the first exacerbation, and up to 5 times higher after the tenth exacerbation.[151] Notably, 85.5% of patients with a history of AE in the previous year will experience one AE in the following year.[148] As each AE occurs, the median survival time between exacerbations decreases, and the patients' quality of survival and health status gradually decline after each AE, with the risk of re-AE peaking three months after discharge.[151]

Natural Killer (NK) Cell Abnormalities

As an essential component of the body's innate immune system, NK cells are involved in the mechanisms of airway remodeling and emphysema, regulating antiviral, antitumor, and immune processes in the body. Therefore, abnormal NK cell status in patients with COPD substantially increases the risk of AE. Abnormal NK cell status can lead to an inflammatory response and tissue damage in the body, affecting a patient's stability and susceptibility status.[152,153] A majority view is that patients have insufficient expression of inhibitory CD94 receptors on the surface of NK cells, which are the main sources of pro-inflammatory cytokines and granzymes. Notably, the expression and release of granzyme B and perforin are increased in patients with COPD, with a consequent increase in NK cell-killing activity.[154] A study has found that the NK cell-killing activity was significantly enhanced in alveolar lavage fluid specimens from patients with COPD,[155] which supports the above view. Additionally, other study has reported that the proportion of NK cells is higher in patients with severe airway obstruction, frequent AE episodes, and poor nutritional status.[156]

Smoking, the number of AE episodes, and certain viral infections affect NK cell stability,[152,156,157] and FPR3 expression levels in NKT cells are low in former smokers. Insufficient FPR3 expression is directly related to severe airflow limitation in COPD.[158] Therefore, abnormalities in the NK cell status not only directly affect the stability of the respiratory system itself but also indirectly affect the course of COPD by altering other risk factors. Recent studies have indicated that NK cells may serve as specific biomarkers of AECOPD.[155–157] As NK cell research continues to advance, it is expected that NK cells or NKT-like cells will be used as therapeutic entry targets to interfere with cytotoxicity and related inflammatory mediator production.

Immunoglobulin G (IgG) Deficiency

The relationship between nonspecific and acquired immunities and the onset and progression of chronic obstructive pulmonary disease (COPD) is evident.[159] B-lymphocytes play a crucial role in the mediation of humoral immunity, which serves as a prominent immune defense mechanism against infections. Immunoglobulins, as integral constituents of the humoral immune response, hold significant importance.[160] Immunoglobulins, as integral constituents of the humoral immune response, hold significant importance. IgG is the predominant serum immunoglobulin that actively engages in the process of phagocytosis, thereby facilitating the eradication of a diverse array of viruses, bacteria, and toxins within the human body.[161] The most common cause of AE is infection. The compromised immune system of the patients heightens the susceptibility to infection, consequently leading to detrimental consequences on the patients' development and prognosis through recurrent infections.[162] Moreover, 25% of patients with COPD have humoral immunodeficiency and reduced IgG levels and are prone to hypogammaglobulinemia (<7.0 g/L).[159,161] This presentation increases the risk of COPD hospitalization by 30%, the risk of future hospitalization by 60%, and the risk of AE by 50%-100%.[159,161,163] Additionally, it positively correlates with the risk of death in hospitalized patients with COPD.[164,165] As the number of AE increased, the proportion and frequency of hypogammaglobulinemia also increased. In COPD patients are more than two AE, hypogammaglobulinemia increased to 35.9%.[161,163] Furthermore, the presence of IgG deficiency is associated

with an elevated susceptibility to non-respiratory ailments, including allergic and autoimmune diseases, as well as cardiovascular system disorders. This deficiency also heightens the likelihood of complications and indirectly exacerbates the risk of AE. Consequently, the implementation of immunoglobulin replacement therapy among individuals with IgG deficiency may effectively mitigate the occurrence of AECOPD within clinical settings.

