

Can Systemic Inflammatory Markers Be Used in Pulmonary Embolism Risk Assessment in Patients with Acute Pulmonary Thromboembolism?

Levent Özdemir¹, Burcu Özdemir², Savaş Gegin², Esra Arslan Aksu¹,
Ahmet Cemal Pazarlı³

¹Department of Chest Diseases, Samsun University Faculty of Medicine, Samsun, Turkey; ²Department of Chest Diseases, Samsun Training and Research Hospital, Samsun, Turkey; ³Department of Pulmonary Diseases, Tokat Gaziosmanpaşa University Faculty of Medicine, Tokat, Turkey

Correspondence: Ahmet Cemal Pazarlı, Email dracp60@gmail.com

Background: Understanding the effect of systemic inflammation on the pathophysiology of thromboembolism may provide an approach to determine the course and prognosis of the disease. The aim of this study was to investigate the usability of systemic inflammatory markers in the risk stratification of pulmonary embolism in patients with acute pulmonary thromboembolism (PTE).

Methods: The data of 234 patients diagnosed with pulmonary embolism by computed tomography pulmonary angiography (CTPA) or ventilation perfusion scintigraphy were evaluated retrospectively. Demographic data, co-morbid conditions, and laboratory parameters of the patients were obtained from the hospital data system. Pulmonary embolism risk classification was performed according to the 2019 ESC guidelines as low, intermediate (intermediate-low, intermediate-high), and high risk. Neutrophil - lymphocyte ratio (NLR), platelets-to-lymphocyte ratio (PLR), lymphocyte - monocyte ratio (LMR), lymphocyte / CRP ratio (LCRPR), systemic inflammatory response index (SIRI) (Neutrophil×Platelet/Lymphocyte) and systemic immune-inflammation index (SII) (Neutrophil×Monocyte/Lymphocyte) were calculated using the patients' hemogram (White blood count (WBC), hemoglobin, hematocrit, platelet, neutrophil, lymphocyte, monocyte), C-reactive protein (CRP), lactate, troponin, and d-dimer values at the time of diagnosis.

Results: In our study, WBC, neutrophils, NLR, PLR, SIRI, SII and CRP levels were significantly lower in low risk, while lymphocyte count and LCRPR were significantly higher. Platelet counts were significantly lower in high risk. D-dimer levels were significantly higher in intermediate-high and high risk. Lactate levels were significantly higher in high risk. Troponin levels were significantly higher in intermediate-high risk and high risk. WBC, neutrophils, D-dimer, troponin, lactate levels and NLR, SII, indices were found to be significant biomarkers in predicting high-risk embolism.

Conclusion: Our findings suggest that systemic inflammatory markers may be a clinically important risk determinant in patients with acute pulmonary thromboembolism.

Keywords: pulmonary embolism (PE), systemic inflammation, inflammatory markers, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII)

Introduction

Pulmonary thromboembolism (PTE) is now a common cause of cardiovascular mortality in high-risk patients, with an increasing incidence and decreasing mortality rate. It typically occurs as a complication of deep vein thrombosis (DVT). "Risk assessment" is the most important step in order to accurately predict the treatment approach and mortality risk in acute PTE cases. Hemodynamic instability, the Pulmonary Embolism Severity Index (PESI), electrocardiography, CT angiography, and cardiac biomarkers are used in PTE risk assessment.¹

In the pathogenesis of pulmonary embolism, increased blood coagulability, endothelial damage, and the presence of inflammation gain significance.² Understanding the effect of systemic inflammation on the pathophysiology of thromboembolism may provide an approach to determining the course and prognosis of the disease. In recent years, non-invasive markers have been investigated to assess disease severity and the degree of inflammation in various diseases. It

has been shown that blood indices, such as the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), can predict the prognosis in patients with malignancy, ulcerative colitis, Crohn's disease, stroke, sepsis, and chronic obstructive pulmonary disease (COPD).³ Similarly, it has been shown that NLR and PLR are promising biomarkers for predicting prognosis in patients with acute pulmonary embolism.⁴ In a study, systemic inflammation index (SII) was shown to be superior to other inflammation-based indices in high-risk pulmonary embolism cases.⁵ The insufficient amount of data in the literature and the lack of systematic studies highlight the importance of this issue and the necessity for further research in this area.

