ORIGINAL RESEARCH

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Prognostic Value of Systemic Immune-inflammatory Index in Pulmonary Embolism

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Abstract

Objective: This study aimed to investigate the extent to which the systemic immune-inflammatory index (SII) is associated with patients with acute pulmonary embolism (PE), compare the SII with other commonly used biomarkers and scoring systems, and evaluate its suitability for routine use in PE risk classification.

Materials and Methods: Patients with acute PE admitted in 2021 were retrospectively reviewed. A cut-off value for the SII was obtained to examine the predictive value of the SII for 30-day mortality as the primary outcome. The secondary outcome of the study was to compare the SII with other predictors of 30-day mortality in patients with acute PE.

Results: A total of 139 patients with a mean age of 68.33±14.58 years were included in the study. The cut-off value for 30-day mortality was an SII of ≥0.904 (sensitivity: 88.5%; specificity: 58.4%; area under the curve: 0.803; p<0.001). Lactate, age, right ventricular dysfunction (RVD), and SII ≥0.904 were independent risk factors for 30-day mortality in PE (p<0.05). The SII has a strong correlation with lactate and the presence of RVD (p<0.001).

Conclusion: The SII was found to be strongly associated with RVD, age, and lactate in patients with acute PE. Prospective studies may prove that the SII can fill the gap of inexpensive, rapid, and accessible prognostic biomarkers in rural emergency departments where echocardiography is not accessible.

Keywords: Neutrophil, lymphocyte, pulmonary embolism, pulmonary embolism severity index, systemic immune-inflammation index, Wells

Introduction

Pulmonary embolism (PE) is defined as the occlusion of the pulmonary artery and/or its distal branches. It is the third leading cause of cardiovascular death, with a short-term 30-day mortality rate of 16% [1]. The symptoms and clinical signs of acute PE are non-specific, but generally include chest pain, dyspnea, presyncope, and hemoptysis [2]. Only 5% of patients with acute PE have symptoms of shock or right ventricular dysfunction (RVD) [3]. Predicting prognosis and mortality is a critical step in PE management. Clinicians routinely use risk scoring systems such as Wells, pulmonary embolism severity index (PESI), and modified Geneva scores to identify high- and low-risk patients. In addition, the 2019 European Society of Cardiology PE guidelines recommend the use of markers such as lactate, troponin, interleukin-6, and brain natriuretic peptide for risk classification [4-6]. Despite these recommendations, there is a lack of biomarkers suitable for routine use, inexpensive enough, and accessible in all emergency departments (EDs).

The systemic immune-inflammatory index (SII) is a new parameter based on neutrophil, lymphocyte, and platelet counts. It can be used to simultaneously assess the inflammatory and immune status of patients. Recent studies have reported that higher SII levels are associated with poor prognosis and high mortality rates in malignancies, intracranial hemorrhage, chronic heart failure, coronary artery disease,

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and even coronovirus disease-2019 (COVID-19) patients [7-12]. Begieneman et al. [13] reported the presence of massive inflammatory cell accumulation in the myocardium of patients with PE who died within 48 h. Although inflammation is known to play an important role in atherosclerosis and thrombosis, the relationship between the SII and clinical outcomes in patients with PE remains unclear.

The aim of this study was to determine the extent to which the SII is associated with acute PE, compare the SII with other commonly used biomarkers and scoring systems, and evaluate its suitability for routine use in acute PE risk stratification.

Materials and Methods

This cross-sectional retrospective study was conducted between January 2021 and December 2021 in the ED of a regional academic hospital providing tertiary healthcare services. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Aksaray University Clinical Research Ethics Committee (decision number: 2022/13-03, date: 21.07.2022). Informed consent was not obtained from patients due to the retrospective nature of the study.

Patient Selection

Patients admitted to the ED in 2021 were retrospectively reviewed. The inclusion criteria were positive computed tomographic pulmonary angiography for acute PE and age older than 18 years. Patients were excluded if: 1) aged <18 years, 2) had missing data (the lack of echocardiographic examination data and the lack of SII values data), 3) with pregnancy, 4) with a hematologic disease that may affect the results of the complete blood count, and 5) had a cardiac arrest before arrival to the ED were excluded from the study.

