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## Clinical paper

# Performance of the systemic immune-inflammation index in predicting survival to discharge in out-of-hospital cardiac arrest

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### Abstract

**Objective:** To investigate whether the systemic immune-inflammatory index (SII) could be used as a prognostic marker of out-of-hospital cardiac arrest (OHCA).

**Methods:** We evaluated patients aged 18 years and older, who presented to the emergency department (ED) due to OHCA between January 2019 and December 2021 and achieved the return of spontaneous circulation after successful resuscitation. Routine laboratory tests were obtained from the first blood samples measured following the patients' admission to ED. The neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) were calculated by dividing the neutrophil and platelet counts by the lymphocyte count. SII was calculated as platelets  $\times$  neutrophils / lymphocytes.

**Results:** Among the 237 patients with OHCA included in the study, the in-hospital mortality rate was 82.7%. The SII, NLR, and PLR values were statistically significantly lower in the surviving group than in the deceased group. The multivariate logistic regression analysis revealed that SII [odds ratio (OR): 0.68, 95% confidence interval (CI): 0.56–0.84,  $p = 0.004$ ] was an independent predictor of survival to discharge. In the receiver operating characteristic analysis, the power of SII to predict survival to discharge [area under the curve (AUC): 0.798] was higher than either NLR (AUC: 0.739) or PLR (AUC: 0.632) alone. SII values below 700.8% predicted survival to discharge with 80.6% sensitivity and 70.7% specificity.

**Conclusion:** Our findings showed that SII was more valuable than NLR and PLR in predicting survival to discharge and could be used as a predictive marker for this purpose.

**Keywords:** Out-of-hospital cardiac arrest, Survival to discharge, Systemic immune-inflammatory index

## Introduction

The inflammatory process has potential value in the prognosis of out-of-hospital cardiac arrest (OHCA) with a very high mortality rate.<sup>1</sup> Despite the increasing rates of successful resuscitation, the hospital discharge rate of patients with the return of spontaneous circulation (ROSC) following OHCA remains low.<sup>2</sup> Post-cardiac arrest syndrome (PCAS) is a systemic inflammatory response syndrome that can occur in patients with ROSC after a cardiac arrest and is associated with high morbidity and mortality.<sup>3</sup> Similar to sepsis, PCAS activates an inflammatory process called ischemic reperfusion injury. In PCAS, the prognosis is associated with the duration of ischemia in the whole body resulting in immune system activation and the

release of inflammatory mediators during reperfusion.<sup>4</sup> Therefore, inflammatory markers may be useful in identifying PCAS and determining its severity.

Prior studies have reported the neutrophil–lymphocyte ratio (NLR) is associated with sudden cardiac death in cases of cardiac arrest and ischemic and non-ischemic heart failure.<sup>4,5</sup> The platelet–lymphocyte ratio (PLR) has been proposed as another inflammatory marker that can reflect the systemic inflammation response, similar to NLR.<sup>6,7</sup> The systemic immune inflammation index (SII) (calculated as neutrophils  $\times$  platelets / lymphocytes) has been defined as a new inflammatory and prognostic biomarker.<sup>8</sup> SII has been shown to have prognostic value, especially in malignant diseases and coronary artery disease.<sup>9,10</sup> In this context, as a marker of the inflammatory process, SII is also likely to be a prognostic factor in patients with

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OHCA. We aimed to determine whether SII was a better prognostic marker than NLR and platelet-lymphocyte ratio (PLR) alone in these patients.

## Methods

### Study design and participants

We retrospectively analyzed the prospectively collected data of patients who were admitted to the emergency department (ED) with OHCA presumed to be of cardiac origin from January 1, 2019, through December 31, 2021. The study included patients aged 18 years and older who achieved ROSC following successful resuscitation performed by emergency medical services. Local ethics committee approval was obtained for the study. Data were collected by researchers and the study included retrospectively analyzed the prospectively collected data, therefore, informed consent was waived.