Genetics

To date, over 20 genes have been identified as significantly linked to the status of COPD.[166] Mannose-Binding Lectin (MBL), a protein that activates the complement system in the body to eliminate pathogens, holds a crucial position in the immune system.[167] The presence of MBL2 polymorphism is associated with inadequate levels of serum MBL, and defects in the MBL gene resulting from MBL2 polymorphism impact the frequency of recurrent respiratory tract infections and the duration of hospitalization for individuals with COPD.[168,169] A comprehensive study comprising a sample size of 1796 individuals was conducted to explore the association between MBL and the susceptibility to COPD exacerbations. The results indicated that individuals with COPD who possessed the MBL2 gene demonstrated a diminished likelihood of experiencing AE, a heightened variety of lung microorganisms, and decreased levels of airway obstruction.[170] Furthermore, three smaller studies have demonstrated that polymorphisms in the human MBL2 gene, leading to MBL deficiency, are associated with a heightened susceptibility to AE and a less favorable prognosis for the ailment. Conversely, studies have indicated that increased level of serum MBL are associated with improved survival rates among patients with COPD and a reduced risk of exacerbations.[171–173]

Furthermore, several studies have demonstrated the involvement of human hedgehog interacting protein (HHIP) in the process of lung development, whereby diminished level of HHIP result in lung hypoplasia.[174] Additionally, the presence of single nucleotide polymorphisms within HHIP has been linked to an increased susceptibility to COPD, airflow limitation, and alterations in lung function.[175] Moreover, a prospective study conducted across 46 clinical centers in 12 countries (n=1719) observed a significant correlation between genetic variants of HHIP and the occurrence of moderate to severe AE within the past year.[176] However, the current investigation into genetic factors linked to AECOPD is still relatively limited in its scope of examining the entire genome. Our comprehension of the genetic factors that contribute to AECOPD remains restricted, thus requiring further exploration of a wider array of genetic variations.

Muscle and Nutritional Status Abnormalities

The most common extrapulmonary manifestations in COPD patients are muscle disorders and wasting, which can become more severe as the patient's condition worsens.[177] Malnutrition leads to abnormalities in muscle mass and function, with a significant positive correlation between COPD progression and adverse events, which can have a significant impact on the respiratory system and the whole body.[177–180] BMI is a common clinical measure of a patient's nutritional status, and studies have shown that a BMI <20 kg/m^2 can be an independent risk factor for mortality in partial respiratory disease.[181] Patients with COPD who are malnourished or potentially malnourished have increased readmission rates, length of stay, other comorbidities, and four times increased risk of death after 2 years.[182–185]

Patients with COPD are prone to nutritional events.[186] The clinical outcome of Malnutrition leads to dysfunction of the respiratory muscles and diaphragm, resulting in decreased lung function, increased dyspnea, limitation of daily activities, and muscle atrophy or weakness. Damage to the respiratory muscles and surrounding muscle groups is significantly correlated with the severity of the disease at the time and frequency of admission, and in severe cases, respiratory failure or more complex cachexia.[177,179]

Other Factors
Negative Mentalities
Patients with depression or anxiety are at an increased risk of COPD progression and death.[187–189] In a clinical study of 376 patients with AECOPD, the prevalence of depression at admission was found to be 44.4%. Furthermore, patients with COPD and depression had lower survival rates, longer hospital stays, and a higher disease burden at one-year follow-up.[190] COPD patients with high depression and anxiety (anxiety > 50, depression > 53) were at higher risk of

AE.[191] Depression is significantly associated with poorer social functioning and economic status, low family or marital happiness, and low educational attainment.[93,190] Some studies have suggested that the pathological mechanisms of negative psychological states effects on AE, among others, may be related to systemic inflammatory responses or neuronal necrosis in the hippocampus.

Seasonal Temperature Variations

A global-scale study of COPD exacerbation and seasonal correlation indicated a nearly two-fold increase in AE risk in winter compared to summer. AE was common between December and February in 9% of patients in the northern region, compared to 5% in summer, and 12% of patients in the southern region had higher AE rates between December and February, compared to 7% in summer.[192] Excluding the tropic regions, COPD has a higher AE rate in winter, and the seasonality of AE is more pronounced. Another Spanish regional study showed that COPD was particularly prevalent in winter, followed by autumn, spring, and summer; additionally, the number of hospitalizations also increased with lower temperatures, with a 4.7% increase for every 1 °C drop in temperature,[193] supporting the effect of seasonal temperature changes on AE.