The aim of this study was to investigate the usability of systemic inflammatory markers in the risk stratification of pulmonary embolism in patients with acute pulmonary thromboembolism (PTE).

Materials and Methods

The study was conducted at the Pulmonary Diseases Department of Samsun Training and Research Hospital between July 2021 and June 2024, by retrospectively evaluating the data of 292 patients diagnosed with pulmonary embolism through computed tomography pulmonary angiography (CTPA) or ventilation-perfusion scintigraphy (Figure 1).

All patients diagnosed with pulmonary embolism aged ≥ 18 years were included in the study. Patients with pulmonary embolism accompanied by infection (pneumonia, COVID-19, urinary tract infection, etc.) patients with malignancy who received chemotherapy and/or radiotherapy, patients receiving immunosuppressive treatment (eg, corticosteroids, methotrexate, etc.), patients with chronic kidney failure and/or those undergoing dialysis, patients using statins or nonsteroidal drugs and patients with incomplete data were excluded from the study.

Demographic data, comorbid conditions, and laboratory parameters of the patients were obtained from the hospital data system. Pulmonary embolism risk classification was performed according to the 2019 ESC guidelines as low, intermediate (intermediate-low, intermediate-high), and high risk (Figure 2).

The neutrophil-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), lymphocyte/CRP ratio (LCRPR), systemic inflammatory response index (SIRI) (Neutrophil \times Monocyte/Lymphocyte), and systemic immune-inflammation index (SII) (Neutrophil \times Platelet/Lymphocyte) were calculated using the hemogram values (white blood count (WBC), hemoglobin, hematocrit, platelet, neutrophil, lymphocyte, monocyte), C-reactive protein (CRP), lactate, troponin, and D-dimer levels of the patients at the time of diagnosis.

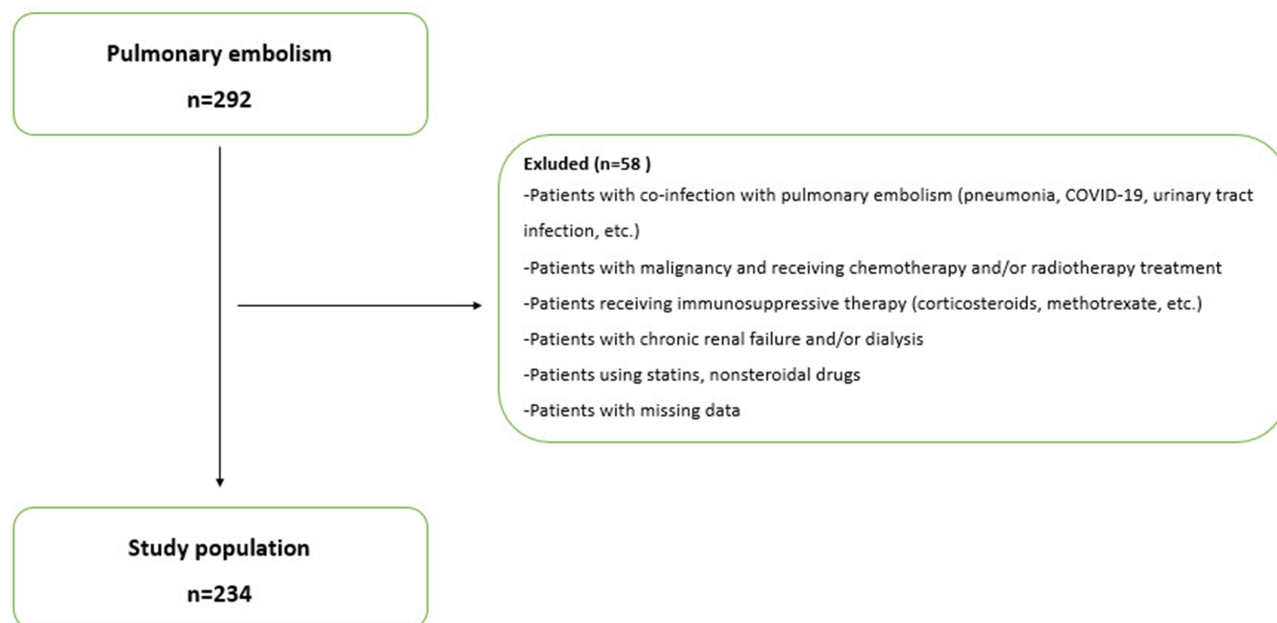


Figure 1 Study population.