The study was conducted in the ED of a university-affiliated training hospital in Aksaray, Turkey. The number of annual average patients admitted to the ED is 400,000, and approximately 200 OHCA cases occur in every year. The hospital has 800 patient beds, 40 emergency room observation beds, 17 operating rooms, 58 adult intensive care beds with level 3 ventilators, 10 intensive care isolation rooms. In Turkey, in the event of a medical emergency, the national emergency number is dialed (1-1-2), and the command control center directs the call to the emergency physician. The emergency doctor determines the severity of the situation and sends the nearest ambulance to the scene. Each ambulance contains a three-person team that provides life support. Emergency medical technicians can provide CPR at the scene and while transporting patients and are authorized to apply advanced life support. According to the national protocol, they cannot stop CPR or declare death without a doctor's medical direction. Therefore, all patients with OHCA evaluated by emergency medical services providers should be transferred to an ED.

Patients whose records could not be obtained and/or contained incomplete information, those who were transferred from another hospital, those with a history of hematological disease, active infection, inflammatory disease, or trauma, pregnant women, OHCA cases of toxic causes, those with a diagnosis of end-stage disease (e.g., cancer and palliative care), patients living alone, and homeless patients were excluded from the study.

### Data collection and process

The patients' demographic data and clinical characteristics were obtained from the hospital's electronic medical database. Their age, gender, duration of resuscitation, initial rhythm (shockable and non-shockable), comorbidities (hypertension, diabetes mellitus, dyslipidemia, and cardiac disease), prehospital defibrillation, location of arrest, witnessed arrest, bystander cardiopulmonary resuscitation (CPR), ROSC duration, and laboratory data (i.e., pH, lactate, neutrophil, platelet, and lymphocyte values) were recorded.

Pre-hospital basic and advanced life support and post-resuscitation care was provided according to the international standard guidelines.<sup>11</sup> All the patients with ROSC were admitted to the intensive care unit and received intensive care support, including standard mechanical ventilation, invasive monitoring, hemodynamic support, sedation, and analgesia. The primary outcome measure of the study was survival to discharge from the hospital.

### Blood analysis

Routine laboratory tests, including hemogram parameters were obtained from the first blood samples measured following the patients' admission to ED. Hematological parameters were assayed using an automatic analyzer (Mindray BC-6000). NLR and PLR were calculated by dividing the absolute neutrophil and platelet counts by the absolute lymphocyte count. SII was calculated as: platelet count  $\times$  neutrophil count / lymphocyte count.

### Statistical analysis

The Statistical Package for the Social Sciences for Windows version 22.0 (SPSS) was used for data analysis. Variables were given as number, percentage, mean  $\pm$  standard deviation, and median (25–75% quartile) values. The distribution of data was analyzed with the Kolmogorov-Smirnov test. Parametric or non-parametric tests were used depending on whether the data showed a normal distribution. The Student-t test or the Mann Whitney-U test was conducted to compare two independent groups. The chi-square test was used to compare categorical variables. The relationship between clinical variables and survival to discharge was investigated with the univariate logistic regression analysis. The receiver operating characteristic (ROC) analysis was employed to calculate the sensitivity and specificity of SII, PLR, and NLR and determine their optimal cut-off values. The optimum cut-off levels of the parameters were determined using Youden's index (sensitivity + 1 – specificity). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios of the parameters were calculated for the optimum cut-off levels. The area under the curve (AUC) values were also calculated. The DeLong test was used to compare the AUC values. The multivariate logistic regression analysis was also performed to identify independent predictors by correcting data for possible interactions between parameters. Multivariate logistic regression analysis was performed according to SII, PLR and NLR cut off values. A p value of <0.05 was accepted as the statistical significance limit in all the tests.

## Results

A total of 237 patients with OHCA were included in the study. The mean age of the patients was  $68 \pm 11$  years, and 56.1% ( $n = 133$ ) were male. The demographic data and hematological parameters of the sample are shown in [Table 1](#). In-hospital mortality occurred in 196 patients (82.7%) ([Fig. 1](#)). The mean (SD) SII, NLR, and PLR values were  $614.3 \pm 190.8$ ,  $2.36 \pm 0.79$ , and  $130 \pm 59$ , respectively in the surviving group and  $957.1 \pm 408.1$ ,  $3.27 \pm 1.21$ , and  $164 \pm 77$ , respectively in the deceased group. Statistically significant parameters were included in the logistic regression model. Variables found to be significant in the univariate logistic regression analysis were included in the multivariate logistic regression model. According to the results, SII [odds ratio (OR): 0.68, 95% confidence interval (CI): 0.56–0.84,  $p = 0.004$ ] was an independent predictor of survival to discharge ([Table 2](#)).

