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Eosinopenia as a biomarker for antibiotic use in COPD exacerbations: protocol for a retrospective hospital-based cohort study

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ABSTRACT

Introduction The acute exacerbation of chronic obstructive pulmonary disease (AECOPD) has a seriously negative impact on patients' healths condition and disease progression. Bacterial infection is closely related to AECOPD, and antibiotics are frequently used in clinical practice. The lack of specific biomarkers for rational antibiotics use always leads to antibiotics abuse in chronic obstructive pulmonary disease (COPD) flare-ups. Eosinopenia has been considered to be related to increased bacterial load of potentially pathogenic organisms at the onset of COPD exacerbations. Therefore, this study aims to investigate whether eosinopenia could be used as a reference for the use of antibiotics in AECOPD.

Methods and analysis In this study, a hospital-based retrospective cohort design will be adopted to analyse the clinical data of inpatients who are primarily diagnosed with AECOPD in West China Hospital of Sichuan University from 1 January 2010 to 31 December 2020. Relevant data will be extracted from the Clinical Big Data Platform for Scientific Research in West China Hospital, including demographic characteristics, blood eosinophil count, procalcitonin, C reactive protein, microbial cultivation, antibiotics use, length of hospital stay, non-invasive ventilation use, intensive care unit transfer and mortality, etc. The collected data will be described and inferred by corresponding statistical methods according to the data type and their distributions. Multiple binary logistic regression models will be used to analyse the relationship between blood eosinophil count and bacterial infection. The antibiotics use, and patient morbidity and mortality will be compared between patients with or without eosinopenia.

Ethics and dissemination This study has been approved by the Biomedical Ethics Review Board of West China Hospital of Sichuan University (Approval No. 2020-1056). And the research results will be published in a peer-reviewed journal.

Trial registration number ChiCTR2000039379.

Strengths and limitations of this study

► This is a pioneering study to comprehensively reveal the role of blood eosinophils in the treatment and prognosis of chronic obstructive pulmonary disease exacerbations by exploring its relationship with bacterial infection, antibiotics use, and patients' morbidity and mortality.
► This study adopts a retrospective cohort study design involving a relatively large representative sample, which gives more reliable results with greater precision and power.
► The data of this study comes from real clinical evidence, and the process of data generation and collection is consistent with the actual clinical medical practice.
► The data may be incomplete and inaccurate due to the development of time, a short period of observation, the insensitivity and unspecificity of disease coding, and the inaccuracy of clinical recordings.

is responsible for considerable and growing morbidity, mortality and healthcare expenses worldwide.[1 2] Acute exacerbation of COPD (AECOPD) that characterised by acute worsening of cough and mucus production and marked gas trapping is closely related to worse health conditions, and increased hospitalisations, readmissions and fatality rate.[3] Minimising the negative impact of the current exacerbation and preventing the development of subsequent events are principal goals of AECOPD treatment.[4]

COPD exacerbations are heterogeneous events that are now thought to be caused by complex interactions among the host, airway bacteria, respiratory viruses and environmental pollution, leading to an increase in the inflammatory burden.[5] Some studies demonstrated that COPD exacerbations are triggered commonly by respiratory viruses and bacteria, which infect the lower airway

