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The predictive role of composite inflammatory ratio parameters in the conscious awareness recovery after severe acute ischemic stroke: a retrospective cohort study

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Abstract

Background Inflammatory mechanisms play a significant role in ischemic stroke. Peripheral neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), which are indicators capable of reflecting the magnitude of the inflammatory response, have been research hotspots. However, few research findings evaluate the prediction significance of these biomarkers in the recovery of conscious awareness following severe acute ischemic stroke.

Methods This was a retrospective cohort study of 142 patients with consciousness disorders after acute ischemic stroke (GCS score ≤ 8) treated from January 2022 to May 2024. The cases were divided into three groups according to the GCS score at discharge as died/ vegetative state (GCS ≤ 3),moderate/ severe coma(GCS = 4–11) and mild coma/ normal (GCS:12–15). Demographic and clinical assessment data were reviewed and abstracted. NLR, PLR, SII and SIRI were calculated based on the peripheral blood tests at admission. The study investigated the correlation between changes in GCS scores from admission to discharge (calculated as the GCS score at discharge minus the baseline GCS score, where a negative value indicates worsening and a positive value indicates improvement) and the levels of NLR, PLR, SII, and SIRI.

Results The level of NLR, PLR, SII and SIRI in died/ vegetative state group were significantly higher than those in moderate/ severe coma group ($p = 0.0429$, $p = 0.0215$, $p = 0.0288$, $p = 0.026$, respectively) and mild coma/ normal group ($p = 0.0085$, $p = 0.0079$, $p = 0.0019$, $p = 0.0017$, respectively). The area under the curve (AUC) values of NLR, PLR, SII, and SIRI to prognosis were 0.670, 0.661, 0.677, and 0.609, respectively. Spearman correlation analysis indicated NLR, PLR and SII were negatively correlated with GCS scores increase during hospitalization (r =- 0.317, p<0.0001 for NLR, r = -0.285, $p = 0.001$ for PLR, r = -0.3331, $p < 0.0001$ for SII, r= -0.199,$p = 0.018$ for SIRI).However, ordinal logistic regression analyses failed to indicate that NLR, PLR, SII and SIRI were independent predictors of poor consciousness response for severe acute ischemic stroke coma patients after adjusting for other confounders.

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Conclusion Patients with poorer consciousness outcomes exhibited a tendency towards elevated NLR, PLR, SII, and SIRI levels which were inversely correlated with GCS scores increase during hospitalization. However, the four indexes did not exhibit sufficient promise to be the valuable predictors for the prognosis of recovery from consciousness following severe acute ischemic stroke.

Keywords Deep-coma patient, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Systemic immune-inflammation index, Systemic inflammation response index

Background and objectives

Stroke is a type of disease that caused by the sudden occlusion or rupture of vessels in the brain companied with insufficient blood supply [1]. It has become the second leading cause of death, the primary cause of mortality and disability in China [2]. Ischemic stroke, accounting for more than 70% of all strokes, is sufficiently severe to cause loss of consciousness with the high mortality [3]. The prognosis of these individuals who suffer from these disorders is usually poor. Many deep comatose patients may never recover conscious awareness. Thus, it has become a prominent public health issue that negatively impacts patients and their families. Therefore, more accurate and early outcome prediction fluid biomarker is needed to explored to help the doctor predict whether the patient will regain conscious awareness so that they can facilitate better clinical decision-making.

As known to all, inflammation has been recognized as a significant factor in the process and outcome of acute ischemic stroke [4, 5]. For one thing, it induces neuronal cell necrosis and apoptosis in the ischemic area directly by releasing oxygen free radicals within 6 h after ischemia onset [5, 6]. Besides, other inflammatory cells also play various roles during AIS. Previous studies also revealed that post-stroke brain damage is always related to intracerebral cellular and inflammatory activation, such as monocytes, macrophages, and neutrophils. They induce the secondary brain injury by expanding the injured area, exacerbating blood-brain barrier damage, microvascular failure and brain edema [7–9]. Therefore, the estimation of inflammatory status may reflect the disease severity degree partly.