In the multivariate regression analysis, survival to discharge was associated with SII, age (OR: 0.93, 95% CI: 0.83–0.97), cardiac disease (OR: 0.67, 95% CI: 0.41–0.92), lactate (OR: 0.69, 95% CI: 0.55–0.86), CPR time (OR: 0.83, 95% CI: 0.75–0.90), and prehospital defibrillation (OR: 2.33, 95% CI: 1.64–5.39). We performed the ROC analysis to determine the predictive power of the SII, NLR, and PLR values to predict survival to discharge ([Fig. 2](#)) and found

**Table 1 – Comparison of factors related to death and survival to discharge in patients with out-of-hospital cardiac arrest.**

Variables	All patients (n = 237)	Outcome		P-value
		Survival to discharge (n = 41)	Death (n = 196)	
Age (years)	68 ± 11	63 ± 10	69 ± 11	0.002*
Gender, male	133 (56.1%)	24 (58.5%)	109 (55.6%)	0.434
Medical history				
Hypertension	102 (43.0%)	17 (41.5%)	85 (43.4%)	0.823
Diabetes mellitus	72 (30.4%)	8 (19.5%)	64 (32.7%)	0.096
Cardiac disease	99 (41.8%)	10 (24.4%)	89 (45.4%)	0.013*
Dyslipidemia	22 (9.3%)	3 (7.3%)	19 (9.7%)	0.774
Public location	41 (17.3%)	13 (31.7%)	28 (14.3%)	0.007*
Witnessed cardiac arrest	144 (60.8%)	32 (78.0%)	112 (57.1%)	0.013*
Bystander CPR	79 (33.3%)	11 (26.8%)	68 (34.7%)	0.331
Prehospital defibrillation by EMS	75 (31.6%)	25 (61.0%)	50 (25.5%)	< 0.001*
Shockable rhythm	74 (31.2%)	25 (61.0%)	49 (25.0%)	< 0.001*
Total CPR time (min)	25 ± 7	18 ± 6	26 ± 6	< 0.001*
Laboratory parameters				
pH	6.94 ± 0.19	7.02 ± 0.15	6.93 ± 0.20	0.004*
Lactate, mmol/L	7.1 (5.0–9.5)	5.1 (3.6–6.7)	7.4 (5.4–9.7)	< 0.001*
Neutrophil count (x10 <sup>9</sup> /L)	6.30 ± 2.54	5.24 ± 1.50	6.52 ± 2.66	0.007*
Platelet count (x10 <sup>9</sup> /L)	296 (235–343)	278 (225–337)	300 (237–343)	0.246
Lymphocyte count (x10 <sup>9</sup> /L)	2.09 ± 0.65	2.39 ± 0.79	2.03 ± 0.60	0.006*
NLR	3.11 ± 1.20	2.36 ± 0.79	3.27 ± 1.21	< 0.001*
PLR	158 ± 75	130 ± 59	164 ± 77	0.008
SII	897.8 ± 400.2	614.3 ± 190.8	957.1 ± 408.1	< 0.001*
Coronary revascularization procedures <sup>†</sup>	43 (18.1%)	18 (43.9%)	25 (12.8%)	< 0.001*

Data are presented as mean ± standard deviation, median (25th–75th quartile) and percentiles or n (%). \*significant at  $p < 0.05$ . <sup>†</sup>coronary angiography and percutaneous coronary intervention, CPR: cardiopulmonary resuscitation, NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; SII: systemic immune-inflammation index.

that SII had higher power to predict survival to discharge than PLR (AUC: 0.632) and NLR (AUC: 0.739) alone (Table 3). The cut-off values of SII, NLR, and PLR in the prediction of survival to discharge were 700.8 (80.6% sensitivity, 70.7% specificity), 2.59 (67.3% sensitivity, 68.2% specificity), and 157.2 (44.9% sensitivity, 78.0% specificity), respectively. We determined that an SII level of <700.8 predicted survival to discharge with a sensitivity of 80.6% and a specificity of 70.7%.