Early mortality risk		Indicators of risk			
		Haemodynamic instability ^a	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥1	RV dysfunction on TTE or CTPA ^b	Elevated cardiac troponin levels ^c
High		+	(+) ^d	+	(+)
Intermediate	Intermediate-high	–	+ ^e	+	+
	Intermediate-low	–	+ ^e	One (or none) positive	
Low		–	–	–	Assessment optional; if assessed, negative

Figure 2 Pulmonary embolism risk classification. ^aOne of the following clinical presentations cardiac arrest, obstructive shock (systolic BP <90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite an adequate filling status, in combination with end-organ hypoperfusion), or persistent hypotension (systolic BP <90 mmHg or a systolic BP drop ≥40 mmHg for >15 min, not caused by new-onset arrhythmia, hypovolaemia, or sepsis). ^bPrognostically relevant imaging (TTE or CTPA) findings in patients with acute PE. ^cElevation of further laboratory biomarkers, such as NT-proBNP ≥600 ng/L, H-FABP ≥6 ng/mL, or copeptin ≥24 pmol/L, may provide additional prognostic information. ^dHaemodynamic instability, combined with PE confirmation on CTPA and/or evidence of RV dysfunction on TTE, is sufficient to classify a patient into the high-risk PE category. In these cases, neither calculation of the PESI nor measurement of troponins or other cardiac biomarkers is necessary. ^eSigns of RV dysfunction on TTE (or CTPA) or elevated cardiac biomarker levels may be present, despite a calculated PESI of I–II or an sPESI of 0.

The study complies with the Declaration of Helsinki and approval for the study was obtained from the Ethics Committee for Non-Interventional Clinical Studies of Samsun University (Date: 26.06.2024, Decision No: 2024/12/5).

Statistics

All data were analyzed using the SPSS V 23 Windows program (SPSS Inc., Chicago, IL, USA). The frequencies and percentage values of categorical variables, as well as the mean and standard deviation values of numerical variables, were calculated. The assumptions of normal distribution and homogeneity of variance were tested using the Kolmogorov–Smirnov and Levene tests. Parametric tests were applied for variables that exhibited normal distribution. ANOVA test was performed for more than two groups. Post hoc tests were performed to assess the differences between groups. Non-parametric tests were applied for variables that did not show a normal distribution. The Kruskal Wallis test was applied for more than two groups. Percentages were obtained by calculating sensitivity and specificity values. In predicting high-risk embolism, WBC, neutrophils, NLO, SII, D-dimer, troponin, lactate levels were assessed by calculating the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. Ordinal logistic regression analysis was performed for the effect of biomarkers on high probability of embolism.

Results

Between July 2021 and June 2024, 234 pulmonary embolism patients with a mean age of 63.4 ± 17.5 (Male: 56 ± 17.8 , Female: 69.9 ± 14.5) were evaluated. Of the patients, 125 (53.4%) were female and 109 (46.6%) were male. Among the pulmonary embolism patients, 65 (27.8%) were classified as low risk, 94 (40.2%) as intermediate-low risk, 39 (16.7%) as intermediate-high risk, and 36 (15.4%) as high risk. The most common comorbidities and risk factors were hypertension (51.7%), ischemic heart disease (41%), and deep vein thrombosis (36.8%). The demographic data of the patients are presented in Table 1.

In our study, WBC, neutrophils, NLR, PLR, SIRI, SII, and CRP levels were significantly lower in the low-risk group compared to the intermediate-low-risk, intermediate-high-risk, and high-risk groups, while lymphocyte count and LCRPR were significantly higher (P1, P2, P3). Platelet counts were significantly lower in the high-risk group compared to the intermediate-low-risk and intermediate-high-risk groups (P4, P5). D-dimer levels were significantly higher in the intermediate-high and high-risk groups compared to the low-risk and intermediate-low-risk groups (P1, P2, P3, P4, P5). Lactate levels were significantly lower in the low-risk group compared to the intermediate-low-risk, intermediate-high-risk, and high-risk groups, and in the intermediate-low-risk group compared to the high-risk group. Troponin levels were significantly higher in the intermediate-high and high-risk groups (P2, P3, P4, P5, P6). LMR was found to be significantly higher in low-risk patients compared to intermediate-low and high-risk patients, while it was significantly lower in intermediate-low-risk patients compared to intermediate-high-risk patients (P1, P3, P4) (Table 2).

