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ORIGINAL ARTICLE

A Study of the Correlation between Immune Markers and the Prognosis of Acute Pulmonary Embolism

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Abstract:

Background: Inflammatory mechanisms play an important role in acute pulmonary embolism (APE). The aim of this study was to compare the predictive value of NLR, SII, SIRI, PLR, and albumin on the poor prognosis of acute pulmonary embolism in order to determine the potential of their application in early recognition of the severity of acute pulmonary embolism.

Methods: Patients with acute pulmonary embolism in the People's Hospital of Inner Mongolia Autonomous Region were selected for this retrospective study. Data on NLR, SII, SIRI, PLR, albumin, demographics and clinical characteristics of the patients at the time of admission were collected for the study. Patients who had an outcome event were defined as the study group and the remaining patients were defined as the control group. The correlation between the indicators of the two groups of patients was analyzed, and a logistic regression model was established to analyze the relationship between inflammatory indicators and the occurrence of outcome events, and the ROC curve of inflammatory indicators predicting the occurrence of outcome events was plotted.

Results: Of the 235 patients diagnosed with APE, 18 (7.7%) had outcome events. Of these, the study group had a higher incidence of syncope ($P = 0.037$) and significantly lower systolic and diastolic blood pressure ($P < 0.001$). Compared with the control group, the study group had a higher NLR ($P = 0.017$), SII ($P = 0.018$), and SIRI ($P = 0.044$), and significantly lower albumin levels ($P < 0.001$). According to univariate logistic regression analysis, after adjusting for covariates such as age and gender, high levels of SII may be a risk factor for the occurrence of an outcome event, whereas low levels of serum albumin still had a significant effect on the outcome event.The ROC curves showed that serum albumin was a stronger predictor of the outcome event (AUC = 0.880, 95% CI: 0.803-0.956).

Conclusions: High SII and low serum albumin levels are associated with poor prognosis in acute pulmonary embolism.

Keywords: Inflammation; Pulmonary embolism; Albumin; SII; SIRI

Introduction

Pulmonary embolism is a frequent and potentially fatal disease[1]. It is the third most lethal cardiovascular disease after acute myocardial infarction and stroke[2]. The incidence of acute pulmonary embolism ranges between 23 and 69 cases per 100,000 people per year; it is not universally life-threatening but covers a wide spectrum of clinical severity and mortality risk. In various studies, early (30-day or hospitalized) mortality rates have been reported to range from less than 1% to well over 50%, depending largely on the baseline clinical profile of the patients studied[3, 4].Therefore, early diagnosis and treatment of APE can significantly reduce the rate of severe illness and mortality, which is the main direction of current research.

Many studies now demonstrate that inflammation promotes thrombosis and plays a key role in the pathophysiology of PE[5]. Currently, many studies have shown that inflammation promotes thrombosis and plays a key role in the pathophysiology of PE. Several indices, such as C-reactive protein[6] and interleukin-6[7] have been shown to be associated with acute pulmonary embolism. In recent years novel inflammatory indices have attracted increasing attention. However, the association of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR)[8], systemic immune inflammatory index (SII), and systemic inflammatory response index (SIRI)[9] with acute pulmonary embolism has been rarely studied. In addition, the correlation between albumin and inflammation is also a research hotspot in recent years. Therefore, this study explored the diagnostic value of these markers in acute pulmonary embolism with the aim of establishing a new APE risk prediction model to improve the accuracy and sensitivity of early identification of acute pulmonary embolism, treatment of acute pulmonary embolism should be initiated early.

The aim of this study was to assess the predictive power of NLR, SII, Siri, PLR, and albumin values on admission for adverse outcomes (hemodynamic disturbance and even death) in patients with acute pulmonary embolism, the potential application of these markers in early identification of outcome events was also discussed.

Materials and Methods

Patients and participants

This study was a retrospective cohort study conducted at the People's Hospital of Inner Mongolia Autonomous Region. Screening and recording of patients diagnosed with acute pulmonary embolism confirmed by computed tomography pulmonary angiography who were hospitalized at the People's Hospital of Inner Mongolia Autonomous Region from January 1, 2018 to October 31, 2023, were conducted from written medical records and hospital data systems. The identification of acute pulmonary embolism follows the diagnostic criteria of the 2019 European Society of Cardiology's Guidelines for the Diagnosis and Treatment of Acute Pulmonary Embolism[10]. Patients diagnosed with active viral or bacterial infections, hematological disorders, CVD (acute stroke, acute coronary syndrome), pregnancy, or malignant tumors (excluding those whose condition has been controlled after treatment) that significantly affect blood cell counts during the study period are excluded.

