DOI: 10.53469/jcmp.2024.06(09).07

Advances in Pulmonary Embolism Biomarkers

Yihan Chen[1], Yating Duan[1], Yali Qi[2,*]

[1]Qinghai University, Xining 810016, Qinghai, China
[2]Qinghai Provincial People's Hospital, Xining 810007, Qinghai, China
**Correspondence Author*

Abstract: ***Pulmonary embolism is the third leading cause of death in cardiovascular disease worldwide, after myocardial infarction and stroke. Traditionally, pulmonary angiography has been considered the gold standard for diagnosing pulmonary embolism. However, with advancements in medical care, less invasive tests such as computed tomography pulmonary arteriography (CTPA) and ventilation/perfusion imaging (V/Q imaging) have emerged, which, while less invasive than traditional angiography, are still complex and carry various risks. Various biomarkers identified to date have demonstrated reliability in the diagnosis, stratification, and prognosis of pulmonary embolism. Therefore, this paper aims to summarize the relevant biomarkers of pulmonary embolism and provide a basis for improving early diagnosis and treatment.***

Keywords: Pulmonary embolism, Biomarkers**.**

1. Introduction

Pulmonary embolism occurs when substances such as air, fat, or blood clots obstruct the blood vessels within the lungs, with venous blood clots being the most common cause. These clots, referred to as pulmonary thromboembolism (PTE), typically originate in the veins of the legs or pelvic region, with approximately half of deep venous thrombi eventually embolizing to the lungs [1]. Epidemiological surveys have shown that pulmonary embolism is the third most common cause of death among patients hospitalized after myocardial infarction and stroke [2]. Biomarkers, which are disease-related molecular changes in tissues and body fluids, serve as standardized, reproducible, non-invasive, and objective measures that aid in diagnosis, prognosis assessment, and monitoring of therapeutic response in specific disease states. In the context of pulmonary embolism, early diagnosis and treatment are critical; however, invasive tests such as pulmonary angiography or ventilation-perfusion imaging carry significant risks. Therefore, combining clinical signs and symptoms with biomarkers is essential for the early diagnosis and effective management of pulmonary embolism.

2. D-dimer

D-dimer is a degradation product of fibrinolysis that elevates in patients with venous thromboembolism as well as in other non-thrombotic disorders [3]. It serves as an important tool in the diagnosis of acute and chronic pulmonary embolism, with an extremely high sensitivity of ≥95% and a negative predictive value of 99% [4,5]. The D-dimer assay produces virtually no false-negative results and, if the D-dimer test is negative, it can be used in combination with other tests to confidently rule out thrombosis [6]. An observational study of 2,017 patients with suspected pulmonary embolism demonstrated that using a D-dimer threshold of 1,000 ng/mL in patients with low clinical probability scores and 500 ng/mL in those with intermediate scores allowed for the safe exclusion of pulmonary embolism without further diagnostic imaging [7]. During the three-month follow-up period, no recurrent venous thromboembolic events occurred in patients with low or moderate clinical probability scores (0%, 95% confidence interval 0.00% to 0.29%), and the dichotomous D-dimer threshold strategy reduced the need for diagnostic imaging by 17.6% (15.9% to 19.2%) compared to outcome reanalysis using a single 500 ng/mL threshold value. Therefore, low D-dimer values essentially rule out the possibility of pulmonary embolism, highlighting the diagnostic value of a negative test result. However, a high D-dimer value is not diagnostic of pulmonary embolism and can only raise suspicion when considered alongside the patient's clinical presentation. This is because D-dimer levels can also be elevated in conditions such as surgery, trauma, infections, liver disease, pregnancy, convulsions, cardiac disease, and certain cancers, resulting in a low positive predictive value overall [6].

3. Troponin

Troponin is a protein complex in the myocyte cytoskeleton, distinct from actin filaments, microtubules, and myosin filaments. The troponin complex consists of three subunits, namely troponin I, T, and C. Of these, the cardiac isoforms of troponin I and T are specific indicators of cardiomyocyte contraction efficiency [8]. Any clinical condition involving impaired myocyte contraction induces the destruction of troponin complexes, leading to elevated serum levels of troponin T, as observed in pulmonary embolism. A study [9] by Bi et al suggested that elevated troponin levels may indicate right ventricular myocardial injury in patients with pulmonary embolism. The assessment of troponin levels is primarily used for its reliable negative predictive value. A study by Cecilia et al. showed that high levels of troponin were associated with mortality during hospitalization or within 30 days post-diagnosis of acute pulmonary embolism [10]. Similarly, a study by Emilie et al. also found an increased risk of 30-day mortality with elevated troponin levels [11]. This finding may contribute to enhanced risk stratification of patients with pulmonary embolism, which is essential for guiding therapeutic decisions.