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease that

and increase airway inflammation.[5–7] It has been found that 40%–55% of COPD exacerbations are associated with bacterial infections.[8 9] COPD flare-ups caused by bacterial infections are characterised by a more severe airway and systemic inflammation responses compared with those caused by non-bacterial infections.[10] Timely initiation of antibiotic therapy helps to reduce in-hospital mortality, treatment failure rate and rehospitalisations and to prolong the time to the next attack.[11] In consequence, antibiotics prophylaxis or empirical antibiotics treatment is heavily used in the early stage of flare-ups, especially in those with severe exacerbations.[12] However, it is critical to note that AECOPD episodes may also be triggered by non-bacterial factors such as viral infections and smoking exposures.[13] Therefore, antibiotic therapy without a verification of bacterial infection leads to a grim overuse of antibiotics in the AECOPD population.[14] A study in France has shown that antibiotic prescriptions attributable to viral lower respiratory tract infections account for 20% of outpatient antibiotic use in the elderly.[15] The considerable drawbacks of antibiotics abuse have been highlighted concerning the possible adverse effects, increased antibiotics resistance and heavy financial burden.[16 17] Besides, antibiotics abuse also leads to a delay in diagnosis as signs and symptoms of bacterial infections may disappear.[18] Appropriate antibiotics prescribing decisions made by healthcare professionals will not only help the management of current exacerbations, but also reduce aforesaid risks. Therefore, the exploration for biomarkers that can reliably predict bacterial infection and indicate antibiotics use in AECOPD patients is in great demand. However, it is still difficult to accurately identify bacterial infection in clinical practice under the direction of current indicators.[9 19] The effect of common biomarkers, such as serum procalcitonin (PCT) and C reactive protein (CRP), on distinguishing causative pathogens during COPD exacerbation is limited as they alone are not sufficient to confirm a bacterial infection diagnosis.[20] And it is also difficult to implement CRP and PCT test in some primary care hospitals.

Normal eosinophil percentage is between 3% and 5% in the peripheral blood, equating to an absolute peripheral eosinophil count of $0.35–0.5\times10^9/L$.[21 22] Previous studies have shown that blood eosinophil count (BEC) decreases in patients with COPD exacerbations with an increase of sputum bacterial counts.[23–25] Also, a study has shown that 2% of BEC may be considered as an indicator to distinguish bacterial from non-bacterial infections in AECOPD patients.[26] What is more, BEC returns to the normal level faster than serum CRP and PCT under appropriate antibiotic therapy,[11] suggesting a high sensitivity of eosinopenia in indicating bacterial infection and its potential role in indicating antibiotic therapy.

STUDY OBJECTIVES

This study is primarily designed to explore that whether the level of peripheral blood eosinophils could be used as a reliable biomarker to predict bacterial infection and antibiotic treatment in hospitalised patients with AECOPD. This study will potentially guide the management strategies and contribute to the development of precision medicine in COPD. Three specific clinical and scientific issues will be addressed as follows:

1. To explore the association between blood eosinopenia and bacterial infection in hospitalised patients with AECOPD.
2. To indicate the role of blood eosinopenia as a reference for antibiotics use in hospitalised patients with AECOPD.
3. To examine the association between blood eosinopenia and prognosis in hospitalised patients with AECOPD.

METHODS AND ANALYSIS
Study design, setting and data sources

This retrospective cohort study will be conducted in West China Hospital of Sichuan University, a national medical centre in western China and a referral hospital with more than 270 000 patients discharged each year. Data of this study will include health records in a 11-year period from 1 January 2010 to 31 December 2020 from the Clinical Big Data Platform for Scientific Research (CBDPSR). CBDPSR is a hospital-based network that integrates 13 health information systems, 4.8 billion medical records and 72 443 800 medical visits. It is focused on improving healthcare deliveries, health outcomes and medical researches. This protocol is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology checklist.[27]

Data extraction will be completed by two experienced respiratory clinicians and two senior engineers from the Information Centre of West China Hospital. Relevant data will be extracted from medical charts and electronic medical records, and re-entered into a research database. Further quality control for data consistency and cleaning will be performed. As some data may be unrecorded or incomplete in the database, patients or their family members will be contacted by telephone to obtain the missing data. Otherwise, the data will be removed from the database. Natural language processing and text information structuring will be used to clean up imaging tests and lung function tests because of the enormous amount of data. Figure 1 shows the flow chart of the study.