Routine blood tests are often widely used to assess the inflammatory processes in various diseases in daily clinic work. It could provide much useful information regarding various cell types i.e. white blood count, lymphocytes, neutrophils, monocytes, platelet (PLT) count. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have recently been reported as potential novel blood biomarkers of baseline inflammatory process, and also served as potential neurological prognosis predictors in patients with ischemic stroke and ICH [10, 11]. Systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI), two systemic inflammation indexes assessing global inflammation, have displayed a good prognosis utility in ICH [12], SAH [13], delayed cerebral vasospasm [14] and out-of-hospital cardiac arrest (OHCA) [15]. Therefore, these composite inflammatory ratios parameters may be more reflective of the inflammatory state and have a great potential to be used for predicting the consciousness outcomes of deep-coma patients. However, these parameters have not been studied together in the group of deep-coma patients with severe ischemic stroke and the relevance between composite inflammatory indexes and early consciousness recovery of these patients still needs to be explored further.

Therefore, this study aims to investigate whether NLR, PLR, SII and SIRI have an early predictive value for predicting the conscious awareness recovery of severe acute ischemic stroke patients in deep-coma.

Subjects and methods

Patients

From January 2022 to May 2024, the records of the deep-coma patients with a GCS score of ≤ 8 admitted to The Second Affiliated Hospital of Henan University of Chinese Medicine within 24 h of the onset of acute stroke were reviewed and the data were retrospectively analyzed. The patients were divided into three separate groups due to the GCS score at discharge: died/ vegetative state (Group 1:GCS ≤ 3),moderate/ severe coma(Group 2:GCS = 4–11) and mild coma/ normal (Group 3:GCS:12–15).

The inclusion criteria were as follows: above 18 years of age; diagnosis of acute stroke confirmed by computed tomography or magnetic resonance imaging of the brain within 48 h of admission; complete clinical data. Exclusion criteria were as follows: incomplete clinical data; malignant hematological disease or severe coagulation disorders; known major comorbidities or late-stage diseases, including severe heart failure, liver failure, end-stage kidney disease, and malignant tumors with a life expectancy of < 3 months; having medication histories affecting the number of blood immune cells.

Clinical and laboratory assessment

The demographic features, GCS scores, blood parameters were obtained from our electronic medical record database. The severity of consciousness disturbance and the prognosis of patients were independently judged by GCS score at discharge by two experienced neurologists [10].

The laboratory examination was performed within 24 h of admission. NLR, PLR, SII and SIRI were calculated according to the equations followed: 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.

Statistical analysis

All analyses were performed using the SPSS software version 24.0 and GraphPad Prism, version 8. Quantitative data are presented as the means ± standard deviations (SDs) or medians (interquartile ranges, IQRs) and were compared using one-way analysis of variance (ANOVA) among three groups. Categorical variables are expressed as frequencies and percentages and were compared using χ2 or Fisher exact tests, when appropriate. Predictive ability was determined based on the receiver operating characteristics (ROC) curves and the area under ROC(AUC). The best cutoff point was defined as that which maximized the Youden index. Two-sided P values < 0.05 were considered statistically significant. The influencing factors were analyzed by ordinal logistic regression. The spearman correlation coefficient was used to examine the relevance between inflammatory indexes and GCS score changes.

Results

Patient characteristic

The demographic characteristics of 142 included patients were elaborated in Table 1, including 66 died/vegetative state patients(group 1), 45 moderate/severe coma patients(group 2) and 31 mild coma/ normal patients(group 3). Mean onset age was significantly higher in groups 1 than those in group 3 ($p = 0.013$). The time from admission to discharge of group 2 was 24.40 ± 16.61 longer than that of group 1 (15.73 ± 13.48, $p = 0.003$). GCS scores at baseline and discharge were significantly higher in groups 2 ($p < 0.000$ for both) and group 3 ($p < 0.0001$for both) compared to those in group 1. Group 2 had a higher prevalence of atrial fibrillation (AF) compared to group 3($p = 0.049$). There was no difference between the groups in terms of gender distribution and the prevalence of other chronic diseases i.e. hypertension (HT); coronary artery disease (CAD); diabetes mellitus (DM); cerebral infarction (CI); intracerebral hemorrhage (ICH).

Inflammatory markers

The level of NLR, PLR, SII and SIRI in group 1 were significantly higher than those in groups 2 ($p = 0.0429$, $p = 0.0215$, $p = 0.0288$, $p = 0.026$, respectively) and group 3 ($p = 0.0085$, $p = 0.0079$, $p = 0.0019$, $p = 0.0017$, respectively) as shown in Fig. 1.

