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ORIGINAL RESEARCH

Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, Systemic Immune Inflammation Index and Efficacy of Remote Ischemic Conditioning in Acute Ischemic Stroke: A Post Hoc Exploratory Analysis of the RICAMIS Study

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Background: We conducted a post-hoc analysis of the RICAMIS trial to investigate the effect of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index (SII) on the efficacy of remote ischemic conditioning treatment.

Methods: In this post-hoc analysis, NLR, PLR, and SII were measured before randomization. Patients were divided into two groups based on their cut-off values: high vs low NLR, high vs low PLR, and high vs low SII groups. Each group was further subdivided into RIC and control groups. The primary endpoint was a poor outcome (mRS 2–6 at 90 days). Differences in the primary endpoint between the RIC and control subgroups were compared, and the interactions of treatment assignment with NLR, PLR, and SII were evaluated.

Results: A total of 1679 patients were included in the final analysis. Compared with the control group, RIC significantly improved functional outcomes regardless of the inflammation status. The improved probability of poor outcome in the RIC vs control group was numerically greater in the high vs low inflammation group (NLR, 7.8% vs 5.1%; PLR, 7% vs 6.5%; SII, 9% vs 5.3%). However, we did not find an interaction effect of an intervention (RIC or control) with different NLR, PLR, or SII on clinical outcomes ($P > 0.05$). In addition, the NLR and SII were independently associated with functional outcomes in all patients, regardless of whether they received RIC.

Conclusion: Inflammation may not affect the efficacy of RIC in patients with acute moderate ischemic stroke, although a lower probability of poor outcome at 90 days was identified in patients with a high vs low inflammatory status.

Keywords: neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, remote ischemic conditioning, ischemic stroke

Background

As a non-pharmacological treatment, the neuroprotective effect of remote ischemic conditioning (RIC), intermittently blocking the blood flow of limbs and producing transient ischemic with the intention of protecting brain, on ischemic stroke has been widely investigated in preclinical and clinical studies, and the results suggested that its potential benefit through multiple neuroprotective mechanisms.[1–5] Our recent remote ischemic conditioning for acute moderate ischemic stroke (RICAMIS) trial provided the first robust evidence for the benefit of RIC in acute moderate ischemic stroke,[6] but

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the patient who will benefit the most from RIC intervention has not been identified, which is an important concern in clinical practice.

Growing evidence suggests a key role of the inflammatory response in ischemic stroke, involving the entire process of its development, progression and repair.[7–11] Preclinical studies have shown that the neuroprotective effect of RIC intervention is mediated by anti-inflammatory effects.[12–16] The inflammatory response is orchestrated by numerous immune cells, such as lymphocytes, granulocytes, and monocytes, and the cell counts of these immune cells provide vital information on inflammatory statuses.[8,10] Recently, several low-priced easy-to-measure white blood cell-based inflammatory indicators have been introduced, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index (SII),[17–21] which have been found to be positively correlated with poor functional outcome of acute ischemic stroke.[22,23] However, the effects of these inflammatory indicators on the efficacy of RIC interventions have not been investigated.

Therefore, we performed an exploratory post hoc analysis of the RICAMIS trial to investigate the effects of the NLR, PLR, and SII on the efficacy of RIC treatment.

Methods

Study Design and Participants

Details of the design, protocol, and statistical analysis plan of RICAMIS have been published.[6] In brief, the RICAMIS trial was a multicenter, open-label, blinded-endpoint, randomized clinical trial to assess the efficacy of 2 weeks of RIC in patients with acute moderate ischemic stroke within 48 h of symptom onset.

In total, 1707 patients based on the per-protocol set (PPS) were enrolled in this post hoc analysis. Eligible patients were 18 years or older, functioning independently before stroke (as indicated by a modified Rankin Scale [mRS] score of 0–1), and diagnosed with acute moderate ischemic stroke (as indicated by baseline National Institutes of Health Stroke Scale [NIHSS] scores of 6–16). Patients were randomly allocated to receive either RIC treatment as an adjunct to guideline-recommended treatment or only guideline-recommended treatment.

