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Review Article

Early detection and prediction of acute exacerbation of chronic obstructive pulmonary disease

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation. Acute exacerbation of COPD (AECOPD) is an acute worsening of respiratory symptoms, which needs additional treatment and can result in worsening health status, increasing risks of hospitalization and mortality. Therefore, it is necessary to early recognize and diagnose exacerbations of COPD. This review introduces the updated definition of COPD exacerbations, the current clinical assessment tools, and the current potential biomarkers. The application of mobile health care in COPD management for early identification and diagnosis is also included in this review.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms due to abnormalities of the airways and/or alveoli that cause persistent, progressive airflow obstruction.[1] The latest cross-sectional study showed that the overall prevalence of spirometry-defined COPD in China was 8.6%.[2] Acute exacerbation of COPD (AECOPD) is a key feature of the disease in many patients. Exacerbations are more likely to occur in patients with a high symptom burden, and further increase the burden of disease,[3] as well as the risk of more frequent severe exacerbation. Therefore, it is necessary to early detect and diagnose AECOPD. However, due to the heterogeneity of COPD exacerbation, there has always been controversy about the definition of it. These changes and controversies lead to difficulties in early identification and treatment.

Controversy over the definition of COPD exacerbation

The key symptom of COPD exacerbation is increased dyspnea caused by airway inflammation, increased mucus production, and marked air trapping. There are also other symptoms including increased sputum purulence and volume, together with increased cough and wheeze. However, exacerbations of COPD are heterogeneous events with different etiologies, pathogeneses, symptoms, frequencies, severities and biomarkers. Most definitions of COPD exacerbations contain both a symptom-based component and an event-based component.[4] Now the most widely accepted definition is from Global Strategy for Prevention, Diagnosis, and Management of COPD (Global Initiative for Chronic Obstructive Lung Disease, GOLD). The 2023 GOLD states that the exacerbation of COPD is “an event characterized by dyspnea and/or cough and sputum that worsen over <14 days”.[1] This definition is adequate for clinical purposes and based on clinical symptoms (typical symptoms include increased dyspnea, cough, increased sputum volume, and/or purulent sputum) and the timing of the events. GOLD classified AECOPD severity as mild, if only symptoms are reported and the patient is treated with inhaled short-acting bronchodilators; moderate, if the patient receives antibiotics, systemic corticosteroids, or both; and severe, if the patient visits an emergency room or is hospitalized because of the event.

The existing definitions based on the patient’s perception of symptoms lack specificity and sensitivity.[5] Other respiratory diseases or non-respiratory diseases may have similar manifestations and cause misdiagnosis. Diagnosis of AECOPD often depends on the patients’ history and symptoms, as well as other necessary examinations. Meanwhile, most patients find it difficult to identify the very early stages of an exacerbation and to distinguish their worsening symptoms from day-to-day variability. Therefore, many experts advocate that we need a new definition that includes proven biomarkers, and classification of a specific symptom like the evolution of the natural history of coronary artery disease (CAD).[5]

In clinical practice and large-scale clinical studies, how to distinguish between acute exacerbation and COPD symptom variation is also controversial. Most studies defined the worsening respiratory symptoms for at least two consecutive days, which disappear and return to the daily baseline level after at least 5 consecutive days, as an exacerbation rather than a variation of COPD symptoms. The definitions for the severity of COPD

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exacerbation can also vary. In the TORCH study, they, respectively, defined a moderate exacerbation and severe exacerbation as one requiring treatment with systemic corticosteroids and/or antibiotics and one requiring hospitalization. In UPLIFT study, an exacerbation is defined as a worsening or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with an antibiotic and/or systemic steroid and is categorized as mild, moderate and severe according to their needed treatment.[6] Meanwhile, in WISDOM study[7] and Tiotropium in Early-stage COPD study,[8] the interval between the next acute exacerbation and this one which is more than 7 days could be defined as a new acute exacerbation, otherwise it will be combined into one. Despite the existence of guidelines and efforts to clarify best practice, there is no international consensus or standardized definition of how the start and end dates for exacerbations should be defined.[9]

