Scientific Research Publishing

Journal of Biosciences and Medicines, 2025, 13(10), 303-319
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Research Progress on the Correlation between Whole Blood Inflammatory Indicators and Pulmonary Embolism

Shangbing Wei[1], Changda Wei[1], Shiguan Luo[2*]

[1]Graduate School, Youjiang Medical University for Nationalities, Baise, China
[2]Department of Cardiothoracic and Vascular Surgery, Baidong Campus, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, China
Email: *1120095181@qq.com

How to cite this paper: Wei, S.B., Wei, C.D. and Luo, S.G. (2025) Research Progress on the Correlation between Whole Blood Inflammatory Indicators and Pulmonary Embolism. *Journal of Biosciences and Medicines*, **13**, 303-319.
https://doi.org/10.4236/jbm.2025.1310026

Received: September 28, 2025
Accepted: October 24, 2025
Published: October 27, 2025

Abstract

Pulmonary embolism (PE) is the most common form of pulmonary thromboembolism and ranks among the leading causes of cardiovascular mortality worldwide. Alongside aortic dissection and acute myocardial infarction, PE is classified as one of the three major life-threatening acute cardiovascular conditions. Its global incidence has been steadily rising, and despite advances in diagnosis and treatment, the mortality rate remains substantial. The pathogenesis of PE is multifactorial and closely intertwined with inflammatory processes. Inflammatory mediators contribute significantly to disease development by promoting thrombus formation, inducing vascular endothelial dysfunction, and fostering a hypercoagulable state. Recent advancements in immunological and hematological assays have enabled the use of whole blood inflammatory markers as valuable tools for evaluating disease risk, predicting prognosis, and monitoring therapeutic response in PE patients. Growing research interest has focused on the clinical relevance of systemic inflammation indices such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), particularly their associations with clinical outcomes in PE. However, these markers still exhibit limitations in sensitivity and specificity, necessitating further validation, standardization, and context-specific application. This article reviews recent progress in the study of whole blood inflammatory indicators in pulmonary embolism, assesses their potential clinical utility and current limitations, and outlines future directions for mechanistic investigations and clinical translation, with the aim of supporting early diagnosis and individualized management strategies for PE.

Keywords

Pulmonary Embolism, Whole Blood Inflammatory Indicators, Risk Assessment, Prognosis, Treatment

1. Preface

Pulmonary embolism (PE) is a clinical condition defined by the obstruction of the pulmonary artery or its branches by emboli of varying origin, resulting in symptoms such as dyspnea, chest pain, hypoxemia, and, in severe cases, hemodynamic instability. Pulmonary thromboembolism (PTE), fat embolism syndrome, amniotic fluid embolism, air embolism, tumor embolism, and other forms of embolism pose significant threats to patients' life and health [1]. Among them, Acute pulmonary embolism (APE) is the most common form of pulmonary embolism and one of the common causes of cardiovascular death worldwide. Together with aortic dissection and acute myocardial infarction, it is known as one of the three major critical conditions of cardiovascular disease. The annual incidence rate is about 1 to 3 percent in Western countries; In the United States, there are approximately 600,000 to 700,000 new cases of PE each year [2]. There is a lack of multi-regional and multicenter epidemiological data in our country. PE is a serious clinical disease whose diagnosis and treatment are challenging. The disease changes rapidly, and the clinical manifestations vary greatly, which can be asymptomatic, atypical, or progressive within a few weeks, or present as sudden dyspnea, chest pain, syncope, and hemoptysis, which are similar to many other diseases [3]. Such as aortic dissection, acute coronary syndrome, etc., often lead to misdiagnosis and missed diagnosis [3]. Autopsy data from patients [4] show that the clinical missed diagnosis rate of pulmonary embolism is as high as 67%, the false positive rate is about 63%, and the correct diagnosis rate is only 9%. At present, the clinical diagnosis of PE mainly relies on imaging and laboratory tests. Digital subtraction angiography (DSA) of the pulmonary artery is the "gold standard" for diagnosing PE, but it is complex to operate, risky, and costly, and requires a high level of technical skills [5]. Other commonly used imaging methods include Computed Tomographic Pulmonary Angiography (CTPA), SPECT/CT pulmonary perfusion imaging, magnetic resonance pulmonary angiography, etc. These imaging methods have disadvantages such as slow timeliness and cumbersome operation in the early identification of PE [6], making them difficult to be widely used in clinical practice. The current methods prevent PE from being identified and diagnosed at an early stage. Therefore, some simple, accessible, low-cost markers are needed to quickly identify, diagnose, and intervene in people with PE.

Recent studies have shown that systemic inflammatory responses play a significant role in the occurrence and development of pulmonary embolism. Inflammation is not only one of the causes of pulmonary embolism, but also has a significant impact on the progression and prognosis of the disease. The inflammatory

response promotes thrombosis and embolic events by activating immune cells and releasing cytokines and procoagulant factors [7]. For example, C-reactive protein (CRP), a classic inflammatory marker, is closely associated with short-term mortality in patients with pulmonary embolism, and an increase in its level suggests a worsening inflammatory state and a poor prognosis [7]. In addition, platelet activation-related indicators such as p-selectin are also associated with right ventricular dysfunction and the risk of recurrence in patients with pulmonary embolism, suggesting a complex interaction [7] between inflammation and the mechanism of thrombosis.

Inflammatory markers based on complete blood cell counts, such as neutrophil counts and their associated ratios, have become a research hotspot in recent years. Neutrophils, as important effector cells of the body's inflammatory response, reflect immune activation and inflammatory status. Studies have found that neutrophil levels are significantly elevated in patients with acute pulmonary embolism and are closely associated with disease risk stratification. Specifically, neutrophil levels were significantly higher in patients at moderate to high risk of acute pulmonary embolism than in those at low risk, and were positively correlated with indicators such as the pulmonary embolism severity score (PESI) [8], high-sensitivity C-reactive protein, and D-dimer. Statistical analysis further indicated that neutrophils were an independent risk factor for medium-high risk acute pulmonary embolism, with diagnostic value superior to pulmonary artery occlusion index and D-dimer, showing a strong dual effect of inflammatory and thrombotic markers [8].

