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Is it Possible to Predict High-Risk Patients in Acute Pulmonary Embolism with Systemic Immune-Inflammation Index?

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Abstract

Background: Acute pulmonary embolism (APE) is a cardiovascular emergency that has a high morbidity and mortality probability. The aim of this study is to investigate the clinical value of SII in predicting high-risk patients admitted to the emergency department with a diagnosis of Acute pulmonary embolism (APE)

Materials and methods: This clinical study, which was conducted according to a cross-sectional study design, included 193 patients diagnosed with APE who presented to the emergency department of a tertiary hospital. According to the guideline, patients with Pulmonary Embolism Severity Index (PESI) class III–V or sPESI ≥I were identified as high risk. ROC (Area Under the Curve) analysis was used to determine the cut-off in predicting high-risk APE.

Result: In our research, 71 of the patients had high-risk APE. In detecting high-risk APE, the systemic immune inflammation index (SII) was found to have excellent diagnostic power (AUC: 0.84), while neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and monocyte to lymphocyte (MLR) were found to have acceptable diagnostic power (AUC: 0.76-0.78), red cell distribution width (RDW) to lymphocyte (RLR) was of fair diagnostic power (AUC: 0.68).

Conclusion: We have shown that SII can be a valuable and useful potential biomarker to identify high-risk patients in patients with APE. We also found that MLR and RLR are biomarkers that can be used to predict severe APE.

Keywords: Acute pulmonary embolism, the severity of pulmonary embolism, systemic immune inflammation index, monocyte to lymphocyte ratio, RDW to lymphocyte ratio.

Introduction

Acute pulmonary embolism (APE) is a cardiovascular emergency that has a high morbidity and mortality probability[1,2]. Early detection, accurate diagnosis, and treatment are crucial for reducing the high mortality rate in these patients. Many diagnostic tests and risk scoring are used for this purpose[1,3]. Blood pressure, biomarker evidence of right ventricular (RV) ischemia, lower extremity venous doppler ultrasonography, echocardiographic evidence of RV overload, computed tomography pulmonary angiography, pulmonary embolism severity index (PESI), and the simplified form of PESI (sPESI) are typically used to risk classifying patients[1,4–6]. But these remain both costly and cumbersome for quick decision making[7].

The pathogenesis of venous thromboembolism has been linked to inflammation markers like IL-6, IL-8, and monocyte chemotactic protein, according to a meta-analysis[8]. APE exhibits elevated levels of pro-inflammatory and pro-coagulant factors produced by platelets and leukocytes[9]. Platelet activation and neutrophil count rise as a result of this acute inflammatory response[10]. However, as the disease develops, the lymphocyte count decreases in response to the release of adrenaline and glucocorticoids by a sympathetic response[11]. Studies have demonstrated the importance of inflammatory indices in predicting prognosis in pulmonary embolism, including neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR), mean platelet volume to platelet ratio (MPR), red cell distribution width (RDW) to platelet ratio (RPR), and RDW[12–15].

A new systemic inflammatory index relying on neutrophil, platelet, and lymphocyte counts, the systemic immune inflammation index (SII) (PLT*NLR), has been widely used to predict clinical outcomes in cancer patients[16–18].

The relationship between SII and pulmonary embolism severity in APE patients has not been fully elucidated. The purpose of this study is to look into the clinical utility of SII in predicting high-risk patients presented to the emergency department with APE.

Materials and Methods

This clinical study, which was conducted according to a cross-sectional study design, included 193 patients diagnosed with APE who presented to the emergency department of

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a tertiary hospital between April 18, 2020, and April 18, 2022. The study was approved by Local Ethics Commission (protocol code:121, decision no:121, issue: E-48670771-514.99 date: 18 April 2022). The institutional review board waived informed consent to conduct this retrospective study. The current study was carried out in accordance with the Helsinki Declaration.

Post-study power analysis

According to the cross-sectional study design, the NLR value, which is the main outcome variable, was used to determine the reliability assessment (post-study power) of the number of patients included in the groups. While NLR was 9.58±7.24 high-risk APE, it was 5.12±3.04 in non-high-risk APE. According to the difference in NLR levels between the independent group averages, the post-study power was 99.85%. According to the difference in the secondary outcome variables PLR, MLR, RLR, and SII, the post-study power was above 80%.

Study Protocol

After obtaining ethics committee approval, the data were retrospectively analyzed from the hospital's data network. In the study, patients upwards of 18 years old with an APE diagnosis confirmed by multidetector computed tomography (CT) pulmonary angiography scanning were enrolled. Patients with missing clinical, laboratory, or radiographic data, pregnant patients, patients with peripheral vascular disease, malignancy, heart failure, hematological disease or liver disease, using anticoagulants or steroids, using immunosuppressive drugs, patients with other acute or chronic infections, and patients underneath the age of 18 were all excluded from the study. Venous peripheral blood samples were obtained from each patient at the time of attendance to the emergency department in order to measure SII and other common laboratory parameters. According to the guideline, patients with PESI class III–V or sPESI ≥I were identified as high risk[1].