Study participants

This study will include inpatients (18–80 years old) admitted to West China Hospital from 1 January 2010 to 31 December 2020 and discharged with a primary diagnosis of AECOPD. The presence of AECOPD will be identified based on the International Classification of Diseases-10 (ICD-10). Patients with a primary diagnosis of ICD-10 code of J44.0 or J44.1 will be included in the study. An initial screening began on March 1, 2021, and yielded 16 219 records. We will only collect inpatient data for analysis because of the large clinical differences between
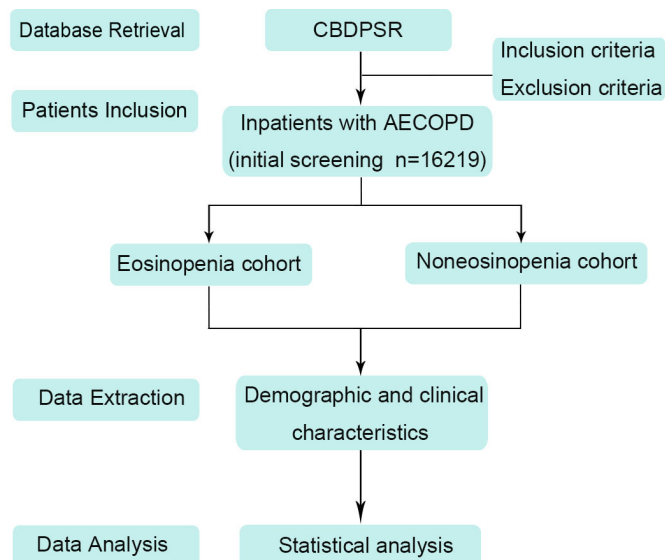
Figure 1 The flow chart of the study. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CBDPSR, Clinical Big Data Platform for Scientific Research.

outpatients and inpatients, as well as an easier access to inpatient information. Patients will be excluded if:

1. They have a different primary diagnosis other than AECOPD at discharge, such as pulmonary tuberculosis, bronchiectasis, pulmonary fibrosis, acute pulmonary embolism, acute pulmonary oedema, pneumothorax or arrhythmia.
2. They have complications that may affect the BEC, such as asthma, leucocythaemia, parasite infection, allergic disorders, eczema, eosinophilic pneumonia, solid tumours, severe immunodeficiency disease or autoimmune diseases.
3. They have severe liver, heart or renal failures.
4. They have incomplete clinical records for analysis, for example, lack of blood routine tests.

Patient and public involvement

As this research is a retrospective study, it does not involve patient recruitment and signing of informed consent. Patients and the public are not involved in the development of the research question, outcome measures, study design, study conduct, as well as study reporting.

Outcomes

Demographic and clinical characteristics, including age, sex, height, weight, course of disease, diagnosis, comorbidities (gastroesophageal reflux disease, coronary heart disease, hypertension, diabetes, osteoporosis, cerebrovascular accident, anxiety and depression), symptoms, smoking history and pack-years, severity of airway limitation based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline, length of hospital stay, intensive care unit (ICU) admission, length of ICU stay, total cost, in-hospital mortality, antibiotic therapy, adjunctive therapy, invasive ventilator or non-invasive ventilator use, AECOPD associated hospital admissions

during the previous year, readmissions within 30 days after discharge, pulmonary function test and imaging examination, will be collected.

Data from laboratory tests that conducted within 24 hours after admission, including serum PCT, CRP and IL-6, bacterial culture, white cell count (WCC), BEC, blood eosinophil percentage, blood neutrophil count (BNC), blood neutrophil percentage (BNP) and arterial blood gas analysis, will be collected. Culture results using samples of sputum or broncho alveolar lavage (BAL) fluid will be recorded for bacterial infection identification. In cases with positive bacterial cultures, the name of pathogens and antibiotic sensitivity results will be extracted. However, bacterial infections in blood, extrapulmonary organs or tissues are supposed to be excluded. Results of nucleic acid test, antibody test, (1-3)-β-d-glucan assay, galactomannan assay and cultivation in valid samples of sputum and BAL fluid will also be collected to identify the viral and fungal infections. The date of chest X-ray and CT scan will be collected, along with the findings. Where possible, a radiologist or a senior physician will be involved in the image reading. Serum PCT, CRP and leucocyte count are commonly used acute phase reactants in bacterial infections. CRP and leucocyte count do not have sufficient specificity in differentiating bacterial infections from noninfectious inflammation and viral infections. PCT is a precursor of the hormone calcitonin, and it has been accepted that PCT is specific to bacterial infections.[28] Some studies have shown that PCT can effectively distinguish patients with bacterial AECOPD from those with non-bacterial AECOPD and guide the rational use of antibiotics.[28–30] And PCT is a better marker for predicting positivity of sputum culture compared with CRP especially in severe and hospitalised patients with AECOPD who require ICU or mechanical ventilation support.[30] Therefore, in this study, bacterial infection will be defined as positive pathogenic bacterial cultures in valid sputum or BAL fluid with increased serum PCT or infectious lesions in imaging results with clinical manifestations with increased sputum purulence.