4. H-TABP, Heart-Type Fatty Acid Binding Protein

Heart-Type Fatty Acid Binding Protein (H-FABP) is a novel marker of myocardial injury. It is a small cytoplasmic protein involved in fatty acid transport in cardiomyocytes [12] that leaks from damaged myocytes due to increased membrane

permeability. H-FABP has advantages over troponin [13], with studies showing its levels are elevated in various conditions, including stroke, Alzheimer's disease, and cardiovascular disease [14]. Cardiac-type fatty acid binding protein is abundantly present in the cytoplasm of cardiomyocytes [15], is rapidly released after the onset of myocardial injury (within 1 hour), and serves as a potential prognostic marker in diseases where myocardial injury occurs, such as acute congestive heart failure (CHF) and acute pulmonary embolism (APE). The results [16] of Moritz et al showed that both left-sided heart disease and lung disease can lead to increased cardiac strain, resulting in increased secretion of H-FABP. Liu et al [17], in their meta-analysis of the prognostic role of H-FABP in pulmonary embolism, demonstrated that elevated H-FABP levels were associated with a more than 10-fold increase in the risk of adverse events in APE patients. The study [18] by Qian et al also suggested that H-FABP is a superior predictor compared to cardiac troponin in patients with APE. Another study [19] showed that elevated H-FABP levels were linked to the development of right ventricular dysfunction following pulmonary embolism. Therefore, H-FABP, as a novel cardiac marker, holds potential for assessing the severity and prognosis of pulmonary embolism.

5. BNP and NT-proBNP

BNP is a key biomarker in the risk stratification of adverse events in patients with pulmonary embolism. The precise pathophysiological mechanisms behind BNP production and secretion remain unclear, but multiple studies have shown that BNP plays a significant role in homeostasis and hemoregulation [8]. Pro-BNP is cleaved into BNP and N-terminal proBNP, with NT-proBNP being physiologically inactive. However, plasma concentrations of NT-proBNP are 5- to 10-fold higher than those of BNP, and its half-life is longer (20 minutes vs. 2 hours), making NT-proBNP more suitable for measurement. When acute pulmonary embolism occurs, it reduces effective blood flow in the pulmonary vascular bed, increases pulmonary artery pressure, and leads to right heart dysfunction. Although the precise pathophysiological mechanism underlying elevated natriuretic peptide levels and their correlation with ventricular dysfunction remains unclear, various studies [20,21] have suggested that NT-proBNP can serve as a marker for the severity of acute pulmonary embolism (APE). NT-proBNP levels may also be elevated in other conditions, such as left ventricular dysfunction, renal impairment, chronic respiratory disease, and advanced age. Elevated BNP and NT-proBNP are nonspecific and thus have a low positive predictive value for detecting right ventricular dysfunction in pulmonary embolism. However, they correlate with cardiac function and hemodynamic indices, and as non-invasive assessments, they have valuable clinical applications in the stratification and prognosis of patients with pulmonary embolism.

6. Inflammation-related Indicators

The main factors that contribute to the development of pulmonary embolism are hypercoagulability, endothelial damage, and inflammation. Pulmonary embolism occurs when vessel wall inflammation triggers thrombus formation in otherwise undamaged vessels due to the concurrent activation of inflammatory and coagulation pathways. Many elements of the immune system, including cytokines, various leukocytes, and chemokines, play a role in the fundamental inflammatory mechanisms driving thromboembolism. Inflammatory markers have been used for diagnosis, prognosis, and mortality assessment in patients with pulmonary embolism. In recent years, an increasing number of studies have highlighted the role of inflammatory factors in the coagulation cascade response. Inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), erythrocyte distribution width (RDW), C-reactive protein (CRP), and interleukin (IL) may offer valuable insights in the diagnosis and prognosis of pulmonary embolism. Phan et al. conducted [22] a retrospective analysis of biological markers in acute pulmonary embolism patients, revealing that elevated NLR and PLR were associated with all-cause mortality in pulmonary embolism, with these markers significantly elevated among non-survivors compared to survivors. Elevated NLR and PLR among non-survivors suggest that acute pulmonary embolism is associated with an inflammatory state. Alsubhi et al. showed [23] that during acute stress, increased secretion of corticosteroids and epinephrine decreases lymphocyte counts and increases leukocyte counts. The more acute and stressed the condition, the higher the NLR and PLR, as they are part of the systemic inflammatory response, making them useful biomarkers in predicting acute pulmonary embolism.