Study Design

Patient demographics (age and sex), heart rate (beats per minute), blood pressure (mmHg), shock index (pulse/systolic blood pressure), medical history (presence of diabetes mellitus, hypertension, chronic obstructive pulmonary disease, deep vein thrombosis), laboratory values [complete blood count, D-dimer (mg/L), troponin (ng/mL), venous blood gas for lactate (mmol/L, before oxygenation)], SII (calculated as neutrophil/lymphocyte ratio x platelet), echocardiographic findings performed <12 hours after diagnosis, clinical risk classification scores (Wells and PESI), length of hospital stay (days), and 30-day mortality were retrospectively recorded. PESI class I-II patients were classified as low risk and those with PESI class III-V patients were classified as high risk. Patients with a Wells score ≤4 were considered unlikely to have PE, whereas those with a score >4 were considered likely to have PE [4].

Echocardiography

In our hospital, all patients diagnosed with acute PE undergo echocardiography within 12 hours. A Philips EPIQ 7c diagnostic echocardiography device (Philips Ultrasound, Bothell WA, USA) is used in the cardiology echocardiography unit. A right ventricle/left ventricle ratio of ≥1 on the end-diastolic apical four-chamber view was accepted as RVD [14,15]. The ejection fraction and pulmonary artery pressure (PAP) were also recorded from the examination results.

Statistical Analysis

The primary endpoint of the study was 30-day mortality. The predictive value of the SII for 30-day mortality was evaluated using receiver operating characteristic (ROC) curves. The cut-off value was determined using the Youden index. Factors influencing mortality were compared using the chi-squared or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U test for continuous and sequential variables. Multivariable logistic regression analysis with a backward stepwise model was performed to identify factors predicting 30-day mortality in patients with acute PE. Age, shock index, D-dimer level, SII, lactate level, PESI, PAP level, and RVD were included in the regression model.

The secondary endpoint of the study was to evaluate the suitability of the SII for routine use in risk stratification. Spearman's correlation tests were performed to evaluate the association between the clinical parameters of SII, RVD, PAP, shock index, and lactate. Data were analyzed using MedCalc software version 20.110, and a p-value of <0.05 was considered statistically significant.

Results

There were 151 patients diagnosed with acute PE in the ED during the study period. Three patients were excluded due to hematologic malignancy, 6 due to echocardiography time >12 h, and 3 due to missing data. Finally, 139 patients with a mean age of 68.33±14.58 years were included in the study. Fifty-four (38.8%) patients were male and 85 (61.2%) were female. The median (interquartile range) SII was 907.04 (1339), and 36 (25.9%) patients had RVD. The median length of hospital stay was 9.61±5.64 days. The 30-day mortality rate was 18.7% (n=26). Table 1 summarizes the clinical, laboratory, and demographic characteristics of the study population.

There was a significant difference in age ($p<0.001$), diastolic blood pressure ($p<0.05$), shock index ($p<0.001$), lactate ($p<0.001$), D-dimer ($p<0.05$), SII ($p<0.001$), PESI score ($p<0.001$), and presence of RVD ($p<0.05$) between patients who died and those who survived. On the other hand, there were no significant differences in sex, chronic diseases, presence of deep vein thrombosis, troponin level, ejection fraction, or Wells score ($p>0.05$). The comparison between patients who died and those who survived is summarized in Table 2.

The ROC analysis showed that the cut-off value for 30-day mortality was an SII of >903.66 [sensitivity: 88.5%; specificity: 58.4%; +likelihood ratio (LR), 2.13; -LR, 0.2; area under the curve: 0.803; 95% confidence interval (CI), 0.727-0.865; p<0.001; Figure 1].

Multivariate logistic regression analysis revealed that lactate, age, RVD, and SII ≥904 were independent risk factors for 30-day mortality in PE (p<0.05). Table 3 presents the details of the regression analysis.

Spearman's analysis showed that SII was moderately correlated with shock index and PAP and strongly correlated with lactate and the presence of RVD (p<0.001) (Table 4).