Importance of early detection and recognition of COPD exacerbation

Acute exacerbation recognition and reporting by patients is generally poor. It is reported that nearly 50% of AECOPDs were unreported and associated with long-term adverse consequences.[10] A cohort study shows that each exacerbation will increase the risk of another exacerbation, and the interval between the next severe exacerbations will be shortened.[11] Early detection and recognition of exacerbations and the beginning of medical intervention are important to prevent the progress of exacerbation. Once diagnosed as COPD exacerbation, the earlier the treatment is started, the faster the patient's symptoms will be relived, and the patient will have better quality of life, and lower risk of hospitalization.[12]

Identification of AECOPD

About 2/3 to 3/4 of acute exacerbations are induced by viral or bacterial infections, while the other 1/3 of the acute exacerbations are induced by noninfectious factors including air pollution, exposure to allergens, poor treatment compliance.[13] AECOPD is characterized by an acute burst of airway inflammation due to triggers, and the inflammatory process may expand systemically.[14] This burst of inflammation worsens the existing airway limitation, which increases airway resistance. Airway and systemic inflammation leads to worsening dyspnea, respiratory muscle dysfunction, and ventilatory insufficiency.

For the heterogeneity of COPD, it is difficult to cluster COPD exacerbations according to clinical characters. Some researchers suggest that exacerbations are clustered according to the underlying predominant inflammatory profile defined on the basis of unsupervised statistical analysis of airway mediators and include a proinflammatory endotype (bacteria-predominant), a T-helper 2 (Th2) endotype (eosinophil-predominant), a T-helper 1 (Th1) endotype (virus-predominant), and a low inflammatory profile (pauci inflammatory).[15] Identification of these endotypes of exacerbation is possible based on sputum markers (interleukin 1β) for pro-inflammatory endotypes and blood markers for Th2 and Th1 endotypes (percentage of eosinophils and C-X-C motif chemokine ligand 10 [CXCL10], respectively).

On the basis of this pathophysiological process, in 2021, the Rome Proposal panel proposed the following definition: "In a patient with COPD, an exacerbation is an event characterized by dyspnea and/or cough and sputum that worsens over ≤14 days, which may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways."[16] These events can be life-threatening and require adequate evaluation and treatment.

Different from the current grading of the severity of AECOPD, based on post-analysis of medical records, the Rome panelists propose three severity categories (mild, moderate, and severe). These grading systems integrate six objectively measured variables that serve as markers of event severity: dyspnea, oxygen saturation, respiratory rate, heart rate, serum C-reactive protein (CRP), and, in selected cases, arterial blood gases. The proposal suggests that clinicians and researchers should use the integration of five easy-to-evaluate parameters (dyspnea, respiratory rate, heart rate, oxygen saturation, and serum CRP) to assess the severity of an exacerbation of COPD.

Before confirming AECOPD diagnosis, clinicians should consider the differential diagnosis, and there are at least 28 diseases that may have similar symptoms to AECOPD. Among them, three diseases (heart failure, pneumonia, and pulmonary thromboembolism) need special consideration.[17–19] A thorough evaluation should be done to exclude these diseases. Meanwhile, these diseases and AECOPD often coexist and influence each other.

The Rome proposal for an updated definition and severity classification of exacerbation of COPD solves many shortcomings of the current definition. It was drafted by an international panel of experts and needs to be popularized by clinicians and researchers.

Clinical tools used to assess AECOPD

Worsening of respiratory symptoms is the key to identify AECOPD. Daily monitoring of symptoms is considered to be an accurate way of capturing all exacerbations. Some standardized methods for quantifying and evaluating symptoms have been established.[20] Many studies were conducted to assess their ability for assessing COPD exacerbations. In studies, Exacerbations of Chronic Pulmonary Disease Tool (EXACT), the St George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT) are all widely validated, and show the effective patient reported outcome (PRO).

