



Review

Pulmonary embolism with chronic obstructive pulmonary disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease. The incidence of COPD is growing annually in China, and it is a significant and growing public health burden. Multivariate analysis showed that COPD was one of the independent risk factors for the occurrence of pulmonary embolism (PE), and the incidence of PE was significantly higher in COPD patients than in normal subjects. However, PE is often overlooked in patients with acute exacerbation of COPD (AECOPD) because there are many similarities in clinical symptoms between PE and AECOPD, which are difficult to distinguish, resulting in the failure of timely treatment and poor prognosis. Therefore, it is of great significance to understand the clinical manifestations, diagnosis, and treatment of COPD combined with PE for making a more accurate diagnosis, providing timely and effective treatment, and improving the prognosis of such patients.

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Epidemiology

In a study published by the World Bank/World Health Organization, chronic obstructive pulmonary disease (COPD) is ranked as the fourth leading cause of chronic disease morbidity and the fifth cause of mortality in the United States, and is expected to become the third leading cause of death in the global disease burden

by 2020.¹ COPD is a common disease characterized by persistent restricted airflow that eventually progresses to chronic conditions such as cor pulmonale and respiratory failure, which can be prevented and treated. Pulmonary embolism (PE) is characterized by an embolus, mainly by thrombus known as pulmonary thromboembolism (PTE), running to the pulmonary artery with blood flow and causing embolism, leading to a progressive increase of the pulmonary artery pressure, right heart failure, and eventually death. COPD patients are prone to PE due to systemic inflammation and other co-existing diseases.² A population-based retrospective cohort study found that 12.31 out of 10,000 COPD patients developed PE each year, approximately four times the rate of non-COPD patients.³ In addition, the

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prevalence of PE has been noted to be higher among acute exacerbations of chronic obstructive pulmonary disease (AECOPD) patients.⁴ Venous thromboembolism (VTE) is a type of disease including deep vein thrombosis (DVT) and PTE. The higher the degree of airway obstruction in COPD patients, the higher the risk of VTE in those patients.⁵ Complicated PE is not uncommon in patients with AECOPD. Different studies have shown that the prevalence of PE in patients with AECOPD is very different. Ali et al⁶ showed that approximately 3.3%–29.1% of patients clinically diagnosed with AECOPD had PE. Dentali et al⁷ showed that chest angiography examination of AECOPD patients with clinically suspected PE was found to have an average prevalence of 12.66% of diagnosed PE. Hassen et al² found during the study that the incidence of PE complication in 131 COPD patients admitted to the ICU due to severe exacerbation was 13.7%. Research by Aleva et al showed that the pooled prevalence of PE in 30% of AECOPD patients with no clear etiology was 16.1% (95% CI, 8.3%–25.8%) among 880 COPD patients.⁸ The prevalence of PE was significantly higher in whites and African Americans than in Asians, and was significantly higher in hospitalized patients than in emergency department patients.⁹ According to the multivariate analysis, age, female, hypertension, $\text{PaCO}_2 \leq 40$ mmHg, clinical signs and symptoms suggestive of DVT, invasive mechanical ventilation, fixation, and peripheral vascular disease were all significantly associated with a higher prevalence of PE in AECOPD patients.^{7,10} There are many risk factors associated with COPD combined with PE. Among them, polycythemia in low-risk COPD patients with PE is one of the independent risk factors associated with in-hospital all-cause mortality.¹¹ Studies have shown that the increase in platelet distribution width (PDW) among COPD patients complicated with PE is related to the occurrence of PE.^{12,13}