Besides, the median neutrophil count was higher in group 1 compared to group 3 ($p = 0.0178$) while the lymphocyte count was lower in group 1 relative to group 3 ($p = 0.0078$). There was no difference between the groups in terms of PLT and monocyte count ($p = 0.466$, $p = 0.96$) (Table 2 and supplementary Fig. 1).

The sensitivity and specificity

An ROC analysis was performed to evaluate the sensitivity and specificity of these.

inflammatory parameters. The area under the ROC curve (AUC) was shown as Fig. 2(NLR, PLR, SII, SIRI) and supplementary Fig. 2(single inflammatory indicators).

According to the ROC analysis, NLR, PLR, SII, SIRI showed good sensitivity and specificity for predicting the

Table 1 Demographic characteristics and comorbidities

	Group 1:	**Group 2:**	**Group 3:**	
	died/vegetative state($n = 66$)	**moderate/severe coma($n = 45$)**	**mild coma/ normal($n = 31$)**	***p*-value**
Age (year)	69.1 ± 14.8	67.5 ± 15.1	61.0 ± 13.5	**0.042**[a]
Hospital (day)	15.7 ± 13.8	24.4 ± 16.6	21.9 ± 13.7	**0.007**[a]
GCS at baseline	4.9 ± 1.7	6.4 ± 1.6	6.4 ± 1.5	< **0.0001**[a]
GCS at discharge	1.4 ± 1.4	9.0 ± 1.9	14.1 ± 0.9	< **0.0001**[a]
Gender				
Male	37(56.1%)	28(62.23%)	17(54.84%)	0.758[a]
Female	29 (43.9%)	17(37.77%)	16(45.16%))	
Comorbidities				
HT	47(71.2%)	36(80.0%)	19(61.3%)	0.202[b]
DM	24(36.4%)	11(24.4%)	5(16.13%)	0.094[b]
CAD	15(22.7%)	9(20.0%)	4(12.90%)	0.525[b]
AF	12(18.2%)	11(24.4%)	1(3.22%)	**0.049**[b]
CI	12(18.2%)	10(22.2%)	5(16.1%)	0.78[b]
ICH	2(3.0%)	3(6.7%)	1(3.22%)	0.615[b]

HT: Hypertension, DM: Diabetes Mellitus, CAD: Coronary Artery Disease, AF: Atrial Fibrillation; CI: Cerebral infarction. ICH: Intracerebral hemorrhage

Variables are expressed with mean ± standard deviation (SD) or n (%) values. a: One-way ANOVA; b: Pearson's Chi-square Test