Information of antibiotic therapy will include whether antibiotics are prescribed during hospitalisation, details about individual antibiotics (eg, name, route, dosage, duration of antibiotic treatment, frequency, time to the first antibiotic prescription from admission) and whether double or triple antibiotic therapy is used. Duration of antibiotic treatment will be defined as days with any antibiotics exposure for respiratory infections during hospitalisation. Antibiotic treatment for infections in other parts of the body will not be recorded. We will define antibiotic therapy as oral or intravenous antibiotics use for five or more consecutive days. Adjunctive therapy will include commonly used medications such as inhaled bronchodilator, theophylline, systemic corticosteroids, maintenance inhaled corticosteroids (ICS) and aerosol ICS during hospitalisation. These therapies will be recorded on the name, route, dosage, duration of treatment, frequency and time to the first prescription from admission. We

define maintenance ICS use as regular ICS use for three or more consecutive months before admission.

Sample size calculation

According to the previous study,[26] the incidence of bacterial infection was 20% in the noneosinopenia group and 30% in eosinopenia group, using 2% as the cut-off in blood routine examination. We used a CI of 95% and a p value of 0.05 to achieve 85% power to detect a difference between the two cohorts. An estimated 1:3 ratio between the two groups was selected given that eosinopenia cases are more common in the AECOPD population.[26 31] The estimated sample size is 948, with 711 in the eosinopenia group, and 237 in the non-eosinopenia group.

Proposed statistical analysis

Patients will be divided into two cohorts with or without eosinopenia according to the level of peripheral eosinophils in blood routine examination. We will use 2% or 0.2×10^9/L as the threshold.[26] Baseline demographic characteristics including age, sex, course of disease, smoking history and pack-years, body mass index (BMI) and clinical information including comorbidity, the severity of airway limitation based on the GOLD guideline will be summarised using descriptive statistics. Quantitative variables including age, PCT, CRP, IL-6, BMI, course of disease, length of hospital stay, length of ICU stay, dose and duration of treatment, AECOPD associated hospital admissions during the previous year, total cost, WCC, BEC and BNC, with a unimodal symmetric distribution, especially those with a normal distribution or an approximate normal distribution, will be summarised using mean±SD, and those with an asymmetric distribution or unclear distribution will be summarised using median and IQR. Categorical variables including sex, smoking history, invasive ventilator or non-invasive ventilator use, ICU admission, in-hospital mortality, antibiotics use, corticosteroids use, bronchodilator use, readmission within 30 days after discharge, positive findings in imaging examination and bacterial culture, will be summarised using frequencies and percentages. Where appropriate, 95% CIs will be provided. The χ^2 test or Fisher's exact test will be performed for the categorical variables. Student's t-test and Mann-Whitney U test will be used for continuous normally and abnormally distributed variables, respectively.

We will identify the effect of blood eosinopenia, with or without other potential covariates, on predicting a bacterial infection by conducting binary logistic regressions. As informed by prior literature,[32–34] the potential covariates in predicting bacterial infection will include but not limited to : (1) age; (2) sex; (3) WCC; (4) BNP; (5) CRP; (6) PCT; (7) IL-6; (8) use of systemic corticosteroids; (9) use of maintenance ICS, (10) GOLD stage and (11) presence of chronic comorbidities. WCC, BNP, CRP, PCT and IL-6 will be converted into binary variables based on the optimal cut-off values, which are 10 000 cells/mm^3, 75 %, 5 mg/L, 0.046 ng/mL, and 7 pg/mL, respectively. The effect of individual predictors on dependent variables will be reported as adjusted ORs with 95% CIs. The logistic regression analysis will be assessed by Hosmer-Lemeshow test. Multivariate analysis will be performed in different models that include different covariates.