Table 1 Demographic Features

Demographic features	
Age (years)	63,4 ± 17,5
Gender	
Female n (%)	125 (53,4)
Male n (%)	109 (46,6)
Co-morbidity and risk factors n (%)	198 (84,6)
Hypertension	121 (51,7)
Ischemic heart disease	96 (41)
Deep vein thrombosis	86 (36,8)
Immobilization	57 (24,4)
Surgical	31 (13,2)
Diabetes	27 (11,5)
COPD	24 (10,3)
Alzheimer's	21 (9)
Asthma	16 (6,8)
Cerebrovascular disease	15 (6,4)
Obesity	6 (2,6)
Bronchiectasis	1 (0,4)
Sleep apnea	1 (0,4)
Pulmonary embolism risk n (%)	
Low Risk	65 (27,8)
Intermediate Risk	
-intermediate-low risk	94 (40,2)
- intermediate-high risk	39 (16,7)
High Risk	36 (15,4)

Abbreviation: COPD, Chronic obstructive pulmonary disease.

Table 2 Association of Biomarkers with Pulmonary Embolism Risk

	Low	Intermediate		High	P1	P2	P3	P4	P5	P6
		Intermediate-low	Intermediate-high							
WBC ($\times 10^9/L$)	8.8 ± 2.2	10±3.1	10.7±3.8	10.9±3	0.010	0.005	0.001	NS	NS	NS
Hemoglobin (g/dl)	13±1.9	12.8±2.1	12.3±2	13±1.8	NS	NS	NS	NS	NS	NS
Hematocrit	39.1±5	39.1±5.5	37.7±4.9	39.8±5	NS	NS	NS	NS	NS	NS
Platelets ($\times 10^9/L$)	237.8±71.2	261.1±87.3	236.7±103.9	223.2±79.1	NS	NS	NS	0.026	0.024	NS
Neutrophils ($\times 10^9/L$)	5.3±1.8	7.3±2.6	8±3.3	8.2±2.8	0.000	0.000	0.000	NS	NS	NS
Lymphocyte ($\times 10^9/L$)	2.4±0.9	1.7±0.7	1.8±0.7	1.8±0.9	0.000	0.005	0.000	NS	NS	NS
Monocyte ($\times 10^9/L$)	0.7±0.3	0.7±0.3	0.7±0.3	0.7±0.3	NS	NS	NS	NS	NS	NS
CRP (mgr/L)	43.4±51.7	65.7±67.8	64.7±67.9	60.1±59.5	0.014	0.013	0.033	NS	NS	NS
D-dimer ($\mu g/mL$)	6.1±8.3	7.1±7.2	13.1±7.4	13.8±12	0.05	0.000	0.000	0.000	0.001	NS
Lactate (mmol/L)	1.4±0.5	2.2±0.9	2.5±1	3±1.4	0.000	0.000	0.000	NS	0.005	NS
Troponin (ng/mL)	0.13±0.15	0.10±0.1	0.56±0.51	1.2±4.1	NS	0.000	0.000	0.000	0.000	0.032
NLR	2.4±1.2	5±3.3	5.4±3.4	6.2±4.2	0.000	0.000	0.000	NS	NS	NS

(Continued)

Table 2 (Continued).