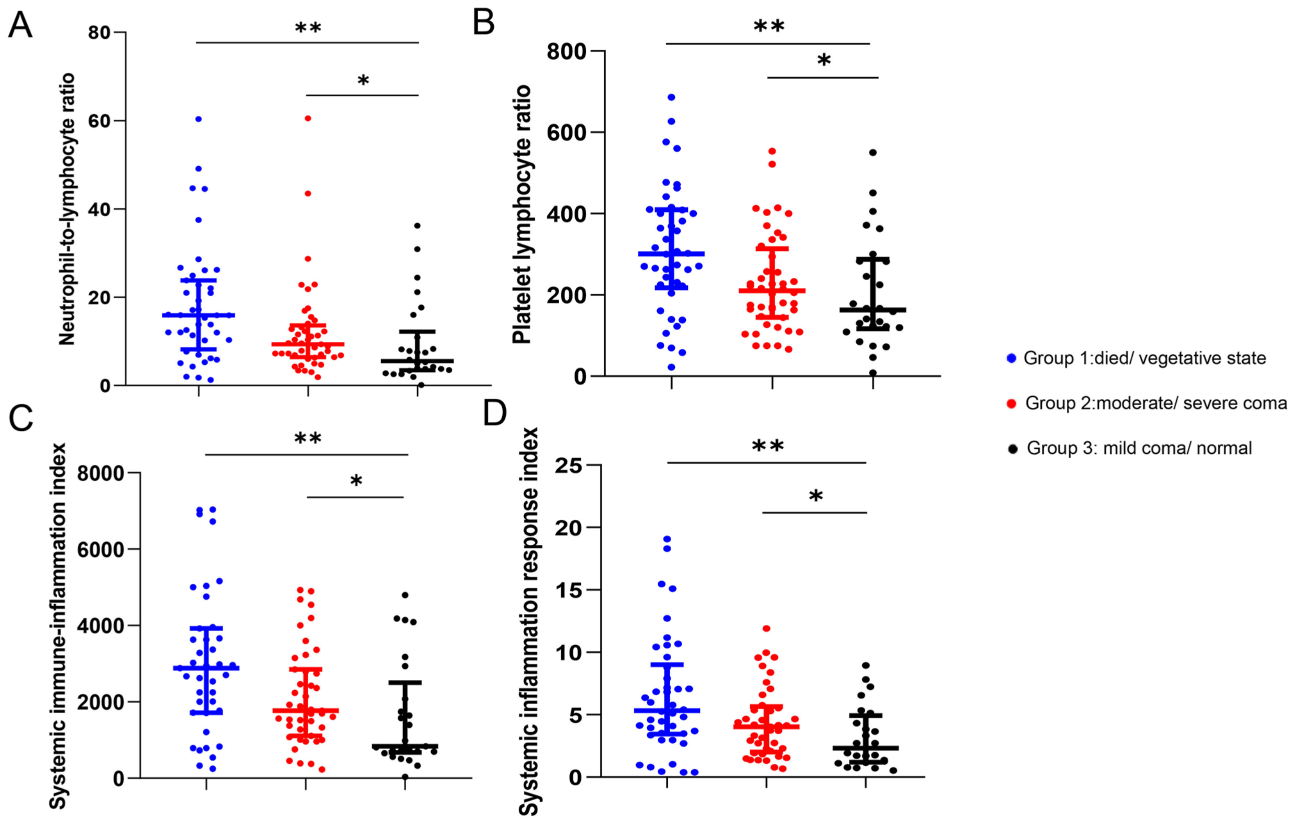

Fig. 1 A comparison of blood inflammatory biomarkers between three groups. (**A**) Comparison of NLR; (**B**) Comparison of PLR; (**C**) Comparison of SII; (**D**) Comparison of SIRI level. NLR: Neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index. *$p<0.05$, **$p<0.01$

Table 2 Comparison of blood inflammatory biomarkers

	Group 1: died/vegetative state($n=66$)	**Group 2: moderate/severe coma($n=45$)**	**Group 3: mild coma/ normal($n=31$)**	***p*-value**
Neutrophil(10^9/L)	10.7(8.2–14.0)	9.5(7.2–12.8)	7.9(5.0-11.8)	**0.0239**[a]
Lymphocyte(10^9/L)	0.8(0.5–1.2)	1.0(0.7–1.3)	1.2(0.6–1.6)	**0.016**[a]
PLT (10^9/L)	187.0(147.8-263.5)	212.0(154.5-242.5)	191.0(163.0-226.0)	0.466[a]
Monocyte(10^9/L)	0.4(0.3–0.6)	0.4(0.3–0.5)	0.5(0.3–0.7)	0.96[a]
NLR	15.1(8.8–22.9)	9.4(6.4–14.4)	7.6(3.8–17.7)	**0.006**
PLR	295.1(157.7-411.4)	205.4(135.8-307.3)	166.9(122.2-282.1)	**0.004**
SII	2912.8(1713.9-4869.1)	1799.9(1193.9-3000.6	1575.4(705.6–3177.0)	**0.0017**
SIRI	5.3(3.0-10.6)	4.1(2.2–6.9)	3.7(1.4–7.2)	**0.0013**

Variables were expressed with median (IQR) and analyzed by One-way ANOVA Test

consciousness outcome of deep-coma patients after acute severe stroke.

The AUC value was 0.670 for NLR with 66.7% sensitivity and 67.1% specificity, 0.661 for PLR with 62.1% sensitivity and 72.4% specificity, 0.677 for SII with 63.6% sensitivity and 68.4% specificity,0.609 for SIRI with 48.5% sensitivity and 71.1% specificity. A cut-off count and 95%CI was indicated in Table 3. Surprisingly, neutrophil also exhibited a good AUC area and sensitivity. However, the specificity was not high. As for other markers, lymphocyte, PLT, monocyte did not display the excellent predictive value in consciousness disorder recovery from acute severe stroke due to the low ROC curve discrimination.