Conclusions

AE is the outcome of multiple risk factors, including individual and environmental factors, which act together in the body to trigger AE (Figure 1, Table 1). The majority of these AE are initiated by respiratory pathogens, including viruses and bacteria. Currently, global research predominantly concentrates on the microscopic level, delving extensively into the
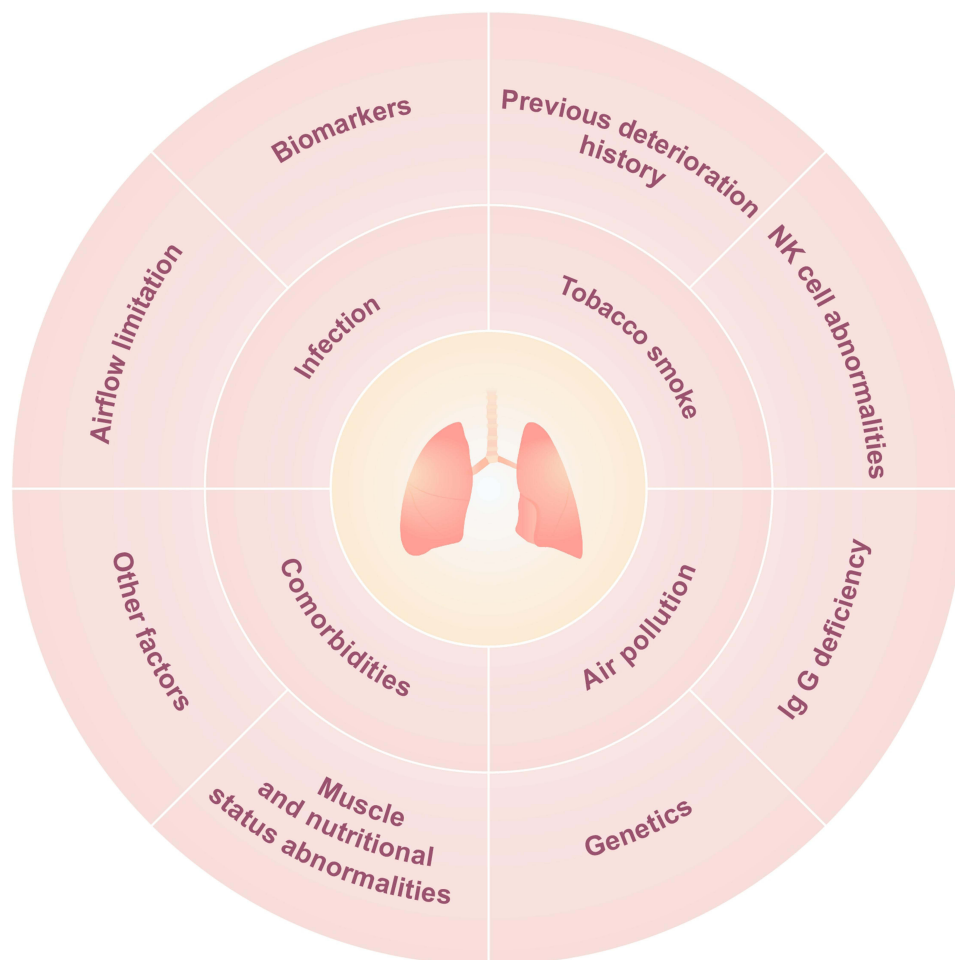
Figure 1 Diagram of risk factors associated with chronic obstructive pulmonary disease.