The SGRQ can identify COPD exacerbation and remission.[21] However, as it is long, difficult for patients to complete, it is rarely used in clinical practice. CAT is a questionnaire which is designed to assess and quantify the impact of COPD symptoms on a patient's health status. While it is being developed to measure the health of stable COPD subjects, studies have found that it also has important significance as a simple tool to assist in the identification of patients at increased risk of exacerbations.[22] Change in CAT score during monitoring visits is useful for detecting acute deterioration in health status.[23] EXACT is the diary of symptoms recorded during AECOPD. EXACT and CAT also show high values in the assessment of acute attack frequency, duration and severity.[24–26] However, in clinical practice, EXACT and CAT are still too complex to be used as a guide for patients. At present, a registration study has been carried out in China to obtain real-world data on the clinical management of COPD after hospitalization and discharge,[23] and a study has also been conducted on the early-warning model of AECOPD.[27]

Recently, a valid COPD Exacerbation Recognition Tool (CERT) is developed to provide patients with simple-to-follow guidance about when to seek medical services when their respiratory symptoms worsen.[28] It aims to help patients in all GOLD groups recognize moderate and severe exacerbations. Another study, named as DETECT (NCT03556475) study, has been completed. The result has not been published. It was a multicenter, observational, cross-sectional study aiming to develop and validate multivariable prediction models for AECOPD occurrence and severity in patients with chronic obstructive pulmonary disease (COPD) in China. Further studies are needed to confirm its validity.

Many researchers developed prognostic prediction tools to enable personalized approaches to disease management. But there is no such tool routinely used in clinical management of COPD. A systematic review published in 2017 identifies 27 prediction models that predict exacerbations in COPD patient. None of them were deemed ready for personalised COPD care.[29] Adibi et al[30] developed a new model, the Acute COPD Exacerbation Prediction Tool (ACCEPT), to predict, at an individual level, rate and severity of COPD exacerbation. ACCEPT was externally validated in ECLIPSE cohort. The result shows that it can be used as a decision tool to personalize COPD treatment and prevent exacerbations.[29,30]

Table 1
Some biomarkers used in AECOPD.

Biomarkers	Significance
PCT	Specific biomarkers of bacterial infection, distinguishing mild and moderate AECOPD, and predicting longer hospital stay.
CRP	Nonspecific, related to severity, predicting longer hospital stay
NLR, PLR	Reflect disease severity
Eos	$\geq 0.34 \times 10^9$/L associated with an increased risk of severe exacerbations
Fibrinogen	Measuring severity, predicting NPPV failure
D-dimer	Predicting in-hospital and 1-year mortality
FeNO	Predicting the treatment response
BNP/NTpro-BNP	Correlated with the prognosis of AECOPD

AECOPD: Acute exacerbation of chronic obstructive pulmonary disease; BNP: B-type natriuretic peptide; CRP: C-reactive protein; Eos: Eosinophil; FeNO: Fractional exhaled nitric oxide; NLR: Neutrophil-to-lymphocyte ratio; NTpro-BNP: N-terminal pro-brain natriuretic peptide; PCT: Procalcitonin; PLR: Platelet to lymphocyte ratio.

In addition to symptomatic COPD assessment tools, lung function and tests of small airways' function are useful tool to assess exacerbations. The more severe the airflow limitation, the higher the risk of acute exacerbation.[31] ΔPeak expiratory flow (ΔPEF) and ΔCAT were independently associated with risk of hospitalized exacerbation.[32] There are limitations to these tools in the early detection of AECOPD. Day-to-day variations in lung function measured by the forced oscillation technique (FOT) may yield greater insight. Zimmermann et al[33] determined the clinical utility of variability in FOT measures in COPD exacerbation. The study found that variability of the inspiratory component of X (indicated by the standard deviation of inspiratory reactance [SDXinsp]) changed significantly on the same day as CAT (1 day before AECOPD, both P=0.02)) and earlier when using 5-day running windows (3 days before AECOPD, P=0.01; accuracy=0.72). Therefore, they concluded that SDXinsp from FOT telemonitoring may be a sensitive biomarker for early detection of AECOPD.