The correlation between NLR, PLR, SII and SIRI and changes in GCS scores during hospitalization

Spearman correlation analysis indicated that NLR, PLR, SII, SIRI were negatively associated with the GCS scores changes (GCS score at discharge minus baseline GCS score) (r= -0.317, $p<0.0001$ for NLR; r= -0.285, $p=0.001$ for PLR; r= -0.3331, $p<0.0001$ for SII, r= -0.199, $p=0.018$) (Fig. 3).

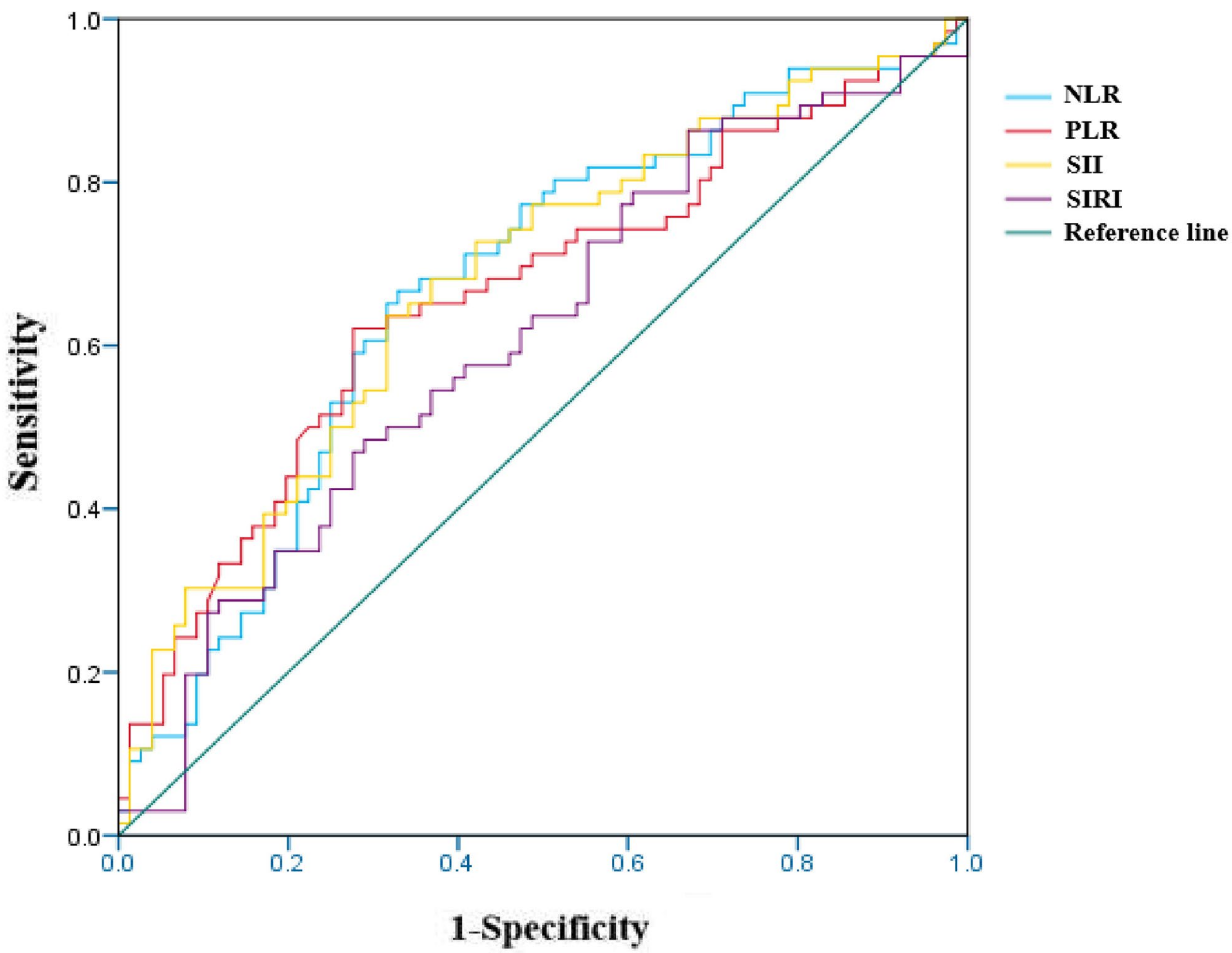

Fig. 2 The ROC curve analysis of NLR, PLR, SII and SIRI for predicting consciousness outcome of deep-coma patients