	Low	Intermediate		High	P1	P2	P3	P4	P5	P6
		Intermediate-low	Intermediate-high							
LMR	3.8±2.5	2.5±1.2	3.1±1.6	3.1±2.3	0.000	NS	0.018	0.024	NS	NS
PLR	108.8±49.3	173±91.6	164.7±122	164.3±106.6	0.000	0.012	0.004	NS	NS	NS
LCRPR	0.43±1.35	0.12±0.21	0.06±0.08	0.07±0.11	0.000	0.002	0.001	NS	NS	NS
SIRI	1.88±1.34	4±3.36	3.79±3.39	4.31±3.15	0.000	0.000	0.000	NS	NS	NS
SII	586.48±353.95	1256.06±875.79	1229.12±866.5	1312.26±920.45	0.000	0.000	0.000	NS	NS	NS

Notes: P1: Comparison between low risk and intermediate-low risk. P2: Comparison between low risk and intermediate-high risk. P3: Comparison between low risk and high risk. P4: Comparison between intermediate-low risk and intermediate-high risk. P5: Comparison between intermediate-low risk and high risk. P6: Comparison between intermediate-high risk and high risk.

Abbreviations: WBC. White blood count; CRP. C-reactive protein; NLR. Neutrophil-to-lymphocyte ratio; LMR. Lymphocyte-to- monocyte ratio; PLR. Platelets-to-lymphocyte ratio; LCRPR. Lymphocyte-to- C-reactive protein ratio; SIRI. Systemic inflammatory response index; SII Systemic immune-inflammation index NS. Non-specific.

ROC analysis was performed for WBC, neutrophils, NLR, SII, D-dimer, troponin, and lactate levels in predicting high-risk pulmonary embolism. According to the ROC curve, the ideal troponin cutoff value was 0.175, with 72.2% sensitivity and 78.3% specificity, while the ideal lactate cutoff value was 2.45, with 62.9% sensitivity and 73.9% specificity. The ROC curve and cut-off values of the other parameters are shown in Table 3 and Figure 3. Ordinal logistic regression analysis was performed for the effect of biomarkers on high probability of embolism (Table 4). The effect of WBC (Wald=4.027; p=0.045), neutrophils (Wald=6.565; p=0.010), D-dimer (Wald=6.514; p=0.011), troponin (Wald=8.518; p=0.004), and lactate (Wald=15.158; p<0.001) levels on the risk of embolism was found to be significant.

Discussion

This study provides significant findings suggesting that systemic inflammatory markers could be an important clinical risk determinant in patients with acute pulmonary thromboembolism. In particular, WBC, neutrophils, D-dimer, troponin, and lactate levels, as well as NLR and SII indices, were found to be significantly elevated in predicting high-risk pulmonary embolism.

Although several cellular indices such as NLR and SII were significant in univariate analysis, they did not remain independently predictive of high-risk PE in multivariate regression. This discrepancy may be explained by confounding clinical factors not accounted for in the current analysis. Prior literature has demonstrated that these markers are associated with clinical outcomes including mortality, bleeding, and identification of low-risk patients. Therefore, their

Table 3 Diagnostic Accuracy of Biomarkers in Predicting High Risk Embolism

	AUC	95% CI	Cut off	p	Sensitivity (%)	Specificity (%)
WBC (×10 ⁹ /L)	0.613	0.518–0.718	9.945	0.031	58.3	57.1
Neutrophils (×10 ⁹ /L)	0.663	0.564–0.750	6.995	0.002	61.1	59.1
SII	0.613	0.487–0.703	1046	0.031	55.6	68.2
D-dimer (µg/mL)	0.689	0.552–0.761	8.56	0.001	63.3	69
NLR	0.650	0.514–0.739	4.73	0.004	61.1	70.7
Lactate (mmol/L)	0.715	0.573–0.796	2.45	0.000	62.9	73.9
Troponin (ng/mL)	0.769	0.665–0.858	0.175	0.000	72.2	78.3

Abbreviations: WBC, White blood count; NLR, Neutrophil-to-lymphocyte ratio; SII Systemic immune-inflammation index.