All study procedures were reviewed and approved by the ethics committees of the participating sites, and written informed consent was obtained from patients or their legally authorized representatives. This trial was registered at ClinicalTrials.gov (NCT03740971).

Procedure

RIC treatment was initiated within 48 h of symptom onset and involved five cycles of cuff inflation (200 mmHg for 5 min) and deflation (for 5 min), for a total procedure time of 50 min, twice daily for 10 to 14 days. Additional details of the RIC treatment can be found in the RICAMIS trial.[5]

Neurologic status (measured by NIHSS score) was evaluated at admission, and at 7 and 12 days after randomization. Follow-up data were collected at 7, 12 and 90 days after randomization.

In this post-hoc analysis, NLR, PLR, and SII were measured before randomization. Using receiver operating characteristic (ROC) curves, we identified the optimal cut-off values of NLR, PLR, and SII for predicting poor functional outcome, defined as mRS score 2–6 at 90 days. Based on these cutoff values, patients were categorized into two groups: high NLR (≥2.95) and low NLR (<2.95), high PLR (≥153.08) and low PLR (<153.08), and high SII (≥730.13×10^9/L) and low SII (<730.13×10^9/L) groups.

Data Collection

The Electronic Data Capture system was utilized to collect clinical data from all study participants, which included demographic characteristics such as age, sex, BMI, current smoking and drinking status, as well as comorbidities such as hypertension, diabetes, dyslipidemia, and history of previous stroke or TIA; clinical characteristics such as time from symptom onset to RIC treatment (OTT), NIHSS score at randomization, pre-stroke mRS, and Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification; and laboratory examinations such as hematologic indices. OTT was recorded as the time from symptom onset to initiating RIC treatment in RIC group or guideline-recommended treatment

after randomization in control group. Pre-stroke mRS was obtained based on the consultant of investigator with patients or caregivers.

Specifically, NLR was calculated by dividing the neutrophil count by the lymphocyte count, PLR was calculated by dividing the platelet count by the lymphocyte count, and SII was calculated by multiplying the platelet count by the neutrophil count and then dividing by the lymphocyte count.

Outcomes

In this secondary analysis of the RICAMIS trial, the primary endpoint was a poor functional outcome at 90 days, which was defined by a mRS score ranging from 2 to 6. The secondary endpoint was the change in NIHSS score between admission and 12 days post-treatment.

Statistical Analysis

The continuous variables in this study were tested for normality using the Shapiro–Wilk test. Normally distributed data were presented as mean ± standard deviation (SD), whereas non-normally distributed data were presented as medians with interquartile ranges (IQR). Categorical variables were presented as frequencies and percentages.

Student's t-tests were used for normally distributed continuous data, whereas the Mann–Whitney *U*-test was used for non-normally distributed continuous data. The Chi-square test or Fisher's exact test was used to compare the categorical variables.

For binary logistic regression analyses of poor functional outcomes (mRS 2–6) at 90 days, odds ratios (ORs) with 95% confidence intervals (Cis) were presented as treatment effects. The change in the NIHSS score between admission and 12 days after treatment was compared using a generalized linear model, and the treatment effects were presented as mean differences (MD) with 95% Cis.

Confounding factors were adjusted in the logistic or generalized linear model, and the adjusted OR or MD and their 95% Cis were calculated. Assessment of the homogeneity of treatment effect by inflammation was evaluated using logistic regression model with independent variables including treatment, inflammatory indicators, and their interaction term, which was under consideration of multiplicative interaction effects.

All statistical analyses were conducted using IBM SPSS 26.0 software, and a p-value of <0.05 was considered statistically significant for all analyses (two-tailed). Details of the confounding factors adjusted for in the analysis can be found in the footnotes.