Laboratory analyses

The complete blood count (CBC) was measured with an automated hematological analyser. Hematological parameters WBC, NEU (neutrophil), LYM (lymphocyte), MON (monocyte), platelet (PLT), RDW, NLR, PLR, monocyte to lymphocyte (MLR), red cell distribution width (RDW) to lymphocyte (RLR), and SII (PLT×NLR) values were recorded.

Primary Purpose

To assess SII's usefulness in predicting high-risk APE.

Statistical analysis

Parametric tests were used without the normality test due to compliance with the Central Limit Theorem[19]. In the assessing the data, while the mean and standard deviation are used while making the data statistics in the continuous variables; frequency and percentage values were used to define categorical variables. The student's t-test was used to compare the means of two independent groups. Chi-square test statistics were used to examine the relationships among categorical variables. ROC (Area Under the Curve) analysis was used to determine the cut-off in predicting high-risk APE. The statistics of specificity, sensitivity, positive predictive value , and negative predictive value were used to determine statistical significance. An AUC of 0.5 to 0.6 was interpreted as poor, 0.6 to 0.7 as fair, 0.7 to 0.8 as acceptable, 0.8 to 0.9 as excellent, and greater than 0.9 as outstanding. The level of statistical significance of the data is considered $p<0.05$. The www.e-picos.com New York software and the MedCalc statistical package program were used to analyze the data.

Results

A total of 195 patients, 71 of whom were high-risk APE, were enrolled in this clinical study. 121 (62.7%) of the patients were male. Table 1 shows the mean and standard deviation values of the studied biomarkers, gender, age, and mortality status. There was a significant difference between the groups in terms of age, PLT, NEU, LYM, MON, NLR, PLR, MLR, RLR, SII, Troponin T, D-Dimer, gender, and mortality ($p<0.05$). HGB, There was no significant difference between the groups regarding the mean of HCT and RDW values ($p>0.05$) (table 1).

In Table 2, the diagnostic accuracy of biomarkers that are important in detecting high-risk APE patients in ROC analysis is given in detail (table 2, figure 1). In detecting high-risk APE, the SII was found to have excellent diagnostic power (AUC: 0.84), while NLR, PLR, and MLR were found to have acceptable diagnostic power (AUC: 0.76-0.78). RLR was of fair diagnostic power (AUC: 0.68).

Discussion

Emergency physicians are always looking for a non-invasive, reliable and easily accessible tool to detect life-threatening conditions in patients. In this study, we investigated the value of SII in predicting high-risk patients in APE in patients with APE. We discovered that SII, a simple, inexpensive, easily accessible, and immediately calculated parameter, has excellent diagnostic power in detecting high-risk patients in APE patients, with an optimal cut-off value of >1235.35. Moreover, this is the first research to suggest that MLR and RLR can be used as biomarkers to detect high-risk individuals in APE patients.

The systemic immune-inflammation index (SII), a brand-new inflammatory index, fully illustrates the balance between the host's immune and inflammatory states. The following definition was given for it: platelet count ×neutrophil count/lymphocyte count[20]. Recent studies have shown that SII is

Table 1: Comparison of basic and laboratory characteristics of high-risk APE and non-high-risk APE

		Total (n=193)	Non-high-risk APE (n=122)	High-risk APE (n=71)	
Features		**x̄±SD**	**x̄±SD**	**x̄±SD**	**p-value**
Age		63.1±**16.**7	59.6±16.5	69.1±15.5	<0.001
PLT (10^3mcL)		256.32±74.21	234.69±63.28	293.48±77.26	<0.001
HGB (g/L)		12.51±1.62	12.51±1.53	12.52±1.76	0.99
HCT (%)		37.15±5.37	36.85±4.82	37.66±6.2	0.34
RDW (fL)		15.02±9.16	14.25±1.4	16.33±14.96	0.25
NEU (10^3mcL)		9.19±3.2	8.09±2.75	11.07±3.07	<0.001
LYM (10^3mcL)		1.72±0.71	1.89±0.76	1.43±0.49	<0.001
MON (10^3mcL)		0.71±0.34	0.63±0.26	0.85±0.41	<0.001
NLR		6.76±5.44	5.12±3.04	9.58±7.24	<0.001
PLR		183.49±152.33	142.99±65.61	253.07±220.08	<0.001
MLR		0.51±0.45	0.37±0.2	0.75±0.68	<0.001
RLR		10.91±9.2	8.86±3.81	14.43±10.51	0.03
SII(PLT*NLR)		1799.99±1615.72	1194.69±803.88	2840.08±2287.97	<0.001
Troponin		26.64±19.91	18.29±16.84	40.98±34.01	<0.001
D-Dimer		2.94±1.8	2.68±1.57	3.39±2.08	0.01
		n(%)	n(%)	n(%)	
Gender	Female	72(37.3)	55(45.1)	17(23.9)	0.002
	Male	121(62.7)	67(54.9)	54(76.1)	
Mortality	No	184(95.3)	122(100)	62(87.3)	<0.001
	Yes	9(4.7)	-	9(4.7)	

Student's t-test / Chi-Square test (p<0.05 significance)