COPD patients often develop coagulation dysfunction. Many mechanisms, including systemic inflammation, oxidative stress, endothelial dysfunction, hypercoagulability, and hypoxemia, may increase the risk of thromboembolism in COPD patients.^{14,15} Inflammation promotes blood hypercoagulability in various ways. Some inflammatory markers in the serum of COPD patients are related to the development of COPD.¹⁶ In particular, interleukin-6 and tumor necrosis factor alpha can activate the coagulation function through tissue factor (TF), and then trigger the coagulation cascade. In addition, these cytokines can further lead to local hypercoagulation by inhibiting plasminogen activators and reducing the fibrinolytic

potential.¹⁷ Growth differentiation factor 15 (GDF-15) is one of the biomarkers of COPD, which is not only related to the severity of thrombosis in DVT patients, but also related to the increased incidence of PE.^{18,19} Clinical studies have shown that blood GDF-15 expression is positively correlated with the annual incidence of COPD and all-cause exacerbation.²⁰ These findings suggest that GDF-15 may not only indicate the severity of thrombosis, but also be a potential therapeutic target for DVT.¹⁹ Studies have also shown that eosinophilia is also associated with AECOPD progression, and the reliability of plasma eosinophilic activation marker levels in AECOPD patients is significantly increased.²¹

Clinical features

Acute PE in patients with AECOPD is usually difficult to diagnose clinically because the clinical manifestations of these two diseases are often similar.²² PE manifests as shortness of breath, chest tightness, chest pain, and hemoptysis, and is often accompanied by hemodynamic instability such as hypotension and hypoxia.²³ Multiple studies have shown that patients with AECOPD combined with PE generally have more chest pain and fewer symptoms of respiratory tract infection than those without PE.^{8,9} The COPD patients with PE were less likely to develop cough, dyspnea, and syncope, whereas COPD patients who are prone to developing PE complications are often associated with lower extremities thrombosis.²⁴ The clinical manifestations of DVT include changes in lower extremity swelling, pain, edema, and increased skin surface temperature. Approximately 30%–50% of DVT patients may develop PE without receiving treatment.²⁵ VTE is more common in hospitalized patients with AECOPD who usually have a history of varicose veins in the lower limbs extremities and a longer immobilization time (≥ 3 days), and are accompanied by lower extremities swelling, pain, difficulties in walking, diuretic use, fever, syncope, and other problems.¹⁰ Lower respiratory tract infections and heart failure have always been considered as the most frequently encountered among the known causes of exacerbation.²⁶ In patients with AECOPD of unknown cause, pleural chest pain and heart failure were more strongly associated with PE, while symptoms of respiratory infection were less frequent.⁸

Studies have shown that D-dimer levels and the Wells criteria can be used to determine whether or not AECOPD patients are evaluated for a thromboembolic

event.²⁶ Patients with AECOPD combined with VTE had higher D-dimer but lower hemoglobin levels than those without VTE.¹⁰ Patients with high levels N-terminal pro B-type natriuretic peptide are more likely to develop PE.²⁷ The plasma level of miR-221 in patients with acute PE was significantly increased when compared with healthy individuals.²⁸ Elevated blood eosinophil levels, defined as ≥ 350 cells/L, in COPD patients can accelerate disease progression and loss of lung function if left untreated.²⁹ The eosinophils level can be used as a biomarker to predict the risk of all-cause mortality in hospitalized patients with COPD exacerbation, and thromboembolism occurs relatively commonly in patients with hypereosinophilic syndrome.^{30,31} According to the literature, eosinophilia can lead to multiple arterial and venous thromboses.³² It has previously been reported that hypereosinophilia can result in hypercoagulability. Eosinophils contain cationic cytotoxic proteins, such as eosinophilic peroxidase and platelet-activating factor, which induce and amplify inflammatory responses, damage cells, promote blood coagulation, and lead to tissue damage. In addition, eosinophil cells can store TFs, which are believed to be the main initiator of blood clotting.³³ In addition, glucocorticoid provided effective short-term control of hypereosinophilia to delay thrombosis.³² Aleva et al⁸ found that in AECOPD patients with PE, 68% of the emboli were located in the main pulmonary arteries, lobar arteries, or interlobar arteries. Hlapčić et al¹³ showed that the platelet index can be used as one of the diagnostic indicators of COPD disease progression. Wang et al¹² found that PDW were often elevated in COPD patients combined with PE. Şahin et al³⁴ suggested that red blood cell distribution width (RDW), platelet/lymphocyte ratio, and neutrophil/lymphocyte ratio can be used for assessing the severity of the COPD exacerbation, which are simple and cost-effective.