Baseline Data Collection

Data on demographic characteristics, anthropometric measurements, laboratory tests and diagnosis from the hospital information system. For patients who underwent repeated laboratory tests, the first test result was included in our analyses. The Simplified PESI (sPESI) score was calculated based on age >80 years, history of cancer, history of chronic cardiopulmonary disease, heart rate 110/minute, systolic blood pressure <100mm Hg, and arterial oxygen saturation <90%[11]. We calculated the NLR, PLR, SII and SIRI according to the following equations: NLR = neutrophil count/ lymphocyte count; PLR = platelet count/lymphocyte count; SII = (neutrophil count × platelet count)/lymphocyte count; and SIRI = (neutrophil count × monocyte count)/lymphocyte count.

Outcome Events.

After anticoagulation with a standard subcutaneous weight-adjusted dose of low-molecular-weight heparin, patients with acute pulmonary embolism who experienced in-hospital all-cause mortality and hemodynamic deterioration (defined as a systolic blood pressure <90 mm Hg or a fall in systolic blood pressure of at least 40 mm Hg for more than 15 minutes that was not due to a new arrhythmia or shock) were included in the study group, and the remaining patients were included in the control group.

Statistical Analyses

Preliminary analyses were performed to compare the control group with the study group of APE hospitalized patients. The normality of the distribution of continuous variables was evaluated using the Shapiro-Wilk test. Since most of the variables were not normally distributed, the Mann-WhitneyU test was used for comparisons of continuous variables presented as median and interquartile range (IQR). Categorical variables were compared between the two groups using the

chi-square test and then summarized using counts and percentages. The ability of sPESI, PLR, NLR, SII, SIRI, and albumin levels to predict the occurrence of an outcome event was assessed by calculating the area under the curve (AUC) of the subject's work characteristics (ROC), which was determined on the basis of the area under the curve (AUC) of the recipient's work characteristics. The optimal cutoff point was defined as the cutoff point at which the Youden index was maximized. Multivariate logistic regression analyses were performed after adjusting for covariates (including age, sex, and other factors) to identify independent predictors of the occurrence of an outcome event. The outcome variable was the occurrence of an outcome event, and predictor variables included univariate analyses of $P < 0.05$ or those considered clinically relevant. Hosmer-Lemeshow was used to test the goodness-of-fit of the model. Restricted cubic spline was used to assess the relationship between independent predictors and outcome events. Statistical analysis was performed using IBM SPSS 21.0 statistical software (IBM SPSS Version 21.0, Armonk, NY, USA). Two-sided p values were used to assess all statistical significance. p values < 0.05 were considered statistically significant. In our study, all statistical analyses were performed using the R software (version 4.2.2).

Results

Clinical characteristics

The table of baseline characteristics (Table 1) presents the main results in terms of age, gender, comorbidities, vital signs, and laboratory parameters in the control (217) and study (18) groups. Comparisons showed no significant differences between the control and study groups in terms of age ($P = 0.484$) or sex distribution ($P = 0.895$). However, there was a significant difference in the scores of the pulmonary embolism severity index (sPESI), with a median of 89 (77, 110) in the control group and 116 (91, 137) in the study group ($P = 0.006$). In addition, the study group had a higher incidence of syncope ($p = 0.037$) and significantly lower systolic ($p < 0.001$) and diastolic ($p < 0.001$) blood pressure compared to the control group. In addition, the neutrophil-to-lymphocyte ratio (NLR) ($p = 0.017$), systemic immunoinflammatory index (SII) ($p = 0.018$), and systemic immune response index (SIRI) ($p = 0.044$) were elevated, and albumin levels were significantly lower in the study group compared with the control group ($p < 0.001$). These findings suggest that there may be a difference between the inflammatory response and the occurrence of outcome events in patients with APE in the two groups, which warrants further investigation.

Table 1:Patient demographics and baseline characteristics

Characteristic	Group		p-value
	Control group, N = 217[1]	Study Group, N = 18[1]	
Age	68 (59, 76)	70 (61, 78)	0.484[2]
Gender			0.895[3]
female	105 (48%)	9 (50%)	
male	112 (52%)	9 (50%)	
sPESI	89 (77, 110)	116 (91, 137)	0.006[2]
Chest pain			0.226[3]
No	125 (58%)	13 (72%)	
Yes	92 (42%)	5 (28%)	
Syncope			0.037[4]
No	203 (94%)	14 (78%)	
Yes	14 (6.5%)	4 (22%)	
Dyspnea			0.834[3]
No	102 (47%)	8 (44%)	
Yes	115 (53%)	10 (56%)	
Hemoptysis			>0.999[4]
No	20 (9.2%)	1 (5.6%)	
Yes	197 (91%)	17 (94%)	