Red cell distribution width (RDW) represents the percentage of erythrocyte size variation, typically ranging from 12-15%, reflecting the heterogeneity in erythrocyte size distribution. An increase in RDW suggests heightened erythrocyte turnover and production, with high RDW levels associated with inflammation, anemia, hematological disorders, oxidative stress, and various erythropoietic disorders [24]. On a molecular level, elevated RDW has been linked to inflammation, malnutrition, and blood/bone marrow dysfunction, all of which are connected to cardiac dysfunction [25,26]. Elevated RDW may also serve as a biomarker for early hypoxemia [2]. In recent years, various studies [27] have indicated that elevated RDW values are associated with increased mortality in patients with pulmonary thromboembolism. In a systematic review and meta-analysis of RDW in acute pulmonary embolism, RDW was identified as a relatively effective predictive index [28]. A study [29] by Yazici et al. found that elevated RDW levels post-admission were associated with increased mortality. The findings [27] of Babaoglu et al. further support that RDW can be used as an early predictor of mortality, particularly in intermediate-risk patients with PE. Therefore, close monitoring of RDW values after hospitalization is important for improving patient outcomes, as RDW can serve as an early predictor of pulmonary embolism severity and mortality risk.

CRP is an acute phase reactant, widely recognized as a marker of inflammation and tissue injury. Incubation of high-purity CRP with peripheral blood mononuclear cells significantly increases the procoagulant activity of tissue factor, suggesting that CRP may contribute to the pathophysiology of the vascular wall. One study [30] highlighted the prognostic role of CRP in predicting early mortality (within 30 days) in acute pulmonary embolism, finding that patients with early

mortality had elevated CRP levels. Notably, high CRP levels were associated with inflammation, effusion, and infarcts in pulmonary embolism. CRP is a cost-effective and easily accessible biochemical marker that can aid in risk stratification and predict early mortality in patients with acute pulmonary embolism.

Interleukins (ILs) are primarily secreted by leukocytes and macrophages and play a key role in regulating various biological processes and immune responses. ILs are involved in several key processes, including the activation, differentiation, proliferation, maturation, migration, and adhesion of immune cells during inflammatory processes and immune responses. A study [31] showed that higher levels of IL-6 and IL-8 were found in patients with venous thromboembolism, which may serve as early predictors in patients with pulmonary embolism.

Additionally, the systemic immunoinflammatory index (SII) and systemic immune response index (SIRI) can also be used as predictors of pulmonary embolism. In a study [32] involving 168 patients with suspected pulmonary embolism who underwent CTPA, 81 patients were diagnosed with PE, while 87 patients without PE served as the control group. The study results showed that SII and SIRI were significantly higher in patients with PE compared to the control group. The SII had a sensitivity of 75.31% and a specificity of 71.26% in identifying PE patients. The sensitivity of SIRI in identifying PE was 82.72%, with a specificity of 68.97%. However, there is a limited number of studies on this topic, and more prospective studies are needed to confirm the diagnostic value of SII and SIRI in pulmonary embolism.