Blood cell-related ratio indicators such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index (SII) have also received extensive attention. Large-scale clinical data analysis shows significant value in predicting 30-day all-cause mortality in patients with pulmonary embolism. High NLR levels are significantly associated with a higher risk of death and can effectively distinguish patients with a lower risk of death, even among those with low-risk pulmonary embolism. Similarly, PLR and SII also showed some predictive potential [9], but NLR's predictive power was more prominent [9]. The advantage of these indicators is that they are derived from routine blood tests, are easy to test, and have a low cost, showing good prospects for clinical application.

In summary, whole blood inflammatory indicators—simple yet effective markers reflecting systemic inflammatory and immune status—play a crucial role in risk stratification and prognostic evaluation in patients with pulmonary embolism. These biomarkers not only facilitate early identification of high-risk individuals but also support the development of individualized therapeutic strategies. Future integration of conventional clinical scoring systems with comprehensive inflammatory profiling holds promise for enhancing diagnostic precision and optimizing treatment outcomes, thereby contributing to reduced morbidity and mortality associated with pulmonary embolism.

2. Types of Inflammatory Markers and Their Clinical Significance

Inflammatory markers are crucial indicators for assessing the body's inflammatory status, particularly in the pathogenesis and prognosis evaluation of pulmonary embolism (PE). Commonly measured in whole blood tests, these markers provide valuable insights into disease progression and patient outcomes.

Elevated levels of C-reactive protein (CRP), a well-established marker of the acute-phase inflammatory response, are commonly indicative of systemic inflammation. Numerous studies have demonstrated that increased serum CRP levels in patients with pulmonary embolism are significantly associated with greater disease severity and an elevated risk of adverse outcomes. For example, a retrospective study showed that the risk of adverse outcomes in patients increased significantly when CRP levels exceeded 124 mg/dL, while CRP, as an independent predictor, has important clinical significance for the prognosis assessment of patients with pulmonary embolism [10]. In addition, the elevated CRP may also reflect the inflammatory state caused by co-infection, which is particularly common in patients with pulmonary embolism. Infection not only exacerbates the inflammatory response but also significantly increases the mortality rate of patients [10]. White blood cell count (WBC), as a direct indicator of the inflammatory response, usually goes hand in hand with the onset of acute inflammation or infection. Changes in white blood cell count and its subsets are particularly important in patients with pulmonary embolism. Studies have shown that the white blood cell and neutrophil counts in patients with pulmonary embolism are significantly elevated and are closely associated [11] with the risk stratification of the disease. The dynamic changes in white blood cells not only indicate an active state of inflammation, but may also be involved in pathological processes such as thrombosis and vascular endothelial injury, thereby influencing the progression of the disease.

The neutrophil-to-lymphocyte ratio (NLR), as a more refined indicator, can comprehensively reflect the inflammatory burden and immune status of the body. In recent years, NLR has been widely used in the assessment of inflammation and prognosis in various diseases, and its value in pulmonary embolism has gradually been recognized. Studies have found that patients with pulmonary embolism who have a higher NLR typically have a poorer prognosis, accompanied by higher mortality and complication rates [12] [13]. In addition, composite indicators such as the Systemic immune Inflammation Index (SII) and the systemic Inflammatory Response Index (SIRI) have been proven to have independent predictive value [11] [12] [14] in diseases such as heart failure, sepsis and pulmonary embolism by combining neutrophil, lymphocyte, monocyte and platelet counts, which further enhance the ability to assess inflammatory status. The platelet-to-lymphocyte ratio (PLR), as another important indicator of inflammation, reflects the activation status of platelets and changes in immune function. In patients with pulmonary embolism, elevated PLR is associated with the severity of the disease and poor prognosis, and when combined with other inflammatory markers, it can improve

the accuracy [14] [15] of prediction. Although the ratio of monocytes to lymphocytes (MLR) is less frequently mentioned in isolation, multiple studies have shown that it is closely associated [14] [16] with inflammatory response and disease prognosis. Studies have shown significant increases in indicators such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index (SII) in patients with acute pulmonary embolism. These indicators were positively correlated with the severity of the disease and short-term and long-term mortality. Specifically, a retrospective cohort study showed that elevated NLR levels in patients with acute pulmonary embolism were significantly associated with an increased risk of 30-day and 1-year death. The study also found that short-term mortality in patients was nearly 13 times higher than that in the baseline group when NLR values exceeded 6. In addition, PLR and C-reactive protein (CRP) as inflammatory indicators also showed some predictive value in patients with pulmonary embolism, but their independent predictive power was not as significant as that of NLR [17]-[19].

The thrombosis mechanism in pulmonary embolism involves the activation of immune cells and the release of pro-inflammatory factors, which induce endothelial cells to express adhesion molecules and reduce nitric oxide bioavailability, thereby impairing endothelial barrier function and promoting a procoagulant state. Concurrently, inflammation enhances tissue factor release, platelet activation, and neutrophil extracellular trap formation, directly driving thrombosis through phosphatidylserine exposure and activation of the coagulation cascade. Moreover, inflammation and the coagulation system engage in a positive feedback loop, further exacerbating vascular dysfunction and thrombus formation. Collectively, these findings indicate that systemic inflammatory markers are key contributors to the development of pulmonary embolism.

3. Application of Whole Blood Inflammatory Markers in the Risk Assessment of Pulmonary Embolism

The role and predictive value of different inflammatory indicators in the occurrence, severity, and prognosis of pulmonary embolism can be analyzed through retrospective studies and prospective cohort studies.

In some retrospective studies, researchers typically collected clinical and laboratory data from patients previously diagnosed with acute pulmonary embolism (APE) to assess the correlation between inflammatory indicators such as systemic immune inflammation index (SII), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and the risk and severity of PE. For example, a retrospective study of 442 patients with acute pulmonary embolism (APE) found that SII levels gradually increased with the severity of pulmonary embolism from non-giant to giant, and SII was an independent predictor of high-risk PE [20], showing high sensitivity and specificity [21] Another retrospective study, which included 138 patients and compared the PE group with the non-PE control group, found that inflammatory indicators such as CRP, white blood cell count, SII, and NLR

were significantly elevated in the PE group and significantly decreased after thrombolytic therapy, suggesting their potential value [22] in treatment monitoring and prognosis assessment.