Results

Patient Characteristics

In this RICAMIS trial, 1776 patients (863 in the RIC group and 913 in the control group) were included in the full analysis set, and 1707 patients (96.1%) (808 [93.6%] in the RIC group and 899 [98.5%] in the control group) were included in the PPS. Of the 1707 PPS patients, 28 (1.6%) were excluded because of missing hematologic indices. Finally, 1679 patients were enrolled in the secondary analysis, including 884 in the high NLR group, 795 in the low NLR group, 639 in the high PLR group and 1040 in the low PLR group, 693 in the high SII group, and 986 in the low SII group. Table 1 shows the baseline characteristics of the RIC and control subgroups across NLR, PLR, and SII groups. There were some imbalances in female and presumed stroke causes in the high NLR and high SII groups. Table 2 provides details of the baseline characteristics of the high- and low-inflammatory indicator subgroups among the RIC and control groups. In the RIC group, older age, fewer current smokers, and higher NIHSS score at admission were found in the high vs low NLR subgroup; older age, lower BMI, fewer current smokers, and higher NIHSS score at randomization were found in the high vs low PLR subgroup; and fewer current smokers, more diabetes, and higher NIHSS score at randomization were found in the high vs low SII subgroup. In the control group, a higher NIHSS score at admission was found in the high vs low NLR subgroup, less diabetes and more previous stroke were found in the high vs low PLR subgroup, and a higher NIHSS score at randomization was found in the high vs low SII subgroup.

Table 1 Baseline Characteristics Grouped According to Inflammatory Indicators and Intervention