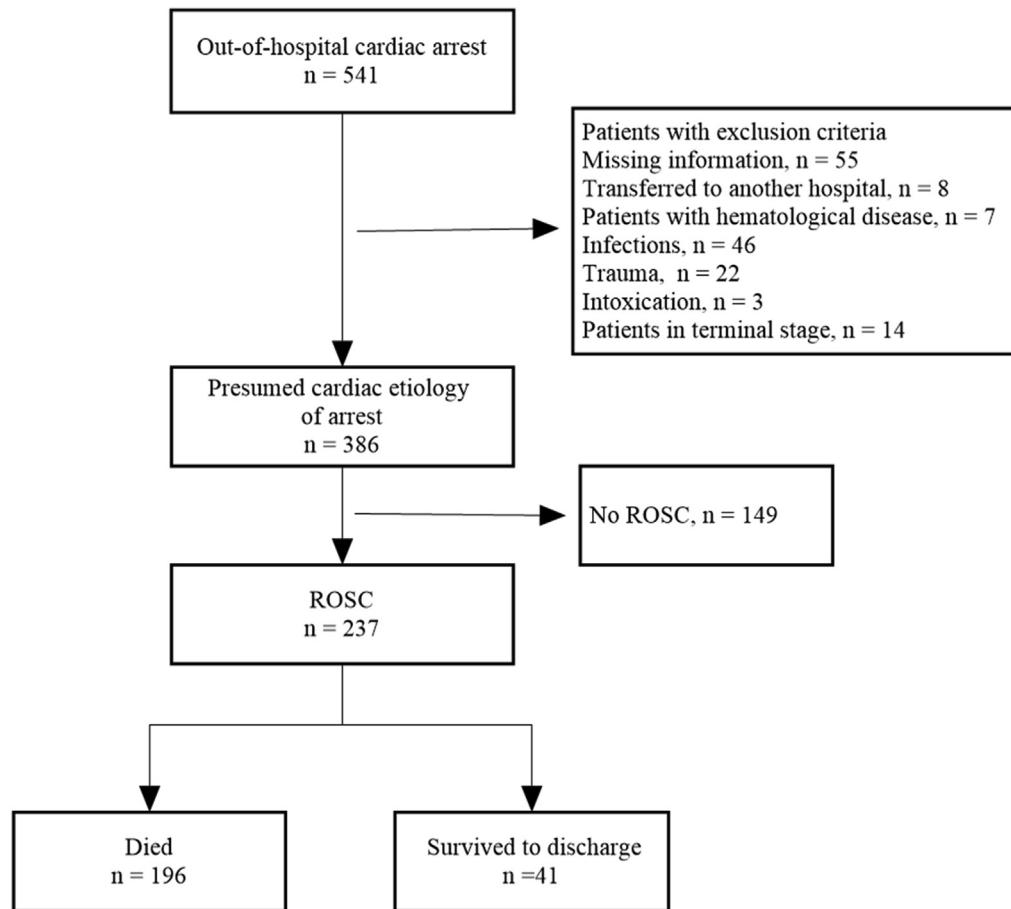
## Discussion

The overall incidence of OHCA is estimated to be approximately 56 per 100,000 population (range: 21–91), and the rate of survival to discharge is estimated to vary between 0.3% and 20.4%.<sup>1,12</sup> To date, many laboratory parameters and neuroimaging methods have been investigated to determine survival in patients that have achieved ROSC. However, there is no single validated method that can be used for this purpose. The use of simpler, low-cost, and easily measurable new markers together with risk models may be beneficial in prognosis prediction and treatment management. In this study, we investigated to utility of several commonly available laboratory tests in predicting survival to discharge in patients with ROSC following OHCA. To our knowledge, this is the first study to examine SII as a predictor of survival to discharge in OHCA.

In this study, the AUC and OR values obtained for SII in the prediction of survival to discharge were higher than those obtained for NLR or PLR alone. We determined that the patients with an SII value

of less than 700.8 had 1.5 times higher probability of surviving to discharge than the remaining patients. In the ROC analysis, SII had 80.6% and 70.7% specificity in predicting survival to discharge. These findings suggest that SII may be a useful predictive and prognostic marker of survival to discharge.