In prospective cohort studies, emphasizing time series data collection and dynamic monitoring can more accurately assess the changing trends of inflammatory indicators and their predictive power for PE risk. For example, a study involving 223 patients with pulmonary embolism grouped patients by the C-reactive protein/albumin ratio (CRP/Alb) showed that this ratio was not only associated with short-term mortality but also could independently predict late death, demonstrating its potential value [23] as an inflammatory prognostic score. Furthermore, another study involving 234 patients with pulmonary embolism found that, in accordance with the European Society of Cardiology (ESC) guidelines, inflammatory indicators such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic inflammation index (SII) were significantly associated with high-risk pulmonary embolism. These indicators play an auxiliary role [11] in risk stratification.

In addition, some studies have focused on the dynamic changes of inflammatory markers in patients with pulmonary embolism (PE) during treatment and their predictive ability for treatment response. For example, changes in inflammatory markers before and after thrombolytic therapy can reflect the therapeutic effect and the degree [22] of disease activity; Another study showed that an increase in the neutrophil-to-lymphocyte ratio (NLR) was significantly associated with medium-high risk acute pulmonary embolism (APE), and its diagnostic value in risk stratification was superior to that of traditional indicators [8].

Biomarker	Cut-Off Value	AUC	Sensitivity	Specificity
Neutrophil Count	≥7.0 × 10^9/L	-	-	-
C-Reactive Protein (CRP)	≥41.4 mg/L	0.896	90.5%	77.6%
Neutrophil-to-Lymphocyte Ratio (NLR)	5.71	0.78	74.65%	72.13%
Systemic Immune-Inflammation Index (SII)	1161	0.957	91%	90%
Platelet-to-Lymphocyte Ratio (PLR)	256.6	0.693	53.6%	82.2%

Note: 1) Cut-off values and performance metrics are context-dependent (e.g., mortality prediction vs. severity stratification). 2) AUC values indicate overall diagnostic/prognostic accuracy (0.5 = no discrimination, 1.0 = perfect discrimination). 3) CRP and NLR show higher sensitivity, while SII demonstrates balanced sensitivity and specificity for severe PE. 4) Neutrophil count data are limited to specific populations (e.g., COVID-19) and lack comprehensive AUC metrics.

4. The Relationship between Whole Blood Inflammatory Markers and the Prognosis of Pulmonary Embolism

4.1. Relationship between NLR and Prognosis of Pulmonary Embolism

The neutrophil-to-lymphocyte ratio (NLR), as an indicator reflecting the inflammatory state of the body, has shown significant value in the prognosis assessment

of patients with acute pulmonary embolism (APE) in recent years. Studies have shown that elevated NLR is significantly associated with short-term and long-term mortality in patients with APE and can serve as an independent prognostic indicator. In the case of a large retrospective study involving 2072 hospitalized patients with acute pulmonary embolism, the group with an NLR higher than the median (5.12) at admission had an adjusted odds ratio (aOR) of 2.82 for 30-day mortality risk and a 95% confidence interval (CI) of 2.14 - 3.70. The one-year mortality risk aOR was 2.51, and the 95%CI was 2.04 - 3.08, both indicating a higher risk of death. In addition, the predictive power of NLR for mortality risk remained significant in tumor-free and hemodynamically stable subgroup analyses, suggesting its wide applicability [24].

The increase of NLR reflects an active inflammatory response, and inflammation plays an important role in the pathogenesis of pulmonary embolism. Mechanistically, the increase in NLR reflects an immune imbalance of enhanced neutrophil-mediated inflammatory response and reduced lymphocyte count, which may lead to impaired right ventricular function of the pulmonary artery, thereby exacerbating the condition. Studies have shown that elevated NLR is significantly associated with the severity and poor prognosis of acute pulmonary embolism (APE). For example, an NLR ≥ 5.46 can predict all-cause mortality (sensitivity 75.0%, specificity 66.9%) [25]. The study also found that NLR was associated with the severity of pulmonary embolism, and patients with elevated NLR often presented with hemodynamic instability, impaired right heart function, and higher simplified pulmonary embolism severity Index (sPESI) scores [26].

Clinically, NLR, as a simple, economical, and easily accessible hematological indicator, has been shown to be of practical value in risk stratification and prognosis assessment for patients with pulmonary embolism. Patients with high NLR need to be vigilant about the risk of death in the short term and may require more aggressive monitoring and treatment strategies. In addition, dynamic changes in NLR are also used for follow-up and efficacy evaluation to further guide clinical decision-making [24].

4.2. Comparison of Other Inflammatory Markers

In the prognostic assessment of pulmonary embolism (PE), in addition to whole blood inflammatory markers, inflammatory and coagulation-related markers such as C-reactive protein (CRP) and D-dimer have also been extensively studied. These indicators have their own strengths and limitations in different studies, and a comprehensive analysis can help improve the accuracy of prognosis judgment for patients with pulmonary embolism.

First, CRP, as a classic acute-phase response protein, has elevated levels that reflect the inflammatory state of the body. In recent years, the CRP/ albumin ratio (CRP/Alb ratio) has been used as a prognostic scoring indicator based on inflammation. In a retrospective study involving 223 patients with acute pulmonary embolism, the CRP/Alb ratio was confirmed as an independent risk factor for pre-

dicting 30-day and long-term mortality in patients. The study showed that patients with a higher CRP/Alb ratio were not only older but also had higher levels of myocardial injury markers (such as troponin) and higher simplified pulmonary embolism severity index (sPESI) scores, all of which suggest a more severe condition. Another study found that the CRP/Alb ratio outperformed CRP or albumin levels alone in ROC curve analysis for death prediction, demonstrating its advantage [23].

D-dimer, as a fibrin degradation product, is a sensitive marker for thrombosis and dissolution and is often used in the diagnosis and disease monitoring of pulmonary embolism. The combination of systemic inflammatory markers can significantly improve the efficacy of prognosis assessment for patients with pulmonary embolism, especially in risk stratification and mortality prediction. One study found that both NLR and D-dimer were significantly elevated in the poor prognosis group ($P<0.05$), and both were independent risk factors for death. The combined detection had a predictive sensitivity of 86.2% and specificity of 67.6% for the risk of death, and the area under the curve (AUC) was significantly higher than that of a single indicator [27]. Therefore, the dynamic changes of D-dimer in patients with pulmonary embolism and its combined application with inflammatory indicators are of great significance for assessing the severity and prognosis of the disease.