Table 3 ROC AUC data and the sensitivity and specificity of these parameters

	AUC	95%(CI)	Optimal Cut-Off Point	Sensitivity	Specificity
Neutrophil	0.605	(0.512—0.698)	>7.11	86.4%	34.2%
Lymphocyte	0.362	(0.269–0.454))	>1.65	13.6%	86.8%
PLT	0.499	(0.401–0.596)	>271	22.7%	92.1%
Monocyte	0.446	(0.349–0.543))	>0.79	18.2%	88.2%
NLR	0.670	(0.581–0.760)	>11.35	66.7%	67.1%
PLR	0.661	(0.570–0.752))	>259.76	62.1%	72.4%
SII	0.677	(0.588–0.766)	>2498.83	63.6%	68.4%
SIRI	0.609	(0.515–0.702)	>2.94	48.5%	71.1%

Independent predictor of consciousness recovery after severe ischemic stroke

The available results had illustrated the association between composite inflammatory ratio parameters and GCS score changes during hospitalization, indicating the potential of those four indexes to predict the consciousness outcome. However, there still may be some confounders affecting the reliability of the conclusions. After confirming the parallelism of the lines with a p-value of 1.00, an ordinal multivariate logistic regression analysis was conducted to identify the factors that could predict the outcome of consciousness after adjusting for potential confounders. The regression result in Table 4 demonstrated that age, baseline GCS score, neutrophil and AF were independent predictors for the prognosis of consciousness in patients with severe ischemic stroke coma. Unfortunately, NLR, PLR, SII, and SIRI were not found to be predictive.