APE: acute pulmonary embolism, **PLT:** platelets, **HGB:** hemoglobin, **HCT:** hematocrit, **RDW:** red cell distribution width, **NEU:** neutrophil, **LYM:** lymphocyte, **MON:** monocyte, **NLR:** neutrophil to lymphocyte ratio, **PLR:** platelet to lymphocyte ratio, **RLR:** RDW to lymphocyte ratio, **MLR:** monocyte to lymphocyte ratio, **SII:** systemic immune inflammation index.

notable for both the diagnosis and prognosis of mortality in VTE[21]. Peng et al. found SII as an independent predictor of VTE after hip fracture in elderly patients[22]. Gok et al classified 442 patients with APE as massive, submassive, and non-massive. They revealed that SII was a strong independent predictor of massive APE, with a cut-off value of >1161[23]. Since according our results obtained, SII can predict high-risk APE with a cut-off of >1235.35. (AUC:0.84).

Neutrophil-to-lymphocyte ratio (NLR) is a biomarker reflecting the balance between systemic inflammation and immunity[24]. Telo et al. found increased PLR and NLR in high-risk patients with APE[25]. Ateş et al. examined the diagnostic differentiation of independent predictors of massive APE compared to the submassive group and found that NLR had 0.893 ± 0.013 AUC[13]. Throughout line with the literature, we discovered that NLR was useful in determining severe APE in our study.

PLR and the CT pulmonary artery obstruction index were found to be positively correlated in one study, which suggests that a higher PLR is linked to a higher thrombus

Table 2: Diagnostic accuracy of inflammatory parameters for differentiation of high-risk APE from non-high-risk APE

High-risk APE (n:71) Non-high-risk APE (122)	AUC	Cut-off	Sensitivity %	Specificity%	AUC 95% CI	P-value	PPV %	NPV%
NLR	0.78	>5.71	74.65	72.13	0.71-0.83	<0.001	60.9	83
PLR	0.77	>154.38	76.06	66.39	0.70-0.83	<0.001	56.8	82.7
MLR	0.76	>0.41	74.65	70.49	0.69-0.82	<0.001	59.6	82.7
RLR	0.68	>8	80.28	50	0.61-0.75	<0.001	48.3	81.3
SII(PLT*NLR)	0.84	>1235.35	87.32	68.85	0.78-0.89	<0.001	62	90.3

AUC, Area under curve; SE, Standard error; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval;

NLR: neutrophil to lymphocyte ratio, **PLR:** platelet to lymphocyte ratio, **MLR:** monocyte to lymphocyte ratio, **RLR:** RDW to lymphocyte ratio, **SII:** systemic immune inflammation index.

load[26]. PLR was significantly higher in patients with massive pulmonary embolism (PE) proportion of patients with submassive or low-risk PE, according to research by Ateş et al[13]. In the study by Phan et al., PLR was statistically significantly lower in patients with massive PE (90.3 (50.4-164)), while it was higher in patients with low-risk PE (173 (109-145))[15]. Kundi et al. discovered that PLR could predict patients with sPESI 1 (high-risk) APE with 149 cut-off, 76.3% specificity, and 77.1% sensitivity, in their study (AUC: 0.860)[27]. Similarly, PLR was able to predict high-risk APE in our study.

LMR has been demonstrated to be a marker of the systemic inflammatory response and a potential prognostic factor in a number of cancers[28]. Duyan et al found that MLR is a valuable parameter in the diagnosis of acute appendicitis in children[29]. LMR levels were substantially lower in survivors after APE than in those who died after APE, according to Ertem et al.[30]. LMR was found to be related to prognosis in patients with intermediate-low and low-risk PE by Köse et al.[12]. Our study found that MLR, an equivalent of LMR, was higher in patients with high-risk APE (AUC: 0.76). According to the literature review, our study was a first in this respect.

Red blood cell distribution width (RDW) is a quantitative measure of the variability in the size of circulating red blood cells. A study concluded that high RDW level is an independent predictor of short-term mortality in PE[31]. RLR is a new biomarker. Wu et al. demonstrated high sensitivity and specificity of RLR in predicting hepatic impairment in patients with hepatitis E virus[32]. Furthermore, it was revealed that RLR has acceptable diagnostic power in the determination of acute appendicitis in pediatric patients[29]. However, this is the first study to show that RLR can predict the severity of APE patients. Our study contributed to the literature in terms of the fair diagnostic power of RLR in predicting high-risk patients with APE.

Limitations

The most important limitations of our study are that it is a single-center and retrospective study. Although the completeness of our dataset is satisfactory, the small number of patients is also one of the limitations. Therefore, our findings cannot be generalized but may be informative and supportive for future studies for more reliable and conclusive results.

Conclusion

As a result, we found that SII is valuable and stronger than other markers in predicting high-risk patients with APE diagnosed in the emergency department. In addition, as a contribution to the literature, we determined that MLR and RLR are biomarkers that can be used to predict severe APE.

Ethics Committee Approval: *The study was approved by Local Ethics Commission (protocol code:121, decision no:121, issue: E-48670771-514.99 date: 18 April 2022). The institutional review board waived informed consent to conduct this retrospective study. The current study was carried out in accordance with the Helsinki Declaration.*

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