In addition, indicators such as the platelet-to-lymphocyte ratio (PLR) and systemic immune inflammation index (SII) have also been of concern in recent years. Elevated PLR is associated with all-cause mortality within 30 days in patients with acute pulmonary embolism. Studies suggest that PLR > 176 is an independent risk factor for major adverse cardiovascular events (OR = 1.003). However, in multivariable models, the predictive power of PLR may be lower than that of NLR [28].

5. Effects of Treatment on Whole Blood Inflammatory Markers

5.1. The Effect of Thrombolytic Therapy

Thrombolytic therapy serves as a critical intervention for pulmonary embolism (PE), especially in high-risk and intermediate-high-risk patients, not only alleviating clinical symptoms and improving hemodynamic stability but also being closely linked to dynamic alterations in systemic and local inflammatory markers. The fluctuations in these inflammatory indicators before and after thrombolysis reflect the body's response to treatment and provide valuable insights into prognostic trajectories, thereby offering significant support for clinical decision-making.

First, multiple studies have demonstrated that thrombolytic therapy significantly improves hemodynamic status and right ventricular function in patients with pulmonary embolism, as evidenced by reduced pulmonary artery pressure, decreased right ventricular afterload, and increased blood oxygen saturation. For instance, a retrospective analysis of 148 PE patients with pulmonary hypertension revealed that following thrombolytic therapy, respiratory rate, heart rate, and par-

tial pressure of carbon dioxide ($PaCO_2$) significantly declined, while partial pressure of oxygen (PaO_2) and oxygen saturation (SaO_2) markedly increased. Additionally, mean pulmonary artery pressure (MPAP) and right ventricular end-diastolic diameter (RVEDD) showed significant improvement, indicating that thrombolytic therapy effectively alleviates pulmonary vascular obstruction and reduces right heart strain [29].

Inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) showed significant changes before and after thrombolytic therapy, and their levels were closely related to the therapeutic effect. The study further pointed out that $PaCO_2 < 35$ mmHg, D-dimer (D-D) ≥ 11mg/L, IL-6 ≥ 24 pg/mL, and CRP ≥ 16 mg/L were all independent risk factors for ineffective thrombolytic therapy, suggesting that the strength of the inflammatory response affects thrombolytic efficacy and patient prognosis [29] to some extent. This suggests that early monitoring of these inflammatory markers in clinical practice helps to adjust treatment plans in a timely manner and optimize individualized treatment strategies.

In addition, the choice of thrombolytic therapy also affects changes in inflammatory indicators and clinical outcomes. Catheter-assisted thrombolysis (CDT) shows an advantage over systemic thrombolysis (ST) in reducing in-hospital mortality and recurrent PE, and both have comparable bleeding risks. A national cohort study involving 145 patients in the CDT group and 1158 patients in the systemic thrombolysis group indicated that the in-hospital mortality rate in the CDT group was significantly lower than that in the ST group (12.7% vs 21.4%), and both the 1-year all-cause mortality rate and the risk of recurrent PE were lower, suggesting that local thrombolysis is more effective in removing thrombi, reducing inflammation and cardiac burden [30]. Another study also supports that CDT can significantly reduce in-hospital mortality and the incidence of shock, although it may prolong the length of hospital stay; however, overall safety is good [31].

5.2. Potential Role of Anti-Inflammatory Treatment

In recent years, the potential role of anti-inflammatory treatment in patients with pulmonary embolism (PE) has attracted increasing attention. Studies have shown that the inflammatory response not only plays a significant role in the occurrence and development of pulmonary embolism, but also affects the prognosis of patients. Therefore, anti-inflammatory treatment is expected to improve clinical outcomes for patients with pulmonary embolism.

First, anti-inflammatory treatment has shown significant effects against infection-related pulmonary vascular inflammation. In the case of a 57-year-old female patient who was diagnosed with pulmonary embolism and later confirmed to have granulomatous pulmonary angiitis caused by *Mycobacterium goodii*. PET-CT monitoring showed significant improvement in inflammation in the patient after more than 12 months of anti-inflammatory and anti-mycobacterial treatment, suggesting the effectiveness [32] of anti-inflammatory treatment in infectious vasculitis with pulmonary embolism. In addition, the tuberculosis-associated hypercoagu-

lable state suggests that anti-inflammatory treatment may reduce the risk of thrombosis by alleviating systemic inflammation. Relevant studies have highlighted the auxiliary role [33] of anti-inflammatory therapies (such as vitamin D, non-steroidal anti-inflammatory drugs, corticosteroids, and antiplatelet drugs) in tuberculosis with thrombosis.

Secondly, studies on COVID-19-related pulmonary embolism have revealed the potential of anti-inflammatory treatment. In patients with severe COVID-19, the use of dexamethasone significantly reduced the peaks of inflammatory markers such as C-reactive protein (CRP) and D-dimer levels, while the incidence of pulmonary embolism was significantly reduced (4.4% versus 20.0%), suggesting that the anti-inflammatory effect may inhibit the formation of immune thrombi, thereby improving the prognosis [34] of patients. In addition, PET/CT showed a significant reduction in lung inflammation in patients with post-COVID-19 lung disease after receiving anti-inflammatory and anti-fibrotic treatments (such as methylprednisolone and pirfenidone), with improved clinical symptoms and inflammatory biomarkers, further supporting the application value [35] of anti-inflammatory treatment in lung inflammation and thrombosis.

Furthermore, the role of anti-inflammatory treatment in pulmonary embolism associated with non-infectious autoimmune diseases has also attracted attention. For example, in patients with systemic lupus erythematosus (SLE) complicated with antiphospholipid syndrome, anti-inflammatory immunomodulatory treatments such as corticosteroids and hydroxychloroquine after pulmonary embolism can help control disease activity and reduce thrombus recurrence [36]. Similar situations also occur in patients with rheumatoid arthritis who develop deep vein thrombosis and pulmonary embolism during high-dose glucocorticoid treatment, suggesting the need to balance the dual effects [37] of inducing inflammation and relieving inflammation in anti-inflammatory treatment.