7. Summary

Patients with pulmonary embolism often present clinically with chest pain, hemoptysis, and dyspnea; however, numerous studies have demonstrated that the clinical manifestations of PE can vary widely. Some patients present with syncope as the primary complaint, others with chest tightness and shortness of breath, and even asymptomatic patients admitted for other illnesses are subsequently diagnosed with PE. Early diagnosis and treatment of pulmonary embolism are crucial, yet achieving early diagnosis remains a challenge, as patients typically do not undergo CTPA as a routine diagnostic procedure upon admission. Therefore, identifying PE-related biological markers through routine examinations, such as blood tests, coagulation profiles, cardiac function tests, and inflammation markers, can be instrumental in the early diagnosis of PE. For patients with a high suspicion of PE based on these indicators, a CTPA examination should be conducted. Concurrently, the patient should be informed about the risk of embolism and preventive anticoagulation should be initiated to ensure early diagnosis and treatment, ultimately reducing PE-related mortality. However, research on some of these PE-related biological markers is still in its early stages, and their sensitivity and specificity require validation through extensive retrospective and prospective studies.

Fund Project

National Key Specialty - Department of Respiratory and Critical Care Medicine (Qinghai Health Office [2023] NO.125).

References

[1] KAHN S R, DE WIT K. Pulmonary Embolism [J]. The New England Journal of Medicine, 2022, 387(1): 45-57.
[2] CHRYSIKOS S, PAPAIOANNOU O, KARAMPITSAKOS T, et al. Diagnostic Accuracy of Multiple D-Dimer Cutoff Thresholds and Other Clinically Applicable Biomarkers for the Detection and Radiographic Evaluation of Pulmonary Embolism [J]. Advances in Respiratory Medicine, 2022, 90(4): 300-309.
[3] DUFFETT L, CASTELLUCCI L A, FORGIE M A. Pulmonary embolism: update on management and controversies [J]. BMJ, 2020: m2177.
[4] KONSTANTINIDES S V, MEYER G, BECATTINI C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS) [J]. European Heart Journal, 2020, 41(4): 543-603.
[5] LINKINS L A, TAKACH LAPNER S. Review of D-dimer testing: Good, Bad, and Ugly [J]. International Journal of Laboratory Hematology, 2017, 39 Suppl 1: 98-103.
[6] COSMI B, LEGNANI C, LIBRA A, et al. D-Dimers in diagnosis and prevention of venous thrombosis: recent advances and their practical implications [J]. Polish Archives of Internal Medicine, 2023, 133(11): 16604.
[7] KEARON C, DE WIT K, PARPIA S, et al. Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability [J]. The New England Journal of Medicine, 2019, 381(22): 2125-2134.
[8] JANISSET L, CASTAN M, POENOU G, et al. Cardiac Biomarkers in Patients with Acute Pulmonary Embolism [J]. Medicina (Kaunas, Lithuania), 2022, 58(4): 541.
[9] BI W, LIANG S, HE Z, et al. The Prognostic Value of the Serum Levels of Brain Natriuretic Peptide, Troponin I, and D-Dimer, in Addition to the Neutrophil-to-Lymphocyte Ratio, for the Disease Evaluation of Patients with Acute Pulmonary Embolism [J]. International Journal of General Medicine, 2021, 14: 303-308.
[10] C B, G M, DR V, et al. Right ventricle assessment in patients with pulmonary embolism at low risk for death based on clinical models: an individual patient data meta-analysis [J]. European heart journal, 2021, 42(33).
[11] E S H, M W J, LE B, et al. Troponin dependent 30-day mortality in patients with acute pulmonary embolism [J]. Journal of thrombosis and thrombolysis, 2023, 56(3).
[12] MOON M G, YOON C H, LEE K, et al. Evaluation of Heart-type Fatty Acid-binding Protein in Early Diagnosis of Acute Myocardial Infarction [J]. Journal of Korean Medical Science, 2021, 36(8): e61.
[13] GOEL H, MELOT J, KRINOCK M D, et al. Heart-type fatty acid-binding protein: an overlooked cardiac biomarker [J]. Annals of Medicine, 2020, 52(8): 444-461.
[14] UNAL E, AKOGLU H, SANRI E, et al. The utility of heart-type free fatty-acid binding-protein (HFABP) levels for differentiating acute ischemic stroke from