Subgroup analyses will be performed to determine whether the association between blood eosinophils and antibiotic therapy is modified by maintenance ICS use and other confounders. Sensitivity analyses will be undertaken to determine the robustness of the association. First, since the cut-off of eosinopenia varies from 0.01% to 4% in previously reported studies,[25 35–38] we will analyse that whether the association changes when different cut-off values are used to define peripheral blood eosinopenia. Second, we will use positive bacterial cultures accompanied with increased serum PCT and purulent sputum as the evidence of respiratory bacterial infection to explore the impact of bacterial infection definition on the association. Third, we will assess the association exclusively in patients with a confirmed diagnosis of AECOPD that supported by a reported obstructive spirometry.

All analyses will be performed using SPSS V.22.0, and a p<0.05 is considered statistically significant.

DISCUSSION

Acute exacerbation is a critical component in the clinical course of COPD and is associated with significant morbidity and mortality. It presents a clinical complexity for clinicians and a disproportionate burden on healthcare resources.[39] Current evidence indicates that the incidence of bacterial exacerbation is approximately 50% in AECOPD episodes, which is even higher in those with advanced COPD.[40] Hence, empirical antibiotic therapy is preferred, especially in hospitalised AECOPD patients, as timely antibiotic treatment is beneficial not only in the current attack by promoting a rapid resolution of acute symptoms and decreasing respiratory-related deaths,[41] but also within the next few months by extending the exacerbation-free intervals.[42] However, since viral infections and non-infectious factors can be also involved in the onset of AECOPD, non-controlled use of antibiotics can be associated with increased treatment failures, bacterial resistance and even chances of relapse.[42] Therefore, rational antibiotic therapy is of great importance in clinical practice, and it is largely based on the appropriate and timely identification for bacterial infections.

Some guidelines recommend antibiotic treatment based on respiratory symptoms and increased purulence in particular.[43 44] However, sputum colour alone may not be sufficient to identify patients possibly benefiting from antibiotics.[45] Results from previous studies have emphasised the use of CRP and PCT as predictors in antibiotics prescription in general practice.[46 47] They are, however, not yet available as point-of-care tests in primary care. Some scoring systems such as systemic inflammatory response syndrome score and CRB-65 score may identify severe AECOPD at high risk of bacterial infections, but

no reports have supported their roles as indicators for antibiotic treatment.[48–50]

Previous studies have shown that AECOPD patients with a low BEC have a poorer prognosis, higher risk of bacterial infection, longer hospital stay and increased mortality than those without.[26 38] This study will be a pioneering retrospective study to identify the role of eosinopenia as a reference for antibiotic treatment, and the characteristics of patients who are most likely to benefit from prescribing antibiotics in hospitalised patients with AECOPD. Our results will highlight the issue of antibiotics use in AECOPD, and also raise awareness among other infective diseases. A prospective multicentre study may be required to confirm the results and to provide more consolidate grounds for the role of blood eosinophils in guiding COPD treatment.

There are also some limitations in our study. First, we will collect clinical data from a ready-made database. The clinical recordings may be incomplete and inaccurate, and the disease coding may be insensitive and unspecific. Second, the time span of our cohort is over 11 years, and the techniques of nucleic acid test for pathogen detection have achieved a great development during the recent decade. Therefore, the nucleic acid results will be recorded based on different techniques. As newly-developing techniques such as next-generation sequencing are generally more sensitive than conventional ones such as traditional PCR, some results from early years could be missed and less accurate (false negative or false positive).

ETHICAL APPROVAL AND DISSEMINATION

The data in our study are available on request. Patient privacy records and information are anonymous and hidden before analysis. Results of the study will be presented in a peer-reviewed publication. We will strictly follow ethical guidelines such as the Helsinki Declaration of the World Medical Congress and the Ethical Review of Biomedical Research Involving Humans (Trial). This study has been approved by the Biomedical Ethics Review Board of West China Hospital of Sichuan University (Approval No. 2020-1056).

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