Discussion

In this retrospective study, we investigated the extent to which SII was associated with 30-day mortality among patients with acute PE diagnosed in the ED. In patients in whom the SII calculated at the time of ED admission is >904, there is an increased likelihood of short-term 30-day mortality [+LR 2.13 (95% CI 1.64-2.76)].

Acute PE is a leading cause of nontraumatic death, accounting for more than 100,000 deaths per year in the United States [16]. It has a wide spectrum, ranging from low-risk patients who can be treated in outpatient clinics and then discharged to high-risk patients who may present with a severe clinical presentation of shock leading to mortality. This risk stratification is important to avoid unnecessary costs and to identify candidates for thrombolytic treatment. Although scoring systems and echocardiographic findings are useful, there is a need for inexpensive, rapid, and accessible biomarkers to predict mortality in patients with acute PE, especially in rural EDs where echocardiography is not accessible.

The SII includes three peripheral blood parameters that comprehensively summarize the immune and inflammatory status of patients. As expected, it has already been reported as a prognostic biomarker in patients with sepsis [17]. In a recent study, Fois et al. [18] reported that patients with higher SII values had significantly worse PaO_2/FiO_2 ratio and chest computed tomography severity scores among patients with COVID-19. They mentioned that the SII may specifically reflect lung damage in patients with COVID-19 rather than a general impairment of their clinical conditions. In addition, the SII has been shown to be associated with worse prognosis in some malignancies, coronary artery disease, and intracerebral hemorrhage [7,10,19-21].

In coronary artery disease, atherosclerosis is strongly associated with an ongoing inflammatory response [22]. NLR is an independent predictor of cardiovascular events and

Table 1. Demographics and laboratory findings of the study population

Age, y, mean ± SD	68.33±14.58
Male sex, n (%)	54 (38.8)
Chronic obstructive pulmonary disease, n (%)	60 (43.2)
Diabetes mellitus, n (%)	39 (28.1)
Hypertension, n (%)	65 (46.8)
Malignancy, n (%)	5 (3.6)
Deep vein thrombosis, n (%)	75 (54)
Systolic blood pressure, mmHg, mean ± SD	109.04±26.21
Diastolic blood pressure, mmHg, mean ± SD	68.06±13.19
Heart rate, beats per min, mean ± SD	104.7±16.55
Shock index, mean ± SD	0.95±0.22
Troponin, ng/mL, median (IQR)	0.05 (0.25)
Lactate, mmol/L, median (IQR)	1.9 (1.23)
D-dimer, mg/L, median (IQR)	5.9 (7.4)
Systemic immune-inflammatory index, median (IQR)	907.04 (1339)
Ejection fraction, %, mean ± SD	56.77±6.11
Pulmonary artery pressure, mmHg, mean ± SD	47.97±13.89
Right ventricle dysfunction, n (%)	36 (25.9)
Wells score, mean ± SD Pulmonary embolism unlikely, n (%) Pulmonary embolism likely, n (%)	6.64±2.2 17 (12.2) 122 (87.8)
Pulmonary embolism severity index score, mean ± SD Low-risk, n (%) High-risk, n (%)	116.45±34.96 26 (18.7) 113 (81.3)
Length of stay in the hospital, d, mean ± SD	9.61±5.64
30-day mortality, n (%)	26 (18.7)

SD: Standard deviation, min: Minute, IQR: Interquartile range, y: Years, d: Days

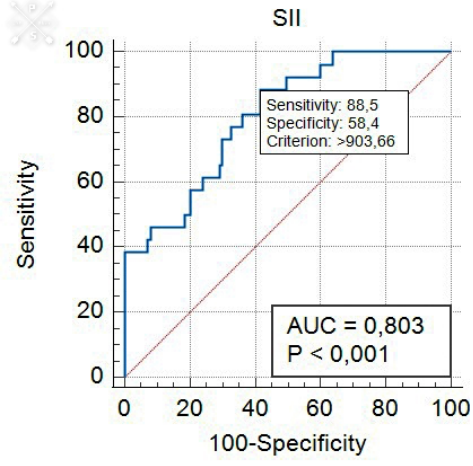

Figure 1. ROC curve of the systemic immune-inflammatory index in predicting 30-day mortality