stroke mimics [J]. Acta Neurologica Belgica, 2024, 124(1): 183-191.
[15] SUN J H, LIU X K, XING X W, et al. Value of Cardiac Troponin, Myoglobin Combined with Heart-type Fatty Acid-binding Protein Detection in Diagnosis of Early Acute Myocardial Infarction [J]. Pakistan Journal of Medical Sciences, 2023, 39(6): 1690-1694.
[16] MIRNA M, ROHM I, JIRAK P, et al. Analysis of Novel Cardiovascular Biomarkers in Patients With Pulmonary Hypertension (PH) [J]. Heart, Lung & Circulation, 2020, 29(3): 337-344.
[17] LIU M, YUAN X, QIU X, et al. Prognostic role of heart-type fatty acid binding protein in pulmonary embolism: a meta-analysis [J]. Thrombosis Research, 2015, 135(1): 20-25.
[18] QIAN H Y, HUANG J, YANG Y J, et al. Heart-type Fatty Acid Binding Protein in the Assessment of Acute Pulmonary Embolism [J]. The American Journal of the Medical Sciences, 2016, 352(6): 557-562.
[19] JENAB Y, POURJAFARI M, SOTOUDEH M, et al. Comparing the effect of cardiac biomarkers on the outcome of normotensive patients with acute pulmonary embolism [J]. Monaldi Archives for Chest Disease = Archivio Monaldi Per Le Malattie Del Torace, 2017, 87(1): 767.
[20] SAGCAN G, DOGAN Z, UZUN H, et al. Impact of Promising Biomarkers on Severity and Outcome of Acute Pulmonary Embolism [J]. International Journal of General Medicine, 2023, 16: 3301-3309.
[21] KOKALJ N, KOZAK M, JUG B. Post-acute pre-discharge echocardiography in the long-term prognostic assessment of pulmonary thrombembolism [J]. Scientific Reports, 2021, 11(1): 1-7.
[22] PHAN T, BRAILOVSKY Y, FAREED J, et al. Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios Predict All-Cause Mortality in Acute Pulmonary Embolism [J]. Clinical and Applied Thrombosis/ Hemostasis: Official Journal of the International Academy of Clinical and Applied Thrombosis/ Hemostasis, 2020, 26: 1076029619900549.
[23] ALSUBHI Y M, ALHADI A H, HAMMUDAH A M, et al. Comparison of laboratory biomarkers for the prediction of in-hospital mortality and severity of acute pulmonary embolism: A multi-center study [J]. Saudi Medical Journal, 2023, 44(9): 898-903.
[24] HAMMONS L, FILOPEI J, STEIGER D, et al. A narrative review of red blood cell distribution width as a marker for pulmonary embolism [J]. Journal of Thrombosis and Thrombolysis, 2019, 48(4): 638-647.
[25] ALLEN L A, FELKER G M, MEHRA M R, et al. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure [J]. Journal of Cardiac Failure, 2010, 16(3): 230-238.
[26] INUZUKA R, ABE J. Red blood cell distribution width as a link between ineffective erythropoiesis and chronic inflammation in heart failure [J]. Circulation Journal: Official Journal of the Japanese Circulation Society, 2015, 79(5): 974-975.
[27] BABAOGLU E, ULASLI S S. Clinical importance of red cell distribution width and red cell index in pulmonary embolism [J]. European Review for Medical and Pharmacological Sciences, 2023, 27(9): 4108-4115.
[28] LIAO Y, YANG C, BAKEER B. Prognostic value of red blood cell distribution width in patients with acute pulmonary embolism: A protocol for systematic review and meta-analysis [J]. Medicine, 2021, 100(18): e25571.
[29] YAZICI S, KIRIŞ T, SADIK CEYLAN U, et al. Relation between dynamic change of red cell distribution width and 30-day mortality in patients with acute pulmonary embolism [J]. The Clinical Respiratory Journal, 2018, 12(3): 953-960.
[30] BÜYÜKŞIRIN M, ANAR C, POLAT G, et al. Can the Level of CRP in Acute Pulmonary Embolism Determine Early Mortality? [J]. Turkish Thoracic Journal, 2021, 22(1): 4-10.
[31] HALICI B, SARINC ULASLI S, GÜNAY E, et al. Assessment of inflammatory biomarkers and oxidative stress in pulmonary thromboembolism: follow-up results [J]. Inflammation, 2014, 37(4): 1186-1190.
[32] USLU M F, YILMAZ M, ATEŞÇELIK M, et al. The utility of the systemic immune inflammation and systemic inflammation response indices in suspected intermediate-risk pulmonary embolism [J]. Croatian Medical Journal, 2024, 65(1): 13-19.