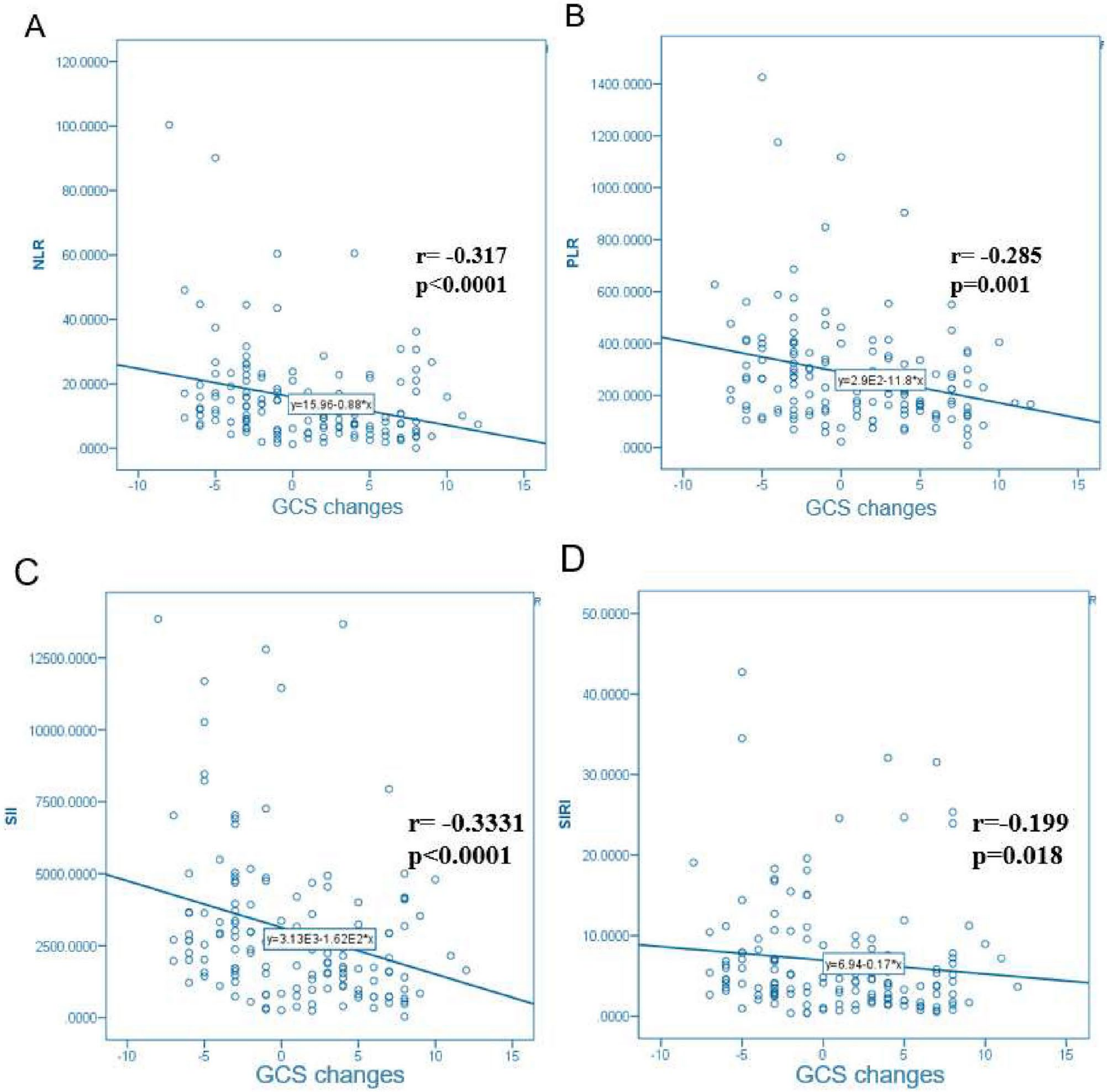

Fig. 3 Correlation between GCS score changes and composite inflammatory biomarkers NLR (**A**); PLR (**B**); SII (**C**); SIRI (**D**)

Table 4 Result of ordinal logistic regression analysis

	β	Standard Error	Waldχ2	Odds Ratio	95% CI	Adjusted *p*-value
Age (years)	-0.041	0.014	8.294	0.960	0.934–0.987	**0.004**
hospital days(day)	0.020	0.012	2.670	1.020	0.996–1.045	0.102
Baseline GCS score	0.588	0.126	21.648	1.800	1.406–2.307	**< 0.0001**
NLR	0.023	0.032	0.519	1.023	0.960–1.113	0.471
PLR	-0.004	0.003	1.414	0.996	0.990–1.090	0.234
SII	0.082	0.047	3.070	1.085	0.990–1.002	0.080
SIRI	-3.755E-5	0.000	0.015	0.100	0.999–1.189	0.903
Neutrophil	-0.198	0.075	7.014	0.820	0.709–1.001	**0.008**
Lymphocyte	0.407	0.547	0.553	1.502	0.514–4.384	0.457
AF	-1.532	0.692	4.902	0.216	0.056–0.839	**0.027**

Discussion

This study investigated whether hematological composite inflammatory parameters may be the consciousness prognosis predictors of deep-coma patients with severe ischemic stroke and the results demonstrated that group 1(died/ vegetative state group) had significantly higher blood NLR, PLR, SII and SIRI values. And high NLR, PLR, SII and SIRI may be negatively relevant to GCS scores changes. However, they were not promising independent predictors for consciousness prognosis through logistic regression results.

In this study, we included the deep-coma patients with severe acute ischemic stroke (GCS ≤ 8 scores at admission). As previously reported, the inflammatory cascade is activated immediately after vessel incidents has occurred and intravascular leukocytes increased followed [16]. It seems like the inflammatory parameter levels may reflect the state of systemic inflammation and the immune response. And the previous researches also indicated that NLR and PLR may predict early neurological deterioration in acute ischemic stroke and ICH patients [17, 18]. Meanwhile, higher SII and SIRI indexes were correlated with greater risk of stroke severity and poor functional outcomes in ICH patients [12, 19]. These studies strongly indicated the potential correlations between composite inflammation indexes and consciousness disorder outcomes of severe acute ischemic stroke. Based on the background, this study aimed to evaluate the performance of NLR, PLR, SII, SIRI in predicting the consciousness prognosis of severe acute ischemic stroke patients.

The results of our study demonstrated that NLR, PLR, SII and SIRI levels in group 1(poorest consciousness prognosis group) were significantly increased compared to those in group 2 and 3. With an estimated AUC value of 0.670 for NLR, 0.661 for PLR, 0.677 for SII, 0.609 for SIRI. Besides, our findings also revealed that NLR, PLR, SII were negatively correlated with the subtraction of baseline GCS score from GCS score at discharge. However, those four indexes did not exhibit great performance as the independent predictor of consciousness prognosis in terms of logistic analysis.