Ischemia, hypoxia, and post-resuscitation reperfusion injury during cardiac arrest lead to activation of the immune system and coagulation pathway.<sup>4</sup> Previous studies have shown that the level of systemic inflammation is associated with the severity of PCAS.<sup>13,14</sup> These studies have investigated various laboratory parameters, including neuron-specific enolase, S-100 protein, procalcitonin, high-sensitivity CRP, and interleukin-6 and revealed their important roles in predicting prognosis after ROSC.<sup>3,14</sup> Systemic ischemia/reperfusion due to PCAS is characterized by the release of systemic inflammatory cytokines and causes platelet activation, which is closely related to thromboembolic conditions.<sup>4</sup> NLR and neutrophils play an important role in the mechanism of ischemia/reperfusion injuries and have been associated with a poor prognosis in cardiovascular diseases.<sup>15</sup> In addition, ischemic damage due to cardiac arrest may lead to more severe apoptosis of T cells and lower the lymphocyte count.<sup>16</sup> In a retrospective study including 1,118 patients with OHCA, Weiser et al.<sup>4</sup> reported that NLR evaluated at the time of hospital admission was associated with mortality independent of epinephrine administration. The authors also stated that the patients with an NLR value of  $\geq 6$  had a lower survival rate compared to those with NLR <6. In contrast, in a recent study, although patients that achieved ROSC after a sudden cardiac arrest and survived until discharge had higher PLR and NLR values, only the delta neutrophil



**Fig. 1 – Flow chart of the participants.**

**Table 2 – Univariate and multivariate analyses of predictive factors for survival to discharge.**

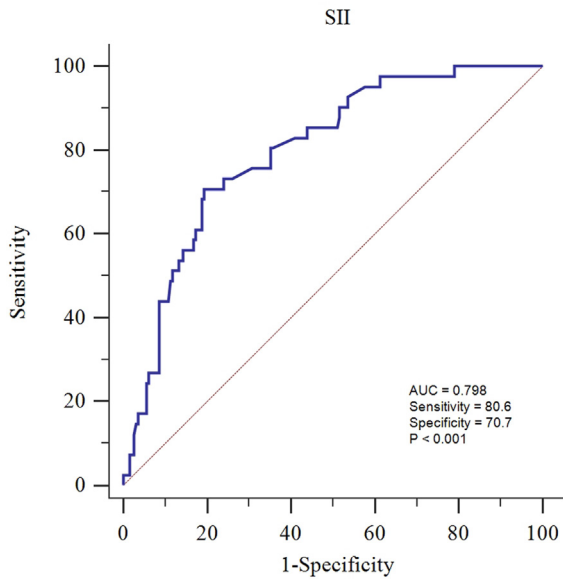
Variables	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (per 1 year)	0.95 (0.88–0.98)	0.005	0.93 (0.83–0.97)	0.004*
Cardiac disease	0.59 (0.36–0.83)	0.015	0.67 (0.41–0.92)	0.013*
Public location	2.08 (1.29–4.12)	0.009	1.34 (0.91–5.78)	0.094
Witnessed cardiac arrest	1.13 (1.04–2.64)	0.015	1.07 (0.89–3.56)	0.276
Prehospital defibrillation	2.41 (1.22–4.79)	< 0.001	2.57 (1.84–5.93)	0.001*
Total CPR time (per 1 min)	0.81 (0.75–0.87)	<0.001	0.83 (0.75–0.90)	<0.001*
Lactate, mmol/L	0.71 (0.61–0.84)	<0.001	0.69 (0.55–0.86)	0.001*
NLR	0.76 (0.61–0.89)	<0.001	0.84 (0.67–2.43)	0.164
PLR	0.83 (0.72–0.97)	0.011	0.94 (0.77–1.68)	0.225
SII	0.72 (0.59–0.86)	<0.001	0.68 (0.56–0.84)	0.004*
Coronary revascularization procedures <sup>†</sup>	1.76 (1.23–2.58)	<0.001	1.88 (0.87–2.74)	0.117

\*significant at  $p < 0.05$ , <sup>†</sup>coronary angiography and percutaneous coronary intervention, OR: odds ratio; CI: confidence interval, CPR: Cardiopulmonary resuscitation, NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; SII: systemic immune-inflammation index.

index was shown to be associated with survival to discharge.<sup>17</sup> In another study, the risk of 30-day mortality increased by 199.3% at  $PLR \geq 180$  in patients with an in-hospital cardiac arrest, and therefore PLR could be used as an indicator of short-term mortality.<sup>18</sup> In the current study, we found lower PLR and NLR values in the patients who survived to discharge compared to the deceased patients. These results suggest that higher PLR and NLR reflect a more sev-

ere systemic inflammatory immune response in patients with OHCA, which is closely related to PCAS development and death.