SII: Systemic immune-inflammatory index, AUC: Area under the curve

mortality in ST-segment elevation myocardial infarction [23]. In addition to NLR, platelets have been considered biomarkers of coronary artery disease by predicting prothrombotic potential and blood vulnerability [24]. Platelet-lymphocyte ratio has been reported to be an effective predictor of severe atherosclerosis [25]. Yang et al. [9] reported that a higher SII was independently associated with a higher future risk of cardiac death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for heart failure in patients with coronary artery disease after coronary intervention. They mentioned that the index could be used as a simple and practical indicator to identify high-risk patients with coronary artery disease after percutaneous coronary intervention.

In patients with acute PE, the primary causes of death are thought to be myocardial injury and acute RVD resulting from an acute increase in intraventricular pressure [4]. Increased

Table 2. Comparison of survivor and death patients

	Alive (n=113, 81.3%)	Death (n=26, 18.7%)	p
Age, y, mean ± SD	66.13±14.59	77.88±10.16	**<0.001**
Male sex, n (%)	45 (39.8)	9 (34.6)	0.623
Chronic obstructive pulmonary disease, n (%)	50 (44.2)	10 (38.5)	0.591
Diabetes mellitus, n (%)	31 (27.4)	8 (30.8)	0.733
Hypertension, n (%)	50 (44.2)	15 (57.7)	0.215
Malignancy, n (%)	3 (2.7)	2 (7.7)	0.235
Deep vein trombosis, n (%)	59 (52.2)	16 (61.5)	0.390
Systolic blood pressure, mmHg, mean ± SD	112.09±26.8	103.46±23.37	0.225
Diastolic blood pressure, mmHg, mean ± SD	69.56±12.69	61.54±13.6	**0.005**
Heart rate, beats per min, mean ± SD	102.6±14.19	110.46±24.09	0.065
Shock index, mean ± SD	0.92±0.19	1.1±0.3	**<0.001**
Troponin, ng/mL, median (IQR)	0.04 (0.25)	0.06 (0.41)	0.501
Lactate, mmol/L, median (IQR)	1.75 (1.13)	3.29 (6.13)	**<0.001**
D-dimer, mg/L, median (IQR)	5.2 (6.1)	8.7 (23.8)	**0.023**
SII, median (IQR)	716 (1034)	1750 (5600)	**<0.001**
Ejection fraction, %, mean ± SD	56.87±6.22	56.35±5.73	0.683
Pulmonary artery pressure, mmHg, mean ± SD	46.89±13.47	52.65±14.98	0.056
Right ventricle dysfunction, n (%)	24 (21.2)	12 (46.2)	**0.009**
Wells score, mean ± SD	6.59±2.21	6.86±2.21	0.581
Pulmonary embolism unlikely, n (%)	15 (13.3)	2 (7.7)	0.433
Pulmonary embolism likely, n (%)	98 (86.7)	24 (92.3)	
PESI score, mean ± SD	108.64±30.89	150.38±31.6	**<0.001**
Low-risk, n (%)	25 (22.1)	1 (3.8)	**0.047**
High-risk, n (%)	88 (77.9)	25 (96.2)	

SD: Standard deviation, min: Minute, IQR: Interquartile range, PESI: Pulmonary embolism severity index, SII: Systemic immune-inflammatory index, y: Years

Table 3. Multivariate logistic regression analysis for 30-day mortality predictors

	Wald	p	Odds ratio	95% Confidence interval
Age	6.456	**0.011**	1.078	1.017-1.143
PAP	1.686	0.194	1.032	0.984-1.083
Shock index	2.817	0.093	7.439	0.714-77.505
D-dimer	0.261	0.610	1.018	0.950-1.091
Lactate	4.866	**0.027**	1.267	1.027-1.563
PESI, high-risk	0.062	0.803	0.743	0.072-7.656
SII ≥0.904	9.476	**0.002**	9.728	2.285-41.410
RVD	8.000	**0.005**	7.112	1.826-27.694