In addition, we analyzed the relationship between the neutrophil, lymphocyte, monocyte, platelet values measured at admission and the consciousness disorder prognosis. The results showed that group 1(died/ vegetative state group) exhibited higher neutrophil levels and lower lymphocyte levels compared to group 3(mild coma/ normal). The logistic regression results indicated that neutrophil count was an independent predictor of conscious recovery following severe ischemic stroke. Furthermore, the ROC curve analysis demonstrated that neutrophil count had an AUC value of 0.670, with a sensitivity of 86.4% and a specificity of 34.2%. Overall, neutrophils demonstrated the potential to serve as a predictor of consciousness recovery in patients with severe ischemic stroke coma. As for lymphocyte, it did not exhibit satisfying AUC value of the ROC curve and sensitivity. Therefore, its effectiveness still needed to be explored further. And there was no difference in monocyte and platelet levels between three groups.

Studies have demonstrated that neutrophils were the first to infiltrate and deteriorated the injured brain by direct neurotoxic effects of releasing proteolytic enzymes, cytokine production and secretion as the pioneer of the immune response [20]. Our results of higher neutrophils levels in poorest consciousness prognosis group (died/ vegetable status) were also consistent with the point. Besides, the innate immune reaction was also mediated by monocytes. The pro-inflammatory monocyte phenotype was thought to contribute to the secondary brain injury while someone announced that this functional specification could also activate immune system processes involved in wound healing and tissue repair [21]. Therefore, the specific role of monocytes may be influenced by multiple monocytes populations recruited. As for lymphocytes, they were considered to be the pivotal factor reducing the neuroinflammation with complicated and diverse influences in acute brain injuries [22]. In this study, higher lymphocyte levels were observed in good prognosis group (group 3). Unfortunately, AUC of ROC curve was less than 0.5(0.362, $p = 0.016$) and the sensitivity was not satisfying (sensitivity 13.6%, specificity 6.8%). Moreover, platelets not only played central roles in the formation of circulating arterial thrombosis and embolism but also promoted the adhesion and cell migration of lymphocytes and intensified the inflammation [23, 24]. However, the platelet count was non-significantly difference between three groups in our study. In addition, we also found the predictive values of age, baseline GCS score ad AF in the prognosis of the consciousness recovery, indicating old, lower baseline GCS score and AF comorbidities tend to indicate a poorer prognosis in terms of consciousness outcomes for deep-coma patients after severe ischemic stroke.

There are some limitations to our study. First, it is single center retrospective research, and the sample size is small, resulting in a slight selection bias. Besides, the sensitivity or specificity of the cut-off value of the ROC curve and correlation coefficient are not very high, so further investigation with larger sample sizes is still necessary to confirm the results. Lastly, we failed to follow-up the patients after discharge, which is still an important part for those patients who were coma status at discharge.

Conclusions

In summary, according to our knowledge, there was no previous study that simultaneously investigated the association between immune-inflammatory biomarkers and the consciousness disorder prognosis with severe acute ischemic stroke. In our study, although the peripheral blood NLR, PLR, and SII of died/ vegetative state group are higher than those in moderate/severe coma and mild coma/normal group, the prediction significance of preoperative composite inflammatory ratio parameters in consciousness recovery after severe ischemic stroke is still not clear. Therefore, it is not recommended to use them as the markers to identify poor prognosis of consciousness. Surprisingly, neutrophil appeared to have value as a promising clinical predictor of the prognosis for conscious recovery following severe ischemic stroke.

Supplementary Information

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Supplementary Material 1

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Author contributions

Yiyuan Xu drafted the main manuscript text and analysis the data. Yanyan Liu collected the data and prepared figures and tables. All authors reviewed the manuscript.

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Not applicable.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate

The study was approved by the Institutional Review Boards and Ethical Committee of The Second Affiliated Hospital of Henan University of Chinese Medicine (HNSZYYWZ-2024001). Due to a retrospective nature of this study, patient's informed consent was waived by the Ethics Review Committee of The Second Affiliated Hospital of Henan University of Chinese Medicine. All experiments were performed in accordance with relevant guidelines and regulations.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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