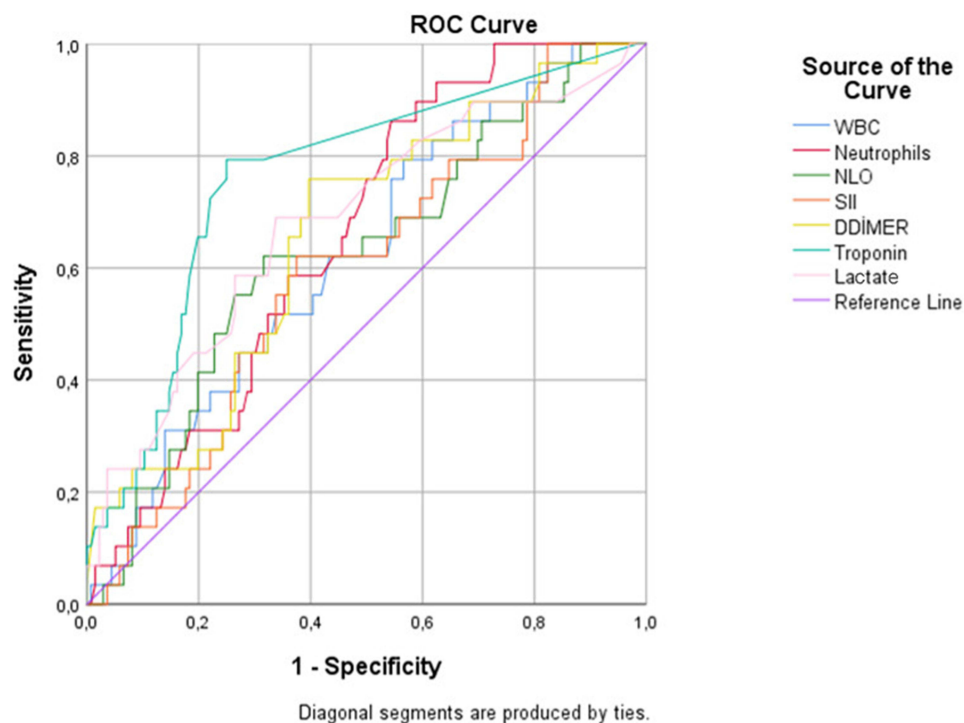


Figure 3 Receiver operating characteristic (ROC) curves of biomarkers in predicting high risk embolism.

prognostic value might be more pronounced in predicting mortality or complications rather than in stratifying patients into high-risk categories according to ESC guidelines.

Supporting this notion, studies by Siddiqui et al^{6,7} have shown that cellular indices are significantly associated with outcomes in venous thromboembolism and pulmonary embolism, including mortality and bleeding risks. The lack of significance in multivariate analysis in our study may reflect interactions with unmeasured clinical variables or limitations in sample size.

In the literature, studies on NLR, PLR, and the SII index indicate that in a study by Karakas et al⁸ evaluating the prognostic value of NLR and PLR in 203 PTE patients, NLR > 5.93 predicted mortality with 87.8% sensitivity and 74.5% specificity, and PLR > 191 predicted mortality with 60.6% sensitivity and 83.2% specificity; in a study by Phan

Table 4 Ordinal Logistic Regression Analysis of Biomarkers

Variable	OR (95% CI)	p
WBC ($\times 10^9/L$)	0.626 (0.396–0.989)	0.045
Neutrophils ($\times 10^9/L$)	2.100 (1.191–3.706)	0.010
NLR	1.039 (0.865–1.249)	0.681
SII	0.999 (0.998–1.000)	0.178
D-dimer ($\mu g/mL$)	1.050 (1.011–1.091)	0.011
Troponin (ng/mL)	4.622 (1.653–12.919)	0.004
Lactate (mmol/L)	1.846 (1.356–2.513)	<0.001

Abbreviations: WBC, White blood count; NLR, Neutrophil-to-lymphocyte ratio; SII Systemic immune-inflammation index; OR, odds ratio; CI, confidence interval.

et al⁹ in 191 PTE patients, NLR > 5.46 predicted mortality with 75% sensitivity and 66.9% specificity, and PLR > 256.6 predicted mortality with 53.6% sensitivity and 82.2% specificity. In the meta-analysis of 7 studies involving 2323 patients with PTE conducted by Wang et al,⁴ it was shown that NLR and PLR were inflammatory markers that could be used to predict prognosis, while in the meta-analysis of 15 studies in PTE patients conducted by Tang et al.³ NLR was found to be a significant predictor of mortality, whereas PLR was not a statistically significant predictor.