Biomarkers of AECOPD

Biomarkers are characteristics that have been objectively measured and evaluated to serve as indicators of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic interventions, which can increase the specificity and sensitivity of disease diagnosis and treatment. It shows great potential in the early identification of disease, the evaluation of disease severity and phenotype classification, and the evaluation of curative effect, and prognosis. AECOPD can be worsened by local and systemic inflammation. Just as the discovery of biomarkers such as cardiac troponin (cTn) has revolutionized the treatment of cardiogenic chest pain, we hope to find some good markers to improve the current diagnostic pattern of AECOPD [Table 1].

Diagnosis and treatment

The incidence of AECOPD is mainly caused by respiratory viruses, bacteria, and other infections. To distinguish the etiology and provide individualized treatment is the most important priority in the management of patients with acute exacerbations.

C-reactive protein (CRP) is an acute-phase protein and the most studied nonspecific acute-phase protein in AECOPD. It can be used as a biomarker for infection in acute exacerbations of COPD. However, CRP is not disease-specific and is elevated in both bacterial and viral infections, limiting its usefulness. Procalcitonin (PCT) and CD64 are specific biomarkers of bacterial infection, which have important diagnostic and therapeutic significance for antibiotic treatment of AECOPD patients.[34,35] In addition, Quint et al[36] showed that plasma interferon-inducible protein-10 (IP-10) concentrations in viral-positive patients with AECOPD were significantly higher than those in viral-negative patients with acute exacerbation, suggesting that elevated serum IP-10 level may be a marker of rhinovirus infection.

Soluble urokinase-type plasminogen activator receptor (suPAR) is positively correlated with immune system activity, and is a novel inflammatory biomarker. A meta-analysis assessed its clinical value in COPD. It found that suPAR level was higher in AECOPD patients and decreased after treatment.[37] suPAR has potential for early identification of AECOPD.

Hydrogen sulfide (H_2S) is a gas signaling molecule that is produced by many cell types in the lungs and participates in important physiological processes. Endogenous H_2S is involved in the pathogenesis of COPD and is associated with disease severity and activity. Saito et al[38] found that the sputum-to-serum ratios of H_2S (H_2S ratio) in AECOPD patients were higher than those in stable COPD, health smokers and non-smokers. The cut-off value of H_2S ratio to detect an AECOPD was ≥0.44. The sensitivity and specificity were 93.1% and 84.5%, respectively. In addition, Sun et al[39] found that dexamethasone failed to inhibit lipopolysaccharide induced tumor necrosis factor-α (TNF-α) release by alveolar macrophages from cigarette smoke exposed rats. However, dexamethasone combined with H_2S can significantly inhibit the release of TNF-α, suggesting that exogenous supplementation of H_2S could improve the response to corticosteroids.

Fractional exhaled nitric oxide (FeNO) has been shown to be a marker of airway inflammation in various pulmonary diseases, including chronic obstructive pulmonary disease (COPD). The increased FeNO level correlated with decreased lung function and COPD symptom deterioration. FeNO can be a biomarker to predict the overall treatment response in AECOPD patients.[40] $FeNO_{200}$ (exhaled nitric oxide at a flow rate of 200 mL/s) is used for evaluating peripheral airway/alveolar inflammation. Although there is no correlation between circulating eosinophil counts and $FeNO_{200}$ in AECOPD patients, $FeNO_{200}$ >10 part per billion (ppb) still implies a good corticosteroid response in AECOPD patients.[41]

Severity assessment

PCT and CRP, as powerful biomarkers, can also be used to assess the severity of disease in AECOPD patients. Pazarli et al[42] found that the serum PCT level were significantly different in AECOPD patients with different severities. When the PCT cutoff value was 0.07 ng/mL, the sensitivity and specificity of the PCT in distinguishing mild and moderate AECOPD were 82% and 91%, respectively. Patel et al[43] also found that the levels of CRP and PCT in saliva of patients with AECOPD were significantly increased, and the concentration of CRP in saliva was closely related to the concentration in blood. They believed that the measurement of CRP in saliva could be a noninvasive method to evaluate the severity of AECOPD.