6. Future Research Directions and Challenges

6.1. Exploration of Novel Inflammatory Markers

In addition to the above indicators, the application value of novel inflammatory markers in pulmonary embolism is also worth exploring to improve the ability to diagnose and evaluate the prognosis of pulmonary embolism. Vascular endothelial growth factor (VEGF) and tumor necrosis factor-α (TNF-α), as typical inflammatory and vascular regulators, have shown potential application value in the pathophysiological process of pulmonary embolism.

First, VEGF, as a key angiogenic factor, is involved in regulating the proliferation of vascular endothelial cells and vascular permeability, and its role in pulmonary embolism is mainly reflected in promoting local vascular repair and neovascularization of emboli. Studies have shown elevated levels of VEGF in the plasma of patients with pulmonary embolism, which may reflect the body's response mechanism to vascular injury under ischemic and hypoxic conditions. In addition, the dynamic changes of VEGF are closely related to vascular remodeling and

blood flow recovery after pulmonary embolism, suggesting potential biomarker value [29] in disease progression and prognosis judgment.

Secondly, TNF-α, as an important pro-inflammatory cytokine, also plays a significant role in the inflammatory response of pulmonary embolism. TNF-α not only activates endothelial cells, promotes platelet aggregation and white blood cell adhesion, but also induces the release of various inflammatory mediators, exacerbates local vascular inflammation, and microenvironment destruction. Especially in the context of COVID-19-associated pulmonary embolism, TNF-α levels are significantly elevated due to virus-induced cytokine storm, further activating the coagulation system and vascular endothelial damage and promoting thrombosis [38] [39]. This suggests that TNF-α is not only an important driver of inflammatory progression in pulmonary embolism, but may also be a potential target for anti-inflammatory treatment and risk assessment.

In addition, the VEGF family—particularly VEGF-A and VEGF-D—plays a dual role in PE. First, it contributes to pathological processes involving angiogenesis and endothelial barrier disruption. VEGF-A is highly expressed in conditions such as chronic obstructive pulmonary disease (COPD) and acute lung injury, where it is associated with airway inflammation and vascular remodeling. Its expression levels are negatively correlated with lung function decline, including reductions in FEV1 [40]. In the context of PE, elevated VEGF-A may exacerbate right ventricular afterload and promote pulmonary edema by increasing vascular permeability and facilitating inflammatory cell infiltration. Second, the VEGF family also participates in protective mechanisms. Recent studies have shown that VEGF-D exerts protective effects via the VEGFR2 signaling pathway. In experimental models of acute lung injury, administration of exogenous VEGF-D significantly reduces vascular permeability, attenuates leukocyte infiltration, and suppresses the expression of pro-inflammatory cytokines such as TNF-α and IL-6, thereby preserving pulmonary vascular barrier integrity [41]. These findings suggest that VEGF-D may represent a promising therapeutic target for pulmonary vascular injury associated with PE.

6.2. Individualized Application of Markers

However, relying solely on a single inflammatory indicator is difficult to meet the demands of precision medicine. The core of individualized application lies in combining inflammatory indicators with the patient's specific physiological characteristics, pathological state, and clinical background. Through this combination, more precise risk assessment and more scientific treatment strategy formulation can be achieved.

First, the individual characteristics of different patients, such as age, gender, comorbidities, and past medical history, have a significant impact on the interpretation of inflammatory indicators. Specifically, there are significant differences in the risk of thromboembolism and related inflammatory states between diabetic patients and the general population. Based on a large retrospective cohort study

in Taiwan region, researchers first analyzed the impact of relevant clinical factors and then constructed a risk prediction model for venous thromboembolism (VTE) based on clinical factors such as age, hospitalization status, hypertension, and chronic kidney disease, confirming that the integration of individual clinical information and biomarkers can significantly improve the accuracy [42] of prediction. Venous thromboembolism includes pulmonary embolism. Therefore, in the application of inflammatory indicators for pulmonary embolism, multi-dimensional clinical characteristics of patients must be considered to achieve stratified risk management.

Secondly, the combined detection strategy of multiple indicators is an important direction for individualized applications. A single inflammatory indicator, such as D-dimer, is highly sensitive but lacks specificity, and it is difficult to use independently as a basis for diagnosis or prognosis. The latest research shows that multi-marker combinations that combine multiple mechanisms, such as coagulation, platelet activation, and endothelial function, can more comprehensively reflect the pathophysiological process of thrombosis, thereby improving the accuracy [43] of diagnosis and risk stratification. For example, the combination of C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), and other inflammatory factors can lead to individualized treatment plans for different inflammatory states and types of immune responses.

In addition, dynamic monitoring of inflammatory markers plays a crucial role in individualized treatment. Inflammatory status changes as the disease progresses and treatment varies, so real-time tracking of inflammatory indicators such as IL-6 and IL-8 can help doctors adjust treatment plans in a timely manner and avoid overtreatment or potential risk omissions [44]. Combining the patient's genetic background, lifestyle, and comorbidities can further enhance the interpretation and application of inflammatory indicators, thereby achieving precise individualized management [45].

7. Summary and Outlook

Whole blood inflammatory markers, being simple, cost-effective, and readily accessible biomarkers, can effectively reflect the body's inflammatory status and are closely linked to the pathogenesis of pulmonary embolism. Their use in risk stratification and prognostic evaluation of pulmonary embolism (PE) aids in assessing disease severity and predicting patient outcomes, thereby providing valuable support for clinical decision-making. Whole blood inflammatory markers, being simple, cost-effective, and readily accessible biomarkers, can effectively reflect the body's inflammatory status and are closely linked to the pathogenesis of pulmonary embolism. Their use in risk stratification and prognostic evaluation of pulmonary embolism (PE) aids in assessing disease severity and predicting patient outcomes, thereby providing valuable support for clinical decision-making.