Both the IMPROVE bleeding score and Padua prediction score (PPS) recommended by guidelines are effective tools to assess the risk of VTE.³⁵ In the American College of Chest Physicians (ACCP) guidelines, PPS can be used to predict a patient's risk grade for VTE, and only patients rated as high-risk should be given pharmacologic prophylaxis of VTE.³⁶ Patients with embolus should receive anticoagulant therapy at the proximal pulmonary artery.³⁷ The ACCP recommends a minimum duration of anticoagulant therapy (3 or ≥ 6 months) depending on the patient's risk assessment status.³⁶ The vena cava filter is beneficial for elderly hospitalized patients with COPD and PE. Stein et al³⁸ reported a 2.1% reduction in the

absolute risk of death for patients over 50 years of age, and a significantly lower case fatality rate for patients over 80 years of age (9.1%) with filter insertion than for patients without filter insertion (14.4%). However, deep venous filters are not recommended as a routine treatment in the absence of contraindications to anticoagulant therapy according to ACCP guidelines.³⁷ Therefore, the risk of thromboembolism in AECOPD patients, especially in hospitalized patients, needs to be carefully assessed.

Diagnosis and treatment

Any patient with chronic cough or expectoration, recurrent lower respiratory tract infections, dyspnea, and/or a history of exposure to risk factors should have a diagnosis of COPD excluded at the time of definitive diagnosis. According to the Global Initiative on Chronic Obstructive Pulmonary Disease (GOLD) standard, pulmonary function test is the most accurate method to diagnose COPD. Patients with forced expiratory volume in one second (FEV₁)/forced vital capacity value < 0.70 using pre-bronchodilator obstructive pulmonary spirometry are diagnosed with COPD.¹ AECOPD grades vary and so does treatment. Patients in different grades are treated in outpatient clinics, hospital wards, or ICU unit for severe cases. Treatment was administered according to the severity of the patient's illness, including oxygen therapy, bronchodilators, use of hormones, antimicrobial therapy, and mechanical ventilation therapy. Moreover, the symptoms and signs of PE are usually non-specific. In the majority of COPD cases, patients with dyspnea, chest pain, syncope or hemoptysis should be highly suspected of the occurrence of PE. However, PE may be asymptomatic or occasionally diagnosed while examining patients for other diseases. Elevated D-dimer does not confirm the diagnosis but can only be used as a way of excluding the diagnosis. Acute PE can be excluded if D-dimer < 500 $\mu\text{g/L}$. Studies have shown that the diagnostic accuracy can be improved by D-dimer test in combination with Simplified Geneva Score pre-test.³⁹ Studies have also shown that albumin ($P = 0.0002$) and RDW ($P = 0.0446$) significantly correlates with the occurrence of acute PE. The combined diagnosis of albumin and RDW had the highest sensitivity and specificity, and the threshold was ≤ 3 g/dL, and > 14 g/dL, respectively.⁴⁰ End-tidal carbon dioxide (ETCO₂) is also a meaningful indicator for the diagnosis of PE. When 34 mmHg is the optimal cut-off point for the diagnosis of PE, PE can be reliably and correctly excluded in combination with clinical probability.⁴¹ Yücel et al⁴² found that considering ETCO₂