Serum amyloid A (SAA) is an extremely sensitive acute reactive protein synthesized by liver cells. When stimulated by inflammatory factors, it can rise rapidly, reaching its peak in 8–12 hours, and can quickly return to normal after the inflammation is controlled. The study of Bozinovski et al[44] showed that SAA was higher than control in AECOPD patients, and SAA was a more sensitive and specific inflammatory marker than CRP in AECOPD. SAA was also shown to be closely related to the

severity of AECOPD and to guide AECOPD classification and whether hospitalization was required.

As a key modulator of inflammation and fibrosis development, as well as tissue injury, fibrinogen has been used as a COPD biomarker for severity assessment. Higher baseline fibrinogen is associated with increased incidence of AECOPD, COPD hospitalization, and all-cause mortality and related to the severity of COPD. One study found that fibrinogen level was higher during AECOPD and returned to baseline 40 days after exacerbation.[45] The level of circulating fibrinogen can be used to measure the severity of AECOPD, and among AECOPD patients managed with NPPV, fibrinogen >3.55 g/L can independently predict NPPV failure.[46]

The main mechanism of AECOPD is the amplification of inflammatory signals, which can cause morphological changes of red blood cells. Red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are the effortless and basic parameters that are readily obtained from the simplest and easily obtainable complete blood count. A systematic review[47] suggests that the RDW might be useful, singly or in combination with other parameters, for the diagnosis and risk stratification of patients with AECOPD. Koç et al[48] found that the RDW was significantly higher in those admitted to the intensive care unit compared to those treated in respiratory wards. The NLR and PLR may also be used as a useful and easily accessible tool for disease severity assessment during acute exacerbations in COPD patients.[49]

Risk prediction

Increased CRP levels in worsening symptoms improve the predictive power of AECOPD.[10] A prospective cohort study found that CRP with a cut-off of 3 mg/L combined with white blood cells (9×10^9/L) and fibrinogen (14 μmol/L) predicted an increased risk of exacerbations in five years and that the exacerbation rate was 62% (*vs.* 24%) in patients with grade C to D GOLD scores compared with patients without high biomarkers. Higher CRP and PCT levels also predicted longer hospital stay.[50]

The presence of eosinophilic inflammation in chronic obstructive pulmonary disease (COPD) has been reported in both stable disease and during exacerbations. Among individuals with COPD in the general population, increased blood eosinophil levels $\geq0.34\times10^9$/L were associated with a 1.76-fold increased risk of severe exacerbations.[51] COPD Gene study found that blood EOS count $\geq300/\mu$L increased the risk of AECOPD by 1.32 times.[52]

Prognosis

A significant and sustained increase in myocardial injury markers is a signal of the critical condition of AECOPD. At present, a number of studies in China and other countries have proved that cardiac biochemical markers represented by the N-terminal pro-brain natriuretic peptide (NT-pro-BNP) of B-type natriuretic peptide (BNP) and cardiac troponin (cTn) are correlated with the prognosis of AECOPD. Høiseth et al[53] found that moderate elevation of cardiac troponin T (cTnT) in AECOPD patients was associated with poor long-term prognosis. The study included 1145 patients with initial diagnosis of AECOPD and normal left ventricular ejection fraction (LVEF). The results showed that elevated admission BNP in patients with AECOPD and preserved left ventricular function is associated with worse in-hospital outcomes and the need for intensive care and can be used to risk-stratify these patients.[54]

The blood of most of AECOPD patients is in a hypercoagulable state with hypoxemia and carbon dioxide retention.[55] The D-dimer is a product of fibrinolysis, which may increase during many conditions associated with thrombosis and thrombolysis. Eleven studies have shown that elevated plasma D-dimer was associated with adverse outcomes. The results of a prospective study showed that serum D-dimer level (≥985 ng/L) was an independent risk factor for in-hospital mortality (RR 6.51, 95% CI: 3.06–13.83) and 1-year mortality (HR 3.48, 95% CI: 2.07–5.85) in AECOPD patients.[56] suPAR is elevated in severe acute and chronic diseases and has been associated with short-term mortality. For AECOPD patients, median suPAR levels were significantly higher among patients who died within 30 days compared with those who survived. Increasing suPAR levels independently predicted 30-day mortality in patients with AECOPD (HR 2.0, 95% CI: 1.7–2.4).[57]

For many years, the challenge of AECOPD has been to find biomarkers of good performance. However, due to the heterogeneity of disease progression, such markers are most likely absent.