Although numerous studies have confirmed the potential value of these inflammatory indicators, inconsistent findings across studies—attributable to variations

in study design, patient populations, and measurement methodologies—have hindered the development of standardized clinical guidelines. Future large-scale, prospective, and multicenter trials are essential to validate the reliability and specificity of these markers across diverse patient groups and to define their precise roles and optimal thresholds in risk stratification and prognostic evaluation. Furthermore, integrating inflammatory indicators with established risk scoring systems, such as PESI and sPESI, may enhance comprehensive risk assessment and improve the accuracy of clinical outcome prediction.

In clinical practice, how to balance the viewpoints reflected by different research results and rationally apply whole blood inflammatory indicators has become an important challenge at present. On the one hand, it is necessary to recognize the value of these indicators as auxiliary tools and avoid over-reliance on a single indicator so as not to overlook the overall clinical situation; On the other hand, it is also necessary to pay attention to its limitations and potential interfering factors such as infections and chronic inflammatory states, which may affect the accuracy of the indicators. Therefore, a scientific assessment and precise management of patients with PE can only be achieved through a comprehensive analysis of clinical manifestations, imaging results, and inflammatory indicators.

Although numerous retrospective and small-scale studies have preliminarily demonstrated the potential value of these inflammatory markers, variability in study design, patient populations, and measurement methodologies has led to inconsistent findings, hindering the development of standardized clinical guidelines. This underscores the need for large-scale, prospective, multicenter trials to validate the consistency and specificity of these markers across diverse patient cohorts and to define their precise roles and optimal thresholds in risk stratification and prognostic evaluation. Furthermore, integrating inflammatory markers with established risk scoring systems—such as PESI and sPESI—may enhance comprehensive risk assessment and improve the accuracy of clinical outcome prediction.

Overall, whole blood inflammatory markers have demonstrated considerable potential in evaluating the risk and prognosis of PE, exhibiting significant clinical relevance. Future advancements will depend on multidisciplinary collaboration, integration of emerging technologies, and big data analytics to further elucidate the biological mechanisms and clinical utility of these markers. Such efforts are expected to enhance diagnostic accuracy and therapeutic strategies for patients with PE and advance the development of precision medicine in this domain.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Boyuk, F. (2021) The Role of the Multi-Inflammatory Index as a Novel Inflammation-related Index in the Differential Diagnosis of Massive and Non-Massive Pulmonary Embolism. *International Journal of Clinical Practice*, **75**, e14966. https://doi.org/10.1111/ijcp.14966

[2] Pulmonary Embolism and Pulmonary Vascular Disease Group of the Respiratory Disease Branch of the Chinese Medical Association, Pulmonary Embolism and Pulmonary Vascular Disease Working Committee of the Respiratory Physician Branch of the Chinese Medical Doctor Association and National Pulmonary Embolism and Pulmonary Vascular Disease Prevention and Control Collaboration Group (2018) Guidelines for Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism. *Chinese Medical Journal*, **98**, 1060-1087. (In Chinese)

[3] Zheng, B., Bian, F., Li, J., Xu, H. and Wang, J. (2021) A Potential Diagnostic Pitfall in ST Elevation: Acute Pulmonary Embolism or ST-Segment Elevation Myocardial Infarction. *Annals of Noninvasive Electrocardiology*, **27**, e12928. https://doi.org/10.1111/anec.12928

[4] Keller, K., Hobohm, L., Ebner, M., Kresoja, K., Münzel, T., Konstantinides, S.V., *et al.* (2019) Trends in Thrombolytic Treatment and Outcomes of Acute Pulmonary Embolism in Germany. *European Heart Journal*, **41**, 522-529. https://doi.org/10.1093/eurheartj/ehz236

[5] Yi, J., Liu, Y.X. and Hu, Z.B. (2016) Comparative Analysis of Three Imaging Examination Methods for Diagnosing Acute Pulmonary Embolism. *Southwest Defense Medical Journal*, **26**, 798-800. (In Chinese)

[6] Xiao, S., Geng, X., Zhao, J. and Fu, L. (2018) Risk Factors for Potential Pulmonary Embolism in the Patients with Deep Venous Thrombosis: A Retrospective Study. *European Journal of Trauma and Emergency Surgery*, **46**, 419-424. https://doi.org/10.1007/s00068-018-1039-z

[7] Galeano-Valle, F., Ordieres-Ortega, L., Oblitas, C.M., del-Toro-Cervera, J., Alvarez-Sala-Walther, L. and Demelo-Rodríguez, P. (2021) Inflammatory Biomarkers in the Short-Term Prognosis of Venous Thromboembolism: A Narrative Review. *International Journal of Molecular Sciences*, **22**, 2627. https://doi.org/10.3390/ijms22052627

[8] Peng, R., Yin, W., Wang, F., Cong, X., Lu, B., Hua, L., *et al.* (2023) Neutrophil Levels Upon Admission for the Assessment of Acute Pulmonary Embolism with Intermediate- and High-Risk: An Indicator of Thrombosis and Inflammation. *Thrombosis Journal*, **21**, Article No. 28. https://doi.org/10.1186/s12959-023-00471-w

[9] Siddiqui, F., Tafur, A., Hussain, M., García-Ortega, A., Darki, A., Fareed, J., *et al.* (2024) The Prognostic Value of Blood Cellular Indices in Pulmonary Embolism. *American Journal of Hematology*, **99**, 1704-1711. https://doi.org/10.1002/ajh.27379

[10] Eggers, A., Hafian, A., Lerchbaumer, M.H., Hasenfuß, G., Stangl, K., Pieske, B., *et al.* (2023) Acute Infections and Inflammatory Biomarkers in Patients with Acute Pulmonary Embolism. *Journal of Clinical Medicine*, **12**, Article 3546. https://doi.org/10.3390/jcm12103546

[11] Özdemir, L., Özdemir, B., Gegin, S., Aksu, E. and Pazarlı, A. (2025) Can Systemic Inflammatory Markers Be Used in Pulmonary Embolism Risk Assessment in Patients with Acute Pulmonary Thromboembolism? *Journal of Inflammation Research*, **18**, 5969-5977. https://doi.org/10.2147/jir.s514111