>28.5 mmHg as limit, 95% patients with low Wells and 100% patients with Modified Geneva system scores could exclude the diagnosis of PE. Patients with low Wells and Modified Geneva scoring system scores with alveolar dead space fraction <0.128 could be completely ruled out the diagnosis of PE as well. On the contrary, the results are helpful for the diagnosis of PE. When the ETCO_2/O_2 of D-dimer positive patients at moderate-risk was less than 0.28, the probability of segmental or massive amounts of PE significantly increased.⁴³ The study also found that the monocyte to large platelet ratio can also be used as a diagnostic tool for PE in AECOPD patients as it is simple, reliable, and widely used, and has high sensitivity and high specificity.⁴ Computed tomography pulmonary angiography is the preferred imaging method for the suspicion of PE, while selective pulmonary angiography is the “gold standard” for the diagnosis. It can be diagnosed directly by signs that manifest as pulmonary artery filling defects, or other indirectly by signs such as wedge-shaped pulmonary fields, banded densities or discoid pulmonary opacities, central pulmonary artery dilatation, and reduced or absent distal vascular branches. Ventilation/perfusion single-photon emission computed tomography (V/Q SPECT) can also be used for diagnosis, especially as a first choice for pregnant women to avoid excessive radiation damage.²³ ESC 2019 and the European Respiratory Society redefined the use of D-dimer in the diagnosis of acute PE, using an age-adjusted cut-off or adapted to clinical probabilities instead of fixed cut-off levels. The guidelines recommend a combination of clinical, imaging, and laboratory findings to determine the severity of pulmonary embolism and recommend different treatment options such as anticoagulants alone or a combination of thrombolytic drugs, catheter intervention, and surgery. Exercise therapy is feasible and safe for patients after surgical treatment of COPD or for patients with appropriate anticoagulation after PE.⁴⁴ Marika et al⁴⁵ suggested that V/Q SPECT is useful for diagnosing both acute and chronic PE, and can be diagnosed when more than one subsegment shows V/Q mismatches representing anatomic lung units. Ventilation imaging using technegas can also be used to diagnose PE in patients with severe COPD, not possible with radiolabeled liquid aerosols.

Controlling the risk factors for the development of COPD is necessary for the fundamental prevention and treatment of COPD. Smoking cessation is a vital intervention. Pharmacotherapy and nicotine replacement therapy can be used as an adjunct to smoking cessation in the absence of contraindications and this improves long-term abstinence rate.⁴⁶ Smoking cessation counseling

and patient education provided by healthcare professionals, as well as government legislation, have been effective in increasing quit rates. The effectiveness and safety of e-cigarette as a new assistant means of smoking cessation need to be further determined.⁴⁷

The GOLD strategy report emphasizes the importance of choosing the right treatment from the beginning.¹ The therapeutic interventions of COPD is mainly divided into pharmacologic or non-pharmacologic therapies. The purpose is to improve the progression of COPD. The grade of COPD is also used to determine whether some treatments are needed. The pharmacologic treatment of stable COPD includes the application of bronchodilators and anti-inflammatory drugs. As bronchodilators, acting β_2 -agonists and muscarinic antagonists can be classified as long-term and short-term, as they improve lung function by increasing FEV1, and by widening the airway, reducing symptoms and the number of disease exacerbations. Long-acting β_2 -agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are a mainstay of COPD treatment alone or in combination with and/or inhaled corticosteroid (ICS), depending on symptoms and exacerbation history as shown in Fig. 1.¹ Triple therapy (ICS/LABAs/LAMAs) has been shown to have a benefit in reducing the worsening of clinical symptom in COPD patients with blood eosinophil count ≥ 100 cells/ μL , reduced lung function ($\text{FEV}_1 \leq 42\%$), and more symptoms (CAT score ≥ 18).⁴⁸ Currently, the main anti-inflammatory drug used in the treatment of COPD is glucocorticoids, but its long-term use can produce many adverse side effects, even as inhalation therapy.⁴⁹ The principle of using bronchodilators and anti-inflammatory drugs in stable COPD of GOLD 2021 is the same as that of GOLD 2020, which adds more evidence-based medical evidence on non-pharmacologic treatment such as double bronchodilators, triple therapy and pulmonary rehabilitation.⁵⁰ Pulmonary rehabilitation training can improve symptoms such as dyspnea and the quality of life of COPD patients by exercising lung function and endurance,⁵¹ including exercise therapy, which can also further reduce the risk of DVT formation in the lower extremities and reduce the incidence of PE. In addition, COPD patients can also be treated with lung volume reduction surgery, minimally invasive bronchoscopic valve, lung transplantation, and other surgical methods to achieve the purpose of treatment.⁵²