Variables	NLR High (n=884)			NLR Low (n=795)			PLR High (n=639)			PLR Low (n=1040)			SII High (n=693)			SII Low (n=986)		
	RIC (417)	Control (467)	P value	RIC (382)	Control (413)	P value	RIC (307)	Control (332)	P value	RIC (492)	Control (548)	P value	RIC (335)	Control (358)	P value	RIC (464)	Control (522)	P value
Demographic and clinical Characteristics																		
Age, mean ± SD	66.4±10.3	65.8±10.5	0.397	64.0±10.5	64.6±9.0	0.373	66.3±10.1	65.6±10.1	0.398	64.6±10.7	65.0±10.0	0.497	65.6±10.2	65.7±10.4	0.918	65.0±10.7	64.9±9.8	0.963
Sex (Female) (%)	153 (36.7)	142 (30.4)	0.048	133 (34.8)	145 (35.1)	0.931	117 (38.1)	105 (31.6)	0.085	169 (34.3)	182 (33.2)	0.698	131 (39.1)	114 (31.8)	0.046	155 (33.4)	173 (33.1)	0.930
BMI, mean ± SD	24.2±3.1	24.2±2.9	0.909	24.4±2.8	24.4±3.0	0.728	24.0±3.0	24.0±2.7	0.737	24.5±2.9	24.4±3.0	0.628	24.1±3.0	24.1±2.8	0.934	24.4±2.9	24.4±3.0	0.861
Current smoker (%)	106 (25.4)	127 (27.2)	0.550	124 (32.5)	109 (26.4)	0.060	74 (24.1)	80 (24.1)	0.998	156 (31.7)	156 (28.5)	0.255	83 (24.8)	97 (27.1)	0.487	147 (31.7)	139 (26.6)	0.081
Current drinker (%)	56 (13.4)	47 (10.1)	0.120	63 (16.5)	54 (13.1)	0.174	40 (13.0)	33 (9.9)	0.220	79 (16.1)	68 (12.4)	0.092	45 (13.4)	40 (11.2)	0.365	74 (15.9)	61 (11.7)	0.052
Hypertension (%)	263 (63.1)	292 (62.5)	0.868	229 (59.9)	240 (58.1)	0.599	190 (61.9)	197 (59.3)	0.510	302 (61.4)	335 (61.1)	0.934	216 (64.5)	218 (60.9)	0.330	276 (59.5)	314 (60.2)	0.830
Diabetes (%)	99 (23.7)	113 (24.2)	0.874	91 (23.8)	98 (23.7)	0.975	70 (22.8)	64 (19.3)	0.274	120 (24.4)	147 (26.8)	0.370	92 (27.5)	81 (22.6)	0.142	98 (21.1)	130 (24.9)	0.160
Dyslipidemia (%)	6 (1.4)	6 (1.3)	0.843	4 (1.0)	3 (0.7)	0.629	2 (0.7)	4 (1.2)	0.469	8 (1.6)	5 (0.9)	0.301	5 (1.5)	5 (1.4)	0.916	5 (1.1)	4 (0.8)	0.608
Previous stroke (%)	129 (30.9)	162 (34.7)	0.236	133 (34.8)	119 (28.8)	0.069	105 (34.2)	120 (36.1)	0.607	157 (31.9)	161 (29.4)	0.376	119 (35.5)	119 (33.2)	0.527	143 (10.8)	162 (31.0)	0.942
Previous TIA (%)	5 (1.2)	5 (1.1)	0.857	3 (0.8)	5 (1.2)	0.548	3 (1.0)	5 (1.5)	0.548	5 (1.0)	5 (0.9)	0.864	3 (0.9)	5 (1.4)	0.537	5 (1.1)	5 (1.0)	0.851
OTT, hour, mean ± SD	24.7±13.3	24.9±13.8	0.882	25.7±13.0	25.6±13.5	0.905	24.8±12.8	24.7±13.7	0.869	25.4±13.4	25.5±13.6	0.890	24.9±13.3	24.5±13.7	0.699	25.4±13.0	25.7±13.6	0.742
Baseline NIHSS, IQR	7 (6, 10)	7 (6, 9)	0.313	7 (6, 8)	7 (6, 8)	0.909	7 (6, 9)	7 (6, 9)	0.502	7 (6, 9)	7 (6, 9)	0.858	7 (6, 10)	7 (6, 10)	0.614	7 (6, 9)	7 (6, 8)	0.837
Pre-stroke mRS 0 (%)	318 (76.3)	347 (74.1)	0.457	279 (73.0)	312 (75.5)	0.419	233 (75.9)	244 (73.5)	0.486	364 (74.0)	414 (75.5)	0.562	254 (75.8)	268 (74.9)	0.769	343 (73.9)	390 (74.7)	0.777
Pre-stroke mRS 1 (%)	99 (23.7)	121 (25.9)		103 (27.0)	101 (24.5)		74 (24.1)	88 (26.5)		128 (26.0)	134 (24.5)		81 (24.2)	90 (25.1)		121 (26.1)	132 (25.3)	
TOAST classification																		
Large artery atherosclerosis (%)	110 (26.4)	153 (32.8)	0.002	98 (25.7)	121 (29.3)	0.339	76 (24.8)	109 (32.8)	0.067	132 (26.8)	165 (30.1)	0.068	85 (25.4)	115 (32.1)	0.007	123 (26.5)	159 (30.5)	0.278
Cardioembolic (%)	2 (0.5)	8 (1.7)		4 (1.0)	3 (0.7)		2 (0.7)	3 (0.9)		4 (0.8)	8 (1.5)		2 (0.6)	4 (1.1)		4 (0.9)	7 (1.3)	
Small artery occlusion (%)	52 (12.5)	83 (17.8)		61 (16.0)	74 (17.9)		44 (14.3)	58 (17.5)		69 (14.0)	99 (18.1)		42 (12.5)	68 (19.0)		71 (15.3)	89 (17.0)	
Other determined (%)	5 (1.2)	4 (0.9)		9 (2.4)	4 (1.0)		2 (0.7)	1 (0.3)		12 (2.4)	7 (1.3)		4 (1.2)	2 (0.6)		10 (2.2)	6 (1.1)	
Undetermined (%)	248 (59.5)	219 (46.9)		210 (55.0)	211 (51.1)		183 (59.6)	161 (48.5)		275 (55.9)	269 (49.1)		202 (60.3)	169 (47.2)		256 (55.2)	261 (50.0)	

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; RIC, remote ischemic conditioning; BMI, body mass index; TIA, transient ischemic attack; OTT, time from symptom onset to RIC treatment; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale.