[12] Shangguan, X., Zhang, Z., Shangguan, X., Wang, J. and Gong, Y. (2025) Association between Whole Blood Cell-Derived Inflammatory Markers and All-Cause Mortality in Patients with Sepsis-Associated Acute Kidney Injury: A Retrospective Study Based on the MIMIC-IV Database. *Journal of Intensive Care Medicine*. https://doi.org/10.1177/08850666251363853

[13] Lu, M., Zhang, Y., Shi, L., Wang, Q., Yang, X., Ma, H., *et al.* (2025) Association of Blood Cell-Derived Inflammatory Markers with Symptoms and Short-Term Treatment Response in Late-Life Depression. *Neuropsychiatric Disease and Treatment*,

21, 1751-1760. https://doi.org/10.2147/ndt.s534235

[14] Lin, Z.B., Teng, Z.H., Xu, Y.R., *et al.* (2025) [Predictive Value of Whole Blood Cell Derived Inflammatory Markers in Combination with NT-proBNP on the Prognosis of Patients with Chronic Heart Failure]. *Chinese Journal of Cardiovascular Diseases*, **53**, 143-150.

[15] Gündüz, Ö., Seven, B., Ozgu-Erdınc, A.S., Ayhan, S.G., Sahin, D., Tekin, O.M., *et al.* (2023) Correlation of Systemic Inflammation Biomarkers and Disease Severity in Pregnant Women with COVID-19. *Revista da Associação Médica Brasileira*, **69**, e20221614. https://doi.org/10.1590/1806-9282.20221614

[16] Zhou, Q., Liu, J., Xin, L., Hu, Y. and Qi, Y. (2023) Systemic Inflammation Response Index as an Emerging Biomarker in Osteoarthritis Patients: A Bibliometric and Large Sample Retrospective Investigation. *Clinical and Experimental Rheumatology*, **42**, 92-103. https://doi.org/10.55563/clinexprheumatol/tygnk6

[17] Duman, D., Sonkaya, E., Yildirim, E., Gidik, E., Tanulku, U., Salturk, C., *et al.* (2021) Association of Inflammatory Markers with Mortality in Patients Hospitalized with Non-Massive Pulmonary Embolism. *Turkish Thoracic Journal*, **22**, 24-30. https://doi.org/10.5152/turkthoracj.2021.190076

[18] Abu Khadija, H., Gandelman, G., Ayyad, O., Jaber, M., Poles, L., Jonas, M., *et al.* (2021) Differential Systemic Inflammatory Responses after TAVI: The Role of Self versus Balloon Expandable Devices. *PLOS ONE*, **16**, e0258963. https://doi.org/10.1371/journal.pone.0258963

[19] Fischer, I., Lala, R., Donaldson, D.M., Schieferdecker, S., Hofmann, B.B., Cornelius, J.F., *et al.* (2024) Prognostic Value of Platelet Levels in Patients with Aneurysmal Subarachnoid Hemorrhage. *Scientific Reports*, **14**, Article No. 16743. https://doi.org/10.1038/s41598-024-67322-0

[20] Konstantinides, S.V., Meyer, G., Becattini, C., *et al.* (2020) 2019 ESC Guidelines for the Diagnosis and Management of Acute Pulmonary Embolism Developed in Collaboration with the European Respiratory Society (ERS). *European Heart Journal*, **41**, 543-603.

[21] Gok, M. and Kurtul, A. (2020) A Novel Marker for Predicting Severity of Acute Pulmonary Embolism: Systemic Immune-Inflammation Index. *Scandinavian Cardiovascular Journal*, **55**, 91-96. https://doi.org/10.1080/14017431.2020.1846774

[22] Kaleli, M.F., Sahin, A.T. and Alsancak, Y. (2024) Evaluation of the Effect of Thrombolytic Therapy on Inflammatory Markers in Patients with Acute Pulmonary Embolism. *Cureus*, **16**, e74926. https://doi.org/10.7759/cureus.74926

[23] Artac, I., Omar, T., Karakayali, M., Ilis, D., Karabag, Y. and Rencuzogullari, I. (2023) Assessment of the Relationship between C-Reactive Protein to Albumin Ratio and Late-Term Mortality in Patients with Acute Pulmonary Embolism. *Asian Cardiovascular and Thoracic Annals*, **31**, 332-339. https://doi.org/10.1177/02184923231167310

[24] Efros, O., Beit Halevi, T., Meisel, E., Soffer, S., Barda, N., Cohen, O., *et al.* (2021) The Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Patients Hospitalized with Acute Pulmonary Embolism. *Journal of Clinical Medicine*, **10**, Article 4058. https://doi.org/10.3390/jcm10184058

[25] Phan, T., Brailovsky, Y., Fareed, J., Hoppensteadt, D., Iqbal, O. and Darki, A. (2020) Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios Predict All-Cause Mortality in Acute Pulmonary Embolism. *Clinical and Applied Thrombosis/Hemostasis*, **26**, 1-7. https://doi.org/10.1177/1076029619900549

[26] Mammadova, A., Taşkaraca, K., Jeyranova, G., Orujlu, A., Tatlılıoğlu, M., Duygulu, S., *et al.* (2025) Correlation between Platelet-to-Lymphocyte Ratio, Neutrophil-to-Lym-

phocyte Ratio and Burden of Thrombus with Disease Severity in Patients with Pulmonary Thromboembolism. *Hämostaseologie*.
https://doi.org/10.1055/a-2506-6705

[27] Shan, T., Li, X., Yan, M. and Pan, X. (2021) Evaluation of Prognosis and Risk of Death by Neutrophil/Lymphocyte Ratio, C-Reactive Protein/Albumin Ratio and Plasma D-Dimer in Patients with Pulmonary Thromboembolism. *International Journal of General Medicine*, **14**, 9219-9225. https://doi.org/10.2147/ijgm.s343039

[28] Ma, Y., Mao, Y., He, X., Sun, Y., Huang, S. and Qiu, J. (2016) The Values of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio in Predicting 30 Day Mortality in Patients with Acute Pulmonary Embolism. *BMC Cardiovascular Disorders*, **16**, Article No. 123. https://doi.org/10.1186/s12872-016-0304-5