Respiratory infection is the main cause of acute COPD exacerbation. Infection causes changes in the levels of a variety of cytokines *in vivo*, including the

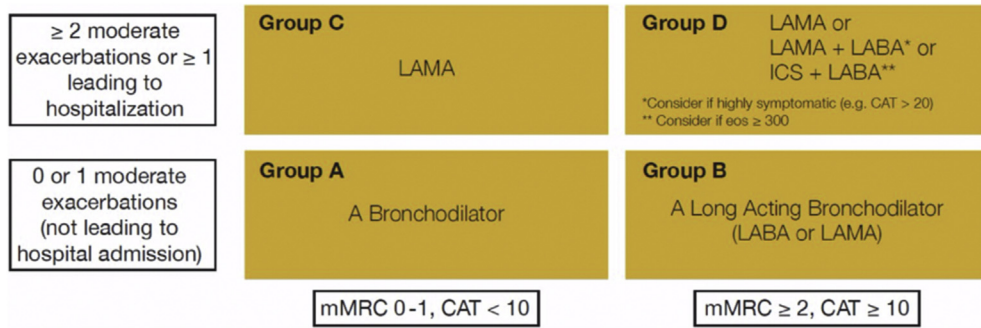


Fig. 1. Initial pharmacologic treatment of COPD, reproduced from Global Initiative for Chronic Obstructive Lung Disease. COPD: chronic obstructive pulmonary disease; CAT: COPD Assessment Test; ICS: inhaled corticosteroid; LABA: long-acting β 2-agonist; LAMA: long-acting muscarinic antagonist; mMRC: modified Medical Research Council dyspnea scale.

elevation of some procoagulants; therefore, the infection is also a risk factor for pulmonary embolism treatment. Anti-infection is not only one of the key treatments for AECOPD, but also reduces the risk of pulmonary embolism. COPD patients are faced with the double problems of the aggravation of their basic pulmonary diseases and potential thrombosis; therefore, it is particularly important to prevent thrombosis thoroughly. Untreated PE carries a high case fatality and morbidity burden, with the risk of death doubling in COPD patients with PE in particular.⁵³ Anticoagulation is the basis of PE treatment; it does not only effectively prevent thrombus formation and relapse, but can promote the dissolution of the fibrinolytic system itself that forms blood clots. Once the diagnosis of acute PE is clear, anticoagulant therapy should be started as early as possible. At the same time, individualized intervention strategies were adopted according to risk stratification, including general support, anticoagulation, thrombolysis, intervention, and surgery.⁵⁴ At present, direct oral anticoagulant (DOAC) is the first-line treatment for PE,⁵⁵ which can also be used for COPD combined with PE. According to the literature, sub-acute pulmonary embolism, as a kind of pulmonary embolism, has poor response to the early use of streptokinase.⁵⁶ PE is an important cause of COPD deterioration in nearly 25% of hospitalized patients. If COPD is not controlled, the incidence rate of patients with PE will increase significantly, and the mortality will be almost double.⁵³ For the treatment of high-risk PE with hemodynamic instability in the acute phase, it is recommended to immediately use unfractionated heparin (UFH) anticoagulation, including intravenous administration and systemic thrombolysis. In the case of contraindication or failure of thrombolysis, pulmonary embolectomy as a surgical treatment can be selected.⁵⁷ In a study by Hara et al,⁵⁸ high-risk PE