Table 2 Baseline Characteristics Grouped According to Intervention and Inflammatory Indicators

Variables	RIC (799)			Control (880)			RIC (799)			Control (880)			RIC (799)			Control (880)		
	NLR high (417)	NLR low (382)	P value	NLR high (467)	NLR low (413)	P value	PLR high (307)	PLR low (492)	P value	PLR high (332)	PLR low (548)	P value	SII high (335)	SII low (464)	P value	SII high (358)	SII low (522)	P value
Demographic and clinical Characteristics																		
Age, mean ± SD	66.4±10.3	64.0±10.5	0.001	65.8±10.5	64.6±9.0	0.075	66.3±10.1	64.6±10.7	0.027	65.6±10.1	65.0±10.0	0.431	65.6±10.2	65.0±10.7	0.379	65.7±10.4	64.9±9.8	0.272
Sex (Female) (%)	153 (36.7)	133 (34.8)	0.581	142 (30.4)	145 (35.1)	0.138	117 (38.1)	169 (34.3)	0.281	105 (31.6)	182 (33.2)	0.627	131 (39.1)	155 (33.4)	0.097	114 (31.8)	173 (33.1)	0.687
BMI, mean ± SD	24.2±3.1	24.4±2.8	0.186	24.2±2.9	24.4±3.0	0.358	24.0±3.0	24.5±2.9	0.014	24.0±2.7	24.4±3.0	0.074	24.1±3.0	24.4±2.9	0.211	24.1±2.8	24.4±3.0	0.206
Current smoker (%)	106 (25.4)	124 (32.5)	0.028	127 (27.2)	109 (26.4)	0.789	74 (24.1)	156 (31.7)	0.021	80 (24.1)	156 (28.5)	0.156	83 (24.8)	147 (31.7)	0.033	97 (27.1)	139 (26.6)	0.878
Current drinker (%)	56 (13.4)	63 (16.5)	0.224	47 (10.1)	54 (13.1)	0.162	40 (13.0)	79 (16.1)	0.242	33 (9.9)	68 (12.4)	0.265	45 (13.4)	74 (15.9)	0.324	40 (11.2)	61 (11.7)	0.815
Hypertension (%)	263 (63.1)	229 (59.9)	0.365	292 (62.5)	240 (58.1)	0.181	190 (61.9)	302 (61.4)	0.886	197 (59.3)	335 (61.1)	0.598	216 (64.5)	276 (59.5)	0.152	218 (60.9)	314 (60.2)	0.825
Diabetes (%)	99 (23.7)	91 (23.8)	0.979	113 (24.2)	98 (23.7)	0.871	70 (22.8)	120 (24.4)	0.608	64 (19.3)	147 (26.8)	0.011	92 (27.5)	98 (21.1)	0.038	81 (22.6)	130 (24.9)	0.437
Dyslipidemia (%)	6 (1.4)	4 (1.0)	0.619	6 (1.3)	3 (0.7)	0.411	2 (0.7)	8 (1.6)	0.228	4 (1.2)	5 (0.9)	0.676	5 (1.5)	5 (1.1)	0.603	5 (1.4)	4 (0.8)	0.361
Previous stroke (%)	129 (30.9)	133 (34.8)	0.243	162 (34.7)	119 (28.8)	0.062	105 (34.2)	157 (31.9)	0.502	120 (36.1)	161 (29.4)	0.037	119 (35.5)	143 (10.8)	0.162	119 (33.2)	162 (31.0)	0.491
Previous TIA (%)	5 (1.2)	3 (0.8)	0.557	5 (1.1)	5 (1.2)	0.845	3 (1.0)	5 (1.0)	0.957	5 (1.5)	5 (0.9)	0.421	3 (0.9)	5 (1.1)	0.799	5 (1.4)	5 (1.0)	0.546
OTT, hour, mean ± SD	24.7±13.3	25.7±13.0	0.318	24.9±13.8	25.6±13.5	0.461	24.8±12.8	25.4±13.4	0.530	24.7±13.7	25.5±13.6	0.354	24.9±13.3	25.4±13.0	0.554	24.5±13.7	25.7±13.6	0.189
Baseline NIHSS, IQR	7 (6, 10)	7 (6, 8)	0.000	7 (6,9)	7 (6, 8)	0.000	7 (6, 9)	7 (6, 9)	0.044	7 (6, 9)	7 (6, 9)	0.122	7 (6, 10)	7 (6, 9)	0.000	7 (6, 10)	7 (6, 8)	0.000
Pre-stroke mRS 0 (%)	318 (76.3)	279 (73.0)	0.295	346 (74.1)	312 (75.5)	0.620	233 (75.9)	364 (74.0)	0.545	244 (73.5)	414 (75.5)	0.497	254 (75.8)	343 (73.9)	0.542	268 (74.9)	390 (74.7)	0.960
Pre-stroke mRS 1 (%)	99 (23.7)	103 (27.0)		121 (25.9)	101 (24.5)		74 (24.1)	128 (26.0)		88 (26.5)	134 (24.5)		81 (24.2)	121 (26.1)		90 (25.1)	132 (25.3)	
TOAST classification																		
Large artery atherosclerosis (%)	110 (26.4)	98 (25.7)	0.303	153 (32.8)	121 (29.3)	0.497	76 (24.8)	132 (26.8)	0.368	109 (32.8)	165 (30.1)	0.521	85 (25.4)	123 (26.5)	0.517	115 (32.1)	159 (30.5)	0.758
Cardioembolic (%)	2 (0.5)	4 (1.0)		8 (1.7)	3 (0.7)		2 (0.7)	4 (0.8)		3 (0.9)	8 (1.5)		2 (0.6)	4 (0.9)		4 (1.1)	7 (1.3)	
Small artery occlusion (%)	52 (12.5)	61 (16.0)		83 (17.8)	74 (17.9)		44 (14.3)	69 (14.0)		58 (17.5)	99 (18.1)		42 (12.5)	71 (15.3)		68 (19.0)	89 (17.0)	
Other determined (%)	5 (1.2)	9 (2.4)		4 (0.9)	4 (1.0)		2 (0.7)	12 (2.4)		1 (0.3)	7 (1.3)		4 (1.2)	10 (2.2)		2 (0.6)	6 (1.1)	
Undetermined (%)	248 (59.5)	210 (55.0)		219 (46.9)	211 (51.1)		183 (59.6)	275 (55.9)		161 (48.5)	269 (49.1)		202 (60.3)	256 (55.2)		169 (47.2)	261 (50.0)	