In the study by Gok et al,⁵ evaluating the use of SII to predict the severity of PTE, it was found that $SII > 1161$ predicted mortality with 91% sensitivity and 90% specificity. Additionally, a relationship was found between the severity of the disease and CRP and troponin levels. In the study by Mermer et al,¹⁰ evaluating the prognostic value of SII in 191 PTE patients, it was found that lactate, D-dimer, and SII were associated with mortality, and $SII > 903.6$ predicted mortality with 88.5% sensitivity and 58.5% specificity. In the study by Bi W et al¹¹ involving 72 patients with PTE, which evaluated whether brain natriuretic peptide (BNP), troponin I (TnI), and D-dimer serum levels, in addition to NLR, could be used to determine prognosis, it was found that serum BNP (sensitivity: 77.6%, specificity: 69.2%), TnI (sensitivity: 77.8%, specificity: 70.5%), and D-dimer (sensitivity: 74.6%, specificity: 61.2–7%) levels could predict the severity of PTE, and when used in combination with NLR, the sensitivity was 88.9% and specificity was 90.4%. In our study, consistent with the literature, NLR (cut-off: 4.73, sensitivity: 61.1%, specificity: 70.1%) and SII indices (cut-off: 1046, sensitivity: 55.6%, specificity: 68.2%) were found to be significantly high in predicting high-risk PTE.

Elevated troponin levels are used in risk classification in PTE, and its prognostic significance has been demonstrated in previous studies.^{5,12,13} In the study by Lee et al, troponin levels were found to be significantly higher in the intermediate-high and high-risk groups compared to the low and intermediate-low-risk groups.¹⁴ Similarly, several studies have supported these findings, emphasizing the prognostic value of troponin levels in high-risk patients.^{5,15} In our study, consistent with the literature, we found troponin levels to be significantly elevated in the intermediate-high and high-risk groups.

D-dimer is one of the vascular biomarkers with a strong negative predictive value in PTE. Bi W et al¹¹ and Gok et al⁵ demonstrated significant differences in D-dimer levels across low, intermediate, and high-risk groups, showing that D-dimer levels were positively correlated with PTE severity and were associated with mortality. In our study, we found D-dimer levels to be significantly higher in the intermediate-high and high-risk groups compared to the low and intermediate-low-risk groups.

C-reactive protein is associated with RV dysfunction, which is a predictor of prognosis in PTE and could be a promising biomarker for PTE risk classification.¹⁶ Araz et al found that high serum CRP levels were significantly associated with mortality and that changes in serum levels could be used in risk classification.¹⁷ In the study by Sagcan et al, CRP levels were found to be lower in the low-risk group compared to the intermediate and high-risk groups.¹⁸ In our study, we found CRP levels to be significantly lower in the low-risk group compared to the intermediate-low, intermediate-high, and high-risk groups.

In a meta-analysis of 6 studies involving 1706 patients by Wang et al,¹⁹ high lactate levels were shown to be a good predictor of mortality in acute PE patients and could be routinely measured in risk classification. Similarly, Mermer et al¹⁰ found that lactate levels were a risk factor for mortality. In our study, similar to the literature, we found lactate levels to be significantly higher in predicting high-risk pulmonary embolism.

WBC and neutrophil counts are important indicators of inflammation in patients with pulmonary embolism. Peng et al²⁰ found that neutrophil levels were significantly higher in patients with intermediate and high-risk PTE compared to those with low-risk PTE or no PTE. Similarly, in our study, we found WBC and neutrophil counts to be significantly lower in the low-risk group compared to the intermediate-low-risk, intermediate-high-risk, and high-risk groups.

The limitations of our study are its single-center design and retrospective nature. Another limitation is the variability in the time from acute pulmonary embolism development to diagnosis among patients, and the unclear effect of this duration on inflammatory markers.

In conclusion, our findings are consistent with other studies in the literature, suggesting that systemic inflammatory markers may be useful in determining prognostic value in patients with acute pulmonary thromboembolism. These findings suggest that systemic inflammatory markers may be a clinically important risk determinant in patients with acute pulmonary thromboembolism.

Data Sharing Statement

All relevant data supporting the findings of this study are available upon request from the corresponding author (Please contact levant2408@myynet.com).

Ethics Statement

The study complies with the Declaration of Helsinki and approval for the study was obtained from the Ethics Committee for Non-Interventional Clinical Studies of Samsun University (Date: 26.06.2024, Decision No: 2024/12/5).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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