patients with massive thrombus should be given DOAC after a single intravenous injection of UFH. The results showed that the hospitalization time of these patients at 3–6 months after treatment was shorter than that in the conventional treatment group, and the reduction rate of pulmonary artery thrombosis was higher. Jing et al⁵⁹ studied 96 patients with hemodynamically stable AECOPD combined with PE and found that low-dose urokinase (500,000 IU/day, 5–7 days) could improve the effective rate of hospitalization and reduce the incidence of adverse events and mean recurrence time within 1 year, but further clinical studies are needed to confirm this. Inferior vena cava filter implantation (IVC) is a good treatment option for high-risk PE patients. Stein et al⁶⁰ conducted a multi-center retrospective study of 440,370 hemodynamically stable AECOPD patients complicated with PE, and the results showed that IVC treatment can reduce the absolute risk of death in patients over 50 years old by 2.1%. The death rate for those over 80 years of age fell from 14.4% to 9.1%. Undoubtedly, in patients with AECOPD complicated by PE without contraindications, it is recommended to immediately initiate standardized anticoagulant therapy and to adjust the treatment strategy according to disease risk stratification and bleeding risk.

Prognosis

PE is one of the common causes of AECOPD, but the symptoms of PE are similar to those of AECOPD, which are easy to be ignored and eventually lead to a high mortality. Piazza et al⁶¹ reported that the hospitalization rate (6.8% vs. 4.0%) and 30-day mortality rate (12.6% vs. 6.5%) were significantly higher in patients with COPD complicated with VTE than in patients without COPD complicated with VTE. The risk

of PE recurrence and fatal PE in COPD patients with PE is higher than in COPD patients with DVT alone. This type of patient usually needs more effective and timely treatment.⁶² In cases registered with RIETE (registry information company), COPD patients at 3 months of follow-up had significantly minor bleeding (4.5% vs. 2.3%), first recurrence of VTE (1.5% vs. 1.1%), or higher mortality (10.8% vs. 7.6%) than those without COPD. Compared with DVT, PE occurred more frequently in COPD patients.⁶³ Similarly, patients with AECOPD combined with PE had slightly higher average length of hospitalization (15.7 vs. 14.2 days, $P = 0.07$) and in-hospital mortality (6.1% vs. 5.1%, $P = 0.62$) compared with those of patients without PE.⁷ Some previous studies have suggested that PE has a higher prevalence during AECOPD, and it also leads to higher morbidity and mortality in COPD patients.⁶⁴ Hassen et al² have showed that the risk of ICU hospitalization and mortality in patients with severe COPD increased with the increase in the incidence of PE. Recently, the results of the ELOPE prospective cohort study demonstrated that nearly half of COPD patients with acute PE, most of whom were at low risk, continued to have dyspnea, movement restriction, and other sequelae within 1 year after the disease, which adversely influences the health-related quality of life.⁶⁵

Conclusions

With the increasing incidence of COPD worldwide, the diagnosis, treatment, and prognosis of COPD have been widely concerned by doctors and patients. PE is considered to be an independent risk factor for poor prognosis in patients with AECOPD, and the mortality rate is higher when combined with PE. However, due to similar clinical symptoms in COPD patients, PE is more likely to be misdiagnosed or ignored. Therefore, in order to prevent thrombosis, early anticoagulant treatment becomes an important part of the treatment of AECOPD patients. In recent years, oral anticoagulants have been widely used in the treatment of COPD complicated with PE. Clinicians should be more alert to the risk of thromboembolism in hospitalized COPD patients, especially those potential patients with unexplained etiologies, or those with etiologies such as obesity and immobilization due to a variety of diseases, malignant tumors, and other risk factors. At the same time, clinicians should prevent the occurrence of PE in COPD patients or improve the survival rate of COPD patients with PE and improve their prognosis. In addition, a number of studies on the epidemiology, risk factors, and prevention of COPD combined with PE

still need to be verified in future clinical studies with large sample sizes.

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Conflict of interest

None.

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