Application of mobile health care in AECOPD

Mobile health (mHealth) is to provide medical services through the use of mobile communication technology, including mobile telemedicine, tablets, hospital information solutions and especially the wearable technology. The combination of mobile medical software and hardware makes the development of the market more quickly, which will have a more positive effect on the management of chronic diseases such as COPD. Mobile health instruments and remote monitoring platforms can provide daily information on external factors that trigger AECOPDs and enable the longitudinal collection of data characterizing a patient's physiological and clinical status. Such digital medicine solutions—by upgrading the detection of acute events—might represent an attractive option for improving the early identification of AECOPDs.[58]

During the COVID-19 pandemic, many clinics used telemedicine services to care for patients with COPD to comply with social distancing recommendations and prevent spread of infection to a high-risk population. The use of telemedicine to assess patients with suspected AECOPD has been suggested.[59] A telemonitoring platform for early identification of AECOPDs should have four parts: first, a platform for assessment of external factors, e.g., air quality sensing devices at home and/or from various open-access environmental data platforms; second, specific questionnaires to identify patients at high risk of AECOPDs and the longitudinal collection of patients' symptoms, e.g., ACCEPT; third, wearable sensors automatically capturing lifestyle data (physical activity, respiratory rate, heart rate, and sleep patterns); fourth, remote patient monitoring technologies for the detection of COPD exacerbations, e.g., spirometers, pulse oximeters, and electronic inhalers, etc.[60] The use of telemonitoring to predict AECOPDs is a confluence of remote sensing, patient utilization of personal technology, and data processing and analysis supported by various artificial intelligence (AI) approaches that contribute to medical decision making.[61] The co-design pattern should include structured patient interviews, health professional focus groups, patient co-creation activities, and health professional prioritization discussions. After a few iterations, the developers share the proposed solution with all stakeholders to test the prototype for validation. Then patient experience and long-term adherence can also be improved through visualization of relevant online information and patient engagement tools.

A Cochrane review[60] summarized the impact of remote monitoring technology on COPD patients. Telemonitoring combined with usual care (8 studies, 1033 participants) had little effect on the number of exacerbations or hospital admissions.[60] Telemonitoring was shown to have a possible positive impact on readmission after hospitalization. There was no evidence of harm from these telemedicine interventions. A more positive view[62] was reported in another systematic evaluation. Remote monitoring of patients with COPD is considered an effective way to reduce emergency room visits. In fact, remote patient monitoring is more effective in COPD than in other chronic diseases. Of the 13 randomized controlled trials included in the systematic evaluation, 30% of patients reported reduced hospital admission, and all cohort studies (n=9) positively supported remote monitoring.

Mobile health is also used in medication use monitor. Digital sensors fitted onto inhalers can capture the date, time and location of medication use, thereby offering an objective signal of rescue inhaler or con-

troller medications use. The sensors regularly transmit medication use data back to the server through a smartphone or wireless hub.[63] The device can also be used to improve the compliance of COPD patients. The Internet of Things (IOT) is the name given to the network of devices and other "things" with built-in sensors, software, electronics, and network connectivity, communicating these objects over wireless networks and sending data to a cloud platform. Some mobile phone-based IoT (mIoT) platforms are developed and used in stable COPD patients with/without respiratory failure.[64,65]

In conclusion, AECOPD is common during COPD, which brings a heavy burden to the patient's family and society. Timely identification of AECOPD will improve the final outcome of COPD patients. However, the current definition of AECOPD based on characteristic symptoms and events is controversial. Biomarkers and PRO are helpful in the diagnosis and treatment of AECOPD. The development of mobile health and wearable devices will change the management pattern of existing chronic diseases such as COPD, especially during the period of COVID-19 pandemic, which has shown sufficient value.

Conflicts of interest

None.

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