Characteristic	Group		p-value
	Control group, N = 217[1]	Study Group, N = 18[1]	
Palpitation			0.202[4]
No	208 (96%)	16 (89%)	
Yes	9 (4.1%)	2 (11%)	
Cancer			0.293[4]
No	188 (87%)	14 (78%)	
Yes	29 (13%)	4 (22%)	
Chronic heart failure			>0.999[4]
No	187 (86%)	16 (89%)	
Yes	30 (14%)	2 (11%)	
COPD			0.613[4]
No	202 (93%)	18 (100%)	
Yes	15 (6.9%)	0 (0%)	
Heart rate	85 (76, 96)	97 (90, 105)	0.050[2]
Systolic blood pressure	131 ± 19	98 ± 26	<0.001[5]
Diastolic blood pressure	78 ± 13	62 ± 16	<0.001[5]
Neutrophils	6.3 (4.2, 9.0)	9.0 (6.1, 11.7)	0.015[2]
Lymphocyte	1.34 (0.97, 1.95)	0.95 (0.70, 1.38)	0.052[2]
Monocyte	0.48 (0.34, 0.65)	0.56 (0.37, 0.75)	0.470[2]
Platelet	195 (156, 246)	190 (147, 265)	0.928[2]
NLR	4.4 (2.7, 7.9)	8.3 (3.7, 13.8)	0.017[2]
PLR	149 (97, 204)	216 (150, 293)	0.059[2]
SII	900 (479, 1,516)	1,627 (822, 3,815)	0.018[2]
SIRI	2.1 (1.1, 4.2)	3.8 (1.7, 9.2)	0.044[2]
Albumin	37.8 (35.2, 41.4)	30.3 (25.4, 33.2)	<0.001[2]

sPESI, The Simplified PESI; COPD, chronic obstructive pulmonary disease ; NLR, neutrophil-tolymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index

In univariate logistic regression analysis, we found that high sPESI (unadjusted RR=1.02, 95% CI: 1.01-1.04, P=0.002), neutrophils (unadjusted RR=1.16, 95% CI: 1.03-1.31, P=0.019), and NLR (unadjusted RR=1.03, 95% CI: 1.00- 1.06, P=0.038) were risk factors for the occurrence of outcome events (Table 2). In addition, high SII values (unadjusted RR=1.00, 95% CI: 1.00-1.00, P=0.004) and high SIRI values (unadjusted RR=1.08, 95% CI: 1.02-1.13, P=0.006) were also risk factors. Of note, high levels of serum albumin (unadjusted RR=0.75, 95% CI: 0.67-0.84, P<0.001) may be a protective factor for APE. In multivariate logistic regression analyses, after adjusting for other confounders including age and sex, high levels of SII on admission (adjusted relative risk [RR]=1.00, 95% confidence interval [CI]: 1.00-1.00, P=0.004) and low levels of serum albumin (adjusted relative risk [RR]=0.72, 95% confidence interval [CI] : 0.64-0.82, P<0.001) remained significant for outcome events.

Table 2: Univariate and multivariate analyses affecting outcome events (logistic regression)

Characteristic	Univariable					Multivariable				
	N	Event N	RR[1]	95% CI[1]	p-value	N	Event N	RR[1]	95% CI[1]	p-value
sPESI	235	18	1.02	1.01, 1.04	0.002	235	18	1.03	1.01, 1.05	0.001
Neutrophils	235	18	1.16	1.03,1.31	0.019					
NLR	235	18	1.03	1.00, 1.06	0.038					
SII	235	18	1.00	1.00, 1.00	0.004	235	18	1.00	1.00,1.00	0.004

Characteristic	Univariable					Multivariable				
	N	Event N	RR[1]	95% CI[1]	p-value	N	Event N	RR[1]	95% CI[1]	p-value
SIRI	235	18	1.08	1.02, 1.13	0.006					
Albumin	235	18	0.75	0.67, 0.84	<0.001	235	18	0.72	0.64, 0.82	<0.001

[1]RR = relative risk; CI = Confidence Interval

ROC analysis was performed to determine the ability of biomarkers to predict outcome events (Figure 2). According to the AUC values, albumin (AUC: 0.880, 95% CI: 0.803 - 0.956), PESI (AUC: 0.697, 95% CI: 0.562 - 0.832), NLR (AUC: 0.669, 95% CI: 0.525 - 0.814), and SII (AUC: 0.668, 95% CI. 0.518 - 0.818) had higher predictive ability compared to SIRI (AUC: 0.643, 95% CI: 0.498 - 0.789). Detailed information on the optimal threshold, specificity, and sensitivity rates are shown in Table 3.