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; RIC, remote ischemic conditioning; BMI, body mass index; TIA, transient ischemic attack; OTT, time from symptom onset to RIC treatment; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale.

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The Effect of Inflammation Statuses on the Efficacy of RIC

Figure 1 shows the distribution of the mRS scores at 90 days in the high vs low NLR, PLR, and SII in RIC and control groups. Table 3 illustrates the efficacy of RIC in patients with a high vs low NLR, PLR, and SII. A significantly lower proportion of patients with poor outcomes was identified in the RIC vs control subgroup in the high NLR group (37.2% vs 45.0%; adjusted OR, 0.620; 95% CI, 0.460–0.834; P = 0.002), and a similar trend was observed in the low NLR group (24.9% vs 30.0%; adjusted OR, 0.730; 95% CI, 0.522–1.020; P = 0.065) without a significant difference. Similar results were found in RIC vs control subgroup in high PLR group (35.2% vs 42.2%; adjusted OR, 0.670; 95% CI, 0.472 to 0.951; P = 0.025), low PLR group (28.9% vs 35.4%; adjusted OR, 0.670; 95% CI, 0.504 to 0.892; P = 0.006), high SII group (37.9% vs 46.9%; adjusted OR, 0.610; 95% CI, 0.436 to 0.854; P = 0.004), and low SII group (26.5% vs 31.8%; adjusted OR, 0.708; 95% CI, 0.526 to 0.953; P = 0.023). No significant difference in the change in NIHSS score between admission and 12 days after treatment was found between the RIC and control subgroups in the high vs low NLR, PLR, and SII groups. Furthermore, we did not find an interaction effect of an intervention (RIC or control) with different NLR, PLR, or SII on clinical outcomes (P > 0.05) (Table 3 and Figure 2). Figure 2 shows that the probability of an mRS score of 2–6 increased with an increase in the NLR, PLR, and SII in both the RIC and control groups.

The Effect of Inflammation Statuses on Clinical Outcomes in RIC Intervention and Non-RIC Intervention

Table 4 illustrates the effect of NLR, PLR, and SII on clinical outcomes in all patients and in the RIC and control groups. A significantly higher likelihood of poor outcome was found in the high vs low NLR subgroup of overall patients (adjusted