SII appears to have prognostic value in some malignant diseases, congestive heart failure, and coronary artery disease.<sup>9,10,19,20</sup> Erdoğan et al. reported that SII could predict severe coronary artery stenosis better than NLR and PLR.<sup>21</sup> Similarly, Liu et al.<sup>22</sup> found that SII had better predictive power for coronary artery disease than NLR



**Fig. 2 – Receiver-operating characteristic curves of the systemic immune-inflammation index for the prediction of survival to discharge.**

and PLR. SII presents as a much more important marker than PLR and NLR in demonstrating inflammation and immune response. In our study, we also determined that SII was more valuable than NLR or PLR alone in predicting survival to discharge in patients with OHCA. Leukocyte, neutrophil, and platelet counts are parameters routinely examined in the complete blood count analysis. We found that SII calculated using these hematological parameters is more valuable than their individual evaluation.

### Limitations

This study has certain limitations. First concerns the single-center design and relatively small cohort size. Second, we did not take into account the effects of CPR characteristics and other biomarkers on

outcomes, which may have affected our results. Third, we calculated the NLR, PLR, and SII using the data obtained from a single blood sample taken at the time of admission to ED following OHCA. Therefore, we were not able to calculate the effect of repeated measurements or examine the relationship of changes in hematological parameters over time with OHCA. Finally, this study was limited by the quality of medical records and the inability to control for all measured and unmeasured confounders. The high probability of death in patients with presumed cardiac origin of OHCA should be interpreted with caution.

### Conclusions

We found a significant correlation between SII level and survival to discharge. Among the patients with OHCA, the SII value was statistically significantly lower in the survivor group compared to the deceased group. Our results showed that SII was more valuable than NLR or PLR alone in OHCA, suggesting that this parameter could be used as a predictive marker. There is a need for prospective studies on this subject to confirm our findings.

### Ethical approval

This study was approved by the ethics committee of the Aksaray University Faculty of Medicine (approval no. 2022/02-08).

### Consent for publication

All authors have read and approved the final version of this manuscript and have consented for publication.

### Financial disclosure

The authors declared that this study has received no financial support.

**Table 3 – Analysis of the area under the ROC curve for survival to discharge.**

	PLR	NLR	SII
AUC (95% CI)	0.632 (0.567–0.693)	0.739 (0.678–0.794)	0.798 (0.742–0.848)
Cut-off value	<157.2	<2.59	<700.8
Sensitivity (95% CI)	44.9 (37.8–52.1)	67.3 (60.3–73.9)	80.6 (74.4–85.9)
Specificity (95% CI)	78.0 (62.4–89.4)	68.2 (51.9–81.9)	70.7 (54.5–83.9)
+LR (95% CI)	2.05 (1.1–3.7)	2.12 (1.3–3.4)	2.75 (1.7–4.5)
-LR (95% CI)	0.71 (0.6–0.9)	0.48 (0.4–0.6)	0.27 (0.2–0.4)
PPV (95% CI)	90.7 (83.1–95.7)	91.0 (85.2–95.1)	92.9 (88.0–96.3)
NPV (95% CI)	22.9 (16.2–30.7)	30.4 (21.3–40.9)	43.3 (31.2–56.0)
P-value	0.059 <sup>a</sup>	0.032 <sup>b</sup>	<0.001 <sup>c</sup>

ROC: receiver operating characteristic; AUC: area under the curve; CI: confidence interval. +LR: positive likelihood ratio; -LR: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value, CI: confidence interval; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; SII: systemic immune-inflammation index.

<sup>a</sup> P values obtained from the paired comparison of the AUC values between NLR and PLR.

<sup>b</sup> P values obtained from the paired comparison of the AUC values between SII and NLR.

<sup>c</sup> P values obtained from the paired comparison of the AUC values between SII and PLR.

## Declaration of Competing Interest

All authors report no conflict of interest.

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