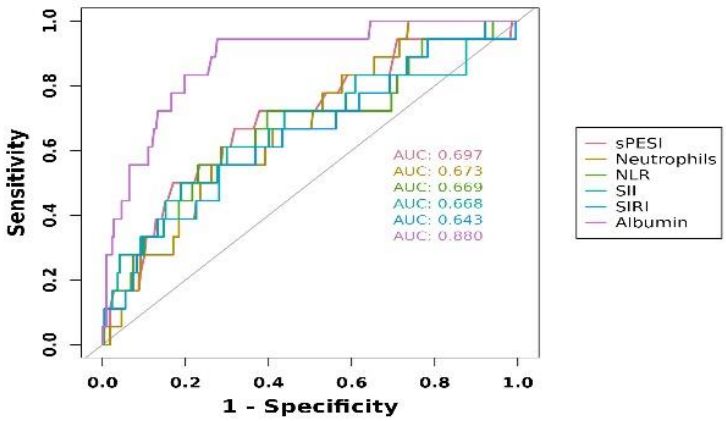

Figure 1: ROC curves of sPESI, Neutrophils、NLR, SII 、SIRI and albumin predicting the occurrence of outcome events

Table 3:Table AUCs and 95% CI

Predictor	AUC	95% CI
sPESI	0.697	0.562 - 0.832
Neutrophils	0.673	0.554 - 0.791
NLR	0.669	0.525 - 0.814
SII	0.668	0.518 - 0.818
SIRI	0.643	0.498 - 0.789
Albumin	0.880	0.803 - 0.956

In this study, we collected data on the study group, the continuous predictor variable lnSII, and the covariates age and sex. possible nonlinear relationships between changes in lnSII and group were examined by logistic regression modeling with an RCS. Nodes between 3 and 7 were tested separately, and the model with the lowest value of the Akaike information criterion was chosen as the RCS. finally, we used the RCS with 3 knots at the 10th, 50th, and 90th percentiles. after adjusting for the effects of age and sex, the RCS analysis showed that lnSII was associated with group in a "U "The inflection point of the RCS curve was determined to be lnSII = 6.16074392931006, representing the inflection point of the relationship between lnSII and group (Figure 1). The inflection point was utilized to categorize the data into two groups: lnSII < 6.16074392931006 and lnSII ≥ 6.160743 9293 1006. Segmented regressions were then performed separately for each group, and the results are shown in Tables 4 and 5.

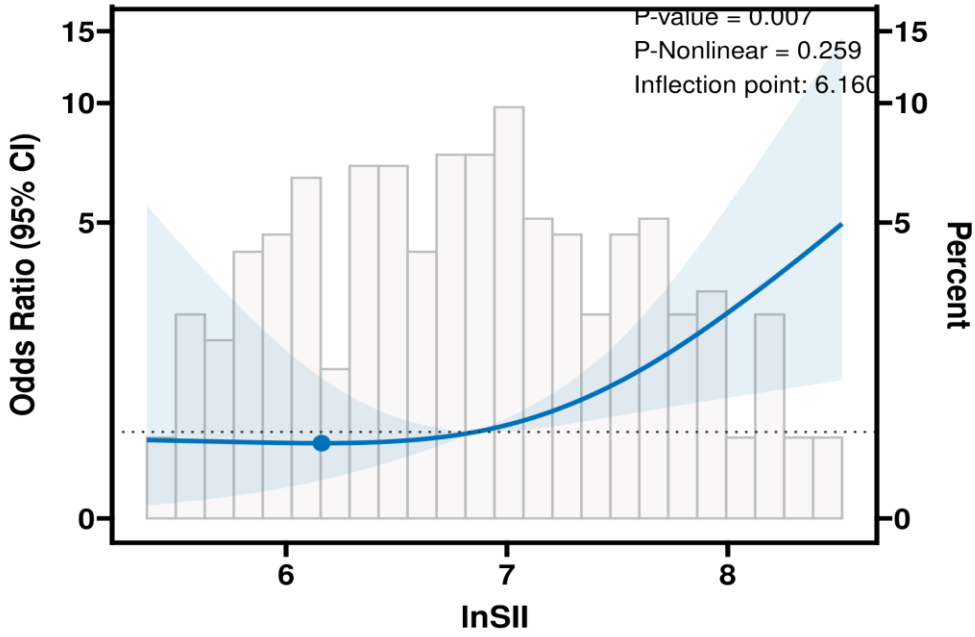

Figure 2. Association between lnSII and group with the RCS function.

Model with 3 knots located at 10th, 50th and 90th percentiles. Y-axis represents the OR to present group for any value of lnSII compared to individuals with reference value (50th percentile) of lnSII. The logistic regression was adjusted for age and gender.

Table 5:Effect of lnSII Level on group: Adjusted Odds Ratios from Segmented Logistic Regression Analysis

Characteristic	OR[1]	95% CI[1]	p-value
lnSII (< 6.16074392931006)	1.46	0.06, 140	0.84
lnSII (≥ 6.16074392931006)	2.76	1.42, 5.47	0.003

[1]OR = Odds Ratio, CI = Confidence Interval
ORs were adjusted for age and gender

Table 5:Effect of Standardized lnSII Level on group: Adjusted Odds Ratios from Segmented Logistic Regression Analysis

Characteristic	OR per SD[1]	95% CI[1]	p-value
lnSII (< 6.16074392931006)	1.14	0.38, 5.61	0.84
lnSII (≥ 6.16074392931006)	2.03	1.28, 3.28	0.003

[1]OR = Odds Ratio, CI = Confidence Interval
ORs were adjusted for age and gender

Discussion

Acute pulmonary embolism (PE) is a significant cause of mortality worldwide, with over 100,000 deaths in 2018 alone[12]. It is the third most common cause of cardiovascular death among hospitalized patients in the Western world following acute myocardial infarction and stroke[13]. Early diagnosis and intervention are critical to the prognosis of acute pulmonary embolism, as most deaths from acute pulmonary embolism occur within the first few hours to days. The presentation of acute PE can ranges from asymptomatic to sudden death, nearly 81% of patients will present with dyspnea, 70% with tachycardia, and 50% with hypoxia. Other common initial symptoms include pleuritic chest pain, syncope, hypotension, and hypocapnia[14]. Inflammation is recognized as a risk factor for venous thromboembolism. Although there are still questions as to whether inflammation is a cause or a consequence of the thrombotic process, most

evidence suggests that inflammation is a direct cause rather than a consequence of venous thromboembolism. Stimulated by an inflammatory response, the body secretes a variety of pro-inflammatory cytokines that mediate vascular endothelial damage and also interact with platelets and endothelial cells to accelerate oxidative stress and promote thrombosis. In the present study, we utilized classical monocyte, neutrophil, and lymphocyte count-derived immune markers, as well as serum albumin, to explore their association with poor prognosis in acute pulmonary embolism.

In this study, we evaluated the prognostic value of sPESI, NLR, PLR, SII, SIRI, and serum albumin in patients with acute pulmonary embolism. Our one-way logistic regression analysis showed that sPESI, Neutrophils, NLR, SII, SIRI, and serum albumin were significantly associated with poor prognosis in APE. On the basis of univariate logistic regression, multivariate logistic regression analysis was performed after adjusting for covariates (including age and gender).Multifactorial logistic regression analysis was performed after adjusting for covariates (including factors such as age and gender), and the results showed that high sPESI and high SII values remained risk factors for poor prognosis in APE. In addition, it is worth noting that low serum albumin levels are suggestive of a possible malignant event in APE. a study by Mirsaeidi M et al[15] showed that hypoalbuminemia is a marker of inflammation rather than malnutrition in the setting of chronic inflammation. The association of low serum albumin with the degree of inflammation rather than malnutrition in patients with pulmonary sarcoidosis was confirmed in a recent report. In patients with pulmonary sarcoidosis, there was a significant inverse correlation between albumin and hematocrit ($r = -0.630$, $P = 0.0001$) and CRP ($r = -0.350$, $P = 0.001$), but there was no relationship between albumin and body mass index (BMI), a crude indicator of nutritional status ($r = 0.015$, $P = 0.574$).

Conclusion

We found by multifactorial logistic regression analysis that high sPESI, high SII, and low levels of serum albumin were associated with the occurrence of adverse outcomes in patients with APE after adjusting for confounding factors such as age and sex. However, this study has limitations because it was a retrospective analysis with a relatively small sample size among a large number of APE studies. In addition, the laboratory indices we collected were measured at the time of admission to the hospital after the diagnosis of pulmonary embolism, and although we excluded patients who were in the acute infectious phase, there may have been other confounding variables affecting the inflammatory response that were not taken into account, thereby altering the results. We suggest that further prospective studies are necessary to understand whether a high inflammatory response state identifies people at risk for thromboembolism and the role of anti-inflammatory drugs in secondary prevention of APE.

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