Table 1 Risk Factors Associated with Acute Exacerbation of COPD

Risk Factors	Correlation
Infection	• Acute infection causes airway epithelial injury and inflammation, which increases the risk of hospitalization due to AECOPD.[30,35–37,49,53]
Tobacco smoke	• Tobacco smoke exposure is a recognized independent risk factor that causes airflow restriction, resulting in reduced lung function, and an increased risk of AE.[55–57] • Evidence suggests that quitting smoking reduces the risk of hospitalization.[194]
Air pollution Comorbidities	• Particulate matter concentrations and air pollution reduce lung function and increase the incidence of serious AECOPD events.[64,66,71,74]
Airway limitation	• High airflow restriction and lower lung function increase the risk of recurrent AE.[107–109]
Biomarkers	• Simple and easily accessible biomarkers can be used to assess the development and progression of COPD and predict the risk of AE.[111,113,123,129,130]
History of previous deterioration	• History of past exacerbations was an independent predictor of frequent exacerbations of COPD.[145] • 85.5% of patients with a history of deterioration within 12 months will have one deterioration within the next 12 months.[148] • The incidence of mortality and poor prognosis in COPD patients was proportional to the number of exacerbations.[151]
Natural killer cell	• The proportion of NK cells predicted AECOPD occurrence, and the proportion of NK cells was higher in patients with frequent AE.[152,156,157]
Immunoglobulin G	• The decrease of Ig G level increases the risk of infection and the incidence of adverse prognosis in COPD patients.[159–162]
Genetics	• Some studies have found some genetic genes related to AECOPD, but their role in predicting COPD deterioration and treatment response is limited, and large-scale prospective studies are still needed to continue to explore the possibility of genetic variation in AECOPD.[167,172,175,195]
Abnormal muscle and nutritional status	• Respiratory muscle and peripheral muscle injury were associated with COPD readmitted rate and disease severity at admission.[177,179] • Low BMI increases the risk of AE and readmission in COPD patients.[181]
Negative psychology	• COPD patients with mental disorders have an increased risk of deterioration and death.[187,189]
Seasonal temperature	• Air temperature was negatively correlated with the risk of AE.[192,193]

mechanisms underlying AECOPD. The objective is to identify novel regulatory pathways and pharmaceutical treatments utilizing genomic and biomarker technologies.

Due to the large size of the COPD population, and with the world population gradually aging and multiple risk factors continuing to attack, the mortality and disability rates of COPD patients will continue to increase in the future. For these reasons, preventive diagnosis and treatment of COPD, early identification, timely diagnosis and treatment, and whole process intervention are particularly important. Long-term standardized management and intervention in COPD patients will likely improve the negative impact of AE in the course of COPD to a greater extent, and improve patients' disease prognosis and quality of life. Currently, there remains a dearth of research literature pertaining to the long-term standardized management intervention for patients with COPD in the context of investigating risk factors and predicting AE. Furthermore, completed studies on standardized management factors may exhibit limitations, including inadequate sample sizes, incomplete incorporation and analysis of indicators, and suboptimal patient adherence.

With the increasing emphasis on chronic diseases in the international health community, most countries are gradually implementing standardized training for respiratory physicians, public health education, early screening of high-risk groups for COPD, and actively build standardized supervision and management system for primary care. These efforts aim to investigate novel medical intervention strategies that can effectively mitigate the occurrence of AE. With the popularization and improvement of network information, the combination of the Internet and medical treatment will become the mainstream trend for precise treatment, full management, and prevention of AE for patients with COPD in both urban and rural communities in the future.

Abbreviations

AECOPD, Acute exacerbations of chronic obstructive pulmonary disease; VitD, Vitamin D; CB, Chronic Bronchitis; CCI, Charlson Comorbidity Index; NIV, non-invasive ventilation; CRP, C-reactive proteins; ACE-2, angiotensin-converting enzyme 2; MMPs, matrix metalloproteinases; NK, Natural killer; HIV, human immunodeficiency virus; mMRC, modified Medical Research Council; FIB, fibrinogen; UA, uric acid; IgG, Immunoglobulin G; MBL, Mannose-Binding Lectin; HHIP, human hedgehog interacting protein.

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Disclosure

The authors report no conflicts of interest in this work.

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