[29] Wei, H. (2025) Efficacy and Influencing Factors of Thrombolytic Therapy in Patients with Pulmonary Embolism Complicated Y Pulmonary Arterial Hypertension. *American Journal of Translational Research*, **17**, 2654-2664.
https://doi.org/10.62347/rjdr4749

[30] Lin, D.S., Lin, Y., Wu, C., Lin, H. and Lee, J. (2021) Midterm Prognosis of Patients with Pulmonary Embolism Receiving Catheter-Directed Thrombolysis or Systemic Thrombolysis: A Nationwide Population-Based Study. *Journal of the American Heart Association*, **10**, e19296. https://doi.org/10.1161/jaha.120.019296

[31] Miao, H., Liang, Y., Li, X., Wang, X., Zuo, H., Zeng, Z., *et al.* (2023) Outcomes of Catheter-Directed Thrombolysis versus Systemic Thrombolysis in the Treatment of Pulmonary Embolism: A Meta-Analysis. *Journal of Geriatric Cardiology*, **20**, 459-468. https://doi.org/10.26599/1671-5411.2023.06.005

[32] Pfeuffer-Jovic, E., Heyckendorf, J., Reischl, U., Bohle, R.M., Bley, T., Buck, A., *et al.* (2021) Pulmonary Vasculitis Due to Infection with *Mycobacterium goodii*: A Case Report. *International Journal of Infectious Diseases*, **104**, 178-180.
https://doi.org/10.1016/j.ijid.2020.12.074

[33] Mitroi, D.M., Balteanu, M.A., Cioboata, R., Vlasceanu, S.G., Zlatian, O.M., Catana, O.M., *et al.* (2025) Hypercoagulability in Tuberculosis: Pathophysiological Mechanisms, Associated Risks, and Advances in Management—A Narrative Review. *Journal of Clinical Medicine*, **14**, Article 762. https://doi.org/10.3390/jcm14030762

[34] Jirak, P., van Almsick, V., Dimitroulis, D., Mirna, M., Seelmaier, C., Shomanova, Z., *et al.* (2022) Dexamethasone Improves Cardiovascular Outcomes in Critically Ill COVID-19, a Real World Scenario Multicenter Analysis. *Frontiers in Medicine*, **9**, Article 808221.
https://doi.org/10.3389/fmed.2022.808221

[35] Khandelwal, Y., Ora, M., Jain, B., Dixit, M., Singh, P., Khan, A., *et al.* (2025) Post-COVID-19 Lung Disease: Utility of Biochemical and Imaging Markers in Uncovering Residual Lung Inflammation and Monitoring Anti-Inflammatory Therapy, a Prospective Study. *European Journal of Nuclear Medicine and Molecular Imaging*, **52**, 4674-4684. https://doi.org/10.1007/s00259-025-07297-w

[36] Baya, W., Fredj, F.B., Hassine, I.B., Anoun, J., Mzabi, A., Karmani, M., *et al.* (2020) Systemic Lupus Erythematosus, Antiphospholipid Syndrome and Hashimoto Thyroiditis Occurring in a Patient with Niemann-Pick Disease: A Second Case. *Pan African Medical Journal*, **36**, Article 367.
https://doi.org/10.11604/pamj.2020.36.367.25116

[37] Marinoska, T., Lauf, C., Schorn, C. and Schwarting, A. (2022) Fehlendes Therapiegespräch: Ist es wirklich eine rheumatoide Arthritis? *DMW—Deutsche Medizinische Wochenschrift*, **147**, 1153-1157. https://doi.org/10.1055/a-1887-3463

[38] Page, E.M. and Ariëns, R.A.S. (2021) Mechanisms of Thrombosis and Cardiovascular

Complications in COVID-19. *Thrombosis Research*, **200**, 1-8. https://doi.org/10.1016/j.thromres.2021.01.005

[39] Bakiera, J., Strzelec-Pawełczak, K., Czarnek, K., Osuchowska-Grochowska, I., Bogucki, J., Markiewicz-Gospodarek, A., *et al.* (2023) Novel Inflammatory Markers in Patients with Severe COVID-19 and a Pulmonary Thrombotic Event. *Central European Journal of Immunology*, **48**, 167-173. https://doi.org/10.5114/ceji.2023.131382

[40] Morichika, D., Miyahara, N., Fujii, U., Taniguchi, A., Oda, N., Senoo, S., *et al.* (2019) A Retinoid X Receptor Partial Agonist Attenuates Pulmonary Emphysema and Airway Inflammation. *Respiratory Research*, **20**, Article No. 2. https://doi.org/10.1186/s12931-018-0963-0

[41] Yuan, Y., Sharma, L., Tang, W., *et al.* (2024) Vascular Endothelial Growth Factor-D Improves Lung Vascular Integrity during Acute Lung Injury. bioRxiv. https://doi.org/10.1101/2024.12.16.628787

[42] Lin, C., Chen, C., Li, C., Liu, C., Lin, W., Lin, C., *et al.* (2021) Derivation and Validation of a Clinical Prediction Model for Risks of Venous Thromboembolism in Diabetic and General Populations. *Medicine*, **100**, e27367. https://doi.org/10.1097/md.0000000000027367

[43] Joy, S., Venkatachalam, K. and Binesh, A. (2026) Emerging Perspectives on Biomarker Panels in Deep Vein Thrombosis: The Combined Roles of D-Dimer, P-Selectin, and Microparticles. *Annals of Vascular Surgery*, **122**, 780-791. https://doi.org/10.1016/j.avsg.2025.08.050

[44] Schmitz, T., Harmel, E., Heier, M., Peters, A., Linseisen, J. and Meisinger, C. (2022) Inflammatory Plasma Proteins Predict Short-Term Mortality in Patients with an Acute Myocardial Infarction. *Journal of Translational Medicine*, **20**, Article No. 457. https://doi.org/10.1186/s12967-022-03644-9

[45] Carollo, C., Sorce, A., Cirafici, E., Ciuppa, M.E., Mulè, G. and Caimi, G. (2025) Silent Inflammation, Loud Consequences: Decoding NLR across Renal, Cardiovascular and Metabolic Disorders. *International Journal of Molecular Sciences*, **26**, Article 8256. https://doi.org/10.3390/ijms26178256