PAP: Pulmonary artery pressure, PESI: Pulmonary embolism severity index, RVD: Right ventricle dysfunction, SII: Systemic immune-inflammatory index

Table 4. Correlations between SII and PAP, shock index, lactate and RVD		
	Correlation coefficient	p
SII - PAP	0.396	**<0.001**
SII - shock index	0.488	**<0.001**
SII - lactate	0.655	**<0.001**
SII - RVD	0.793	**<0.001**
PAP: Pulmonary artery pressure, RVD: Right ventricle dysfunction, SII: Systemic immune-inflammatory index		

pulmonary vascular resistance causes RV dilatation, inotropic and chronotropic stimulation, and systemic vasoconstriction, followed by RV ischemia. RV contractility, RV output, and left ventricular preload decreases [4]. Decreased left ventricular filling and decreased cardiac output lead to platelet activation [26]. In addition, impaired hepatic and renal perfusion contributes to increased platelet activation [27]. It is known that there is a massive accumulation of inflammatory cells in the myocardium of patients of acute PE who died within 48 hours [13]. Previous studies, including those on neutrophils and lymphocytes, have shown that NLR can be used as a prognostic factor in PE [28,29]. A recent study by Gok and Kurtul [30] reported that SII was a strong independent predictor of massive acute PE, with an optimal cut-off value of >1161. The SII may be a useful, novel biomarker for predicting the severity of acute PE in addition to older inflammatory and prognostic biomarkers, such as C-reactive protein and troponin. Our results contribute to these findings. Considering that the potential prognostic value of the SII is similar to that of RVD, with a strong correlation (correlation coefficient: 0.793, $p<0.001$) and increases as a result of RVD and associated immune response, the SII may help clinicians to predict RVD and associated short-term 30-day mortality in acute PE cases.

According to our results, the SII, which is a combination of NLR and platelets, was an independent predictor of 30-day mortality in patients with acute PE, with a sensitivity of 88.5% and specificity of 58.4%. Access to echocardiography is limited in most rural EDs, especially during night shifts. Even when echocardiography is accessible, obtaining images to assess RVD can be difficult in patients with dyspnea who are receiving mechanical ventilation support or who cannot lie in the supine position. Complete blood counts are easy to perform, are inexpensive, provide information on several cell types, and can be used to risk stratify patients diagnosed with acute PE.

Study Limitations

The study has potential weaknesses due to its retrospective nature and several limitations. 1) The number of patients included was small, especially missing data on echocardiographic findings, which led us to exclude some potentially eligible patients, 2) the other prognostic cardiac indicators, such as brain natriuretic peptide, were not compared with the SII because they are not routinely checked in our hospital in patients with acute PE, 3) treatment information, including thrombolysis, which may affect short-term 30-day mortality, could not be verified, 4) there was no significant difference in the Wells score, a widely used scoring system in acute PE, between patients who died and those who survived. Therefore, the Wells score was not included in the regression analysis. We believe that this is due to the fact that our hospital serves a local area, and the patient population does not have sufficient heterogeneity due to the relatively small number of patients.

Conclusion

In conclusion, SII ≥904 can be used as a practical prognostic factor together with RVD, age, and lactate in patients with acute PE. Prospective studies may prove that the SII can fill the gap of inexpensive, rapid, and accessible prognostic biomarkers in rural EDs where echocardiography is not accessible. Large-scale and prospective studies are needed to obtain better results on the association between the SII and mortality in acute PE.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Aksaray University Clinical Research Ethics Committee (decision number: 2022/13-03, date: 21.07.2022).

Informed Consent: Informed consent was not obtained from patients due to the retrospective nature of the study.

Authorship Contributions

Surgical and Medical Practices: İ.K., A.Ç., Concept: M.M., A.Ç., Design: M.M., İ.K., A.Ç., Data Collection or Processing: İ.K., A.Ç., Analysis or Interpretation: A.Ç., Literature Search: M.M., A.Ç., Writing: M.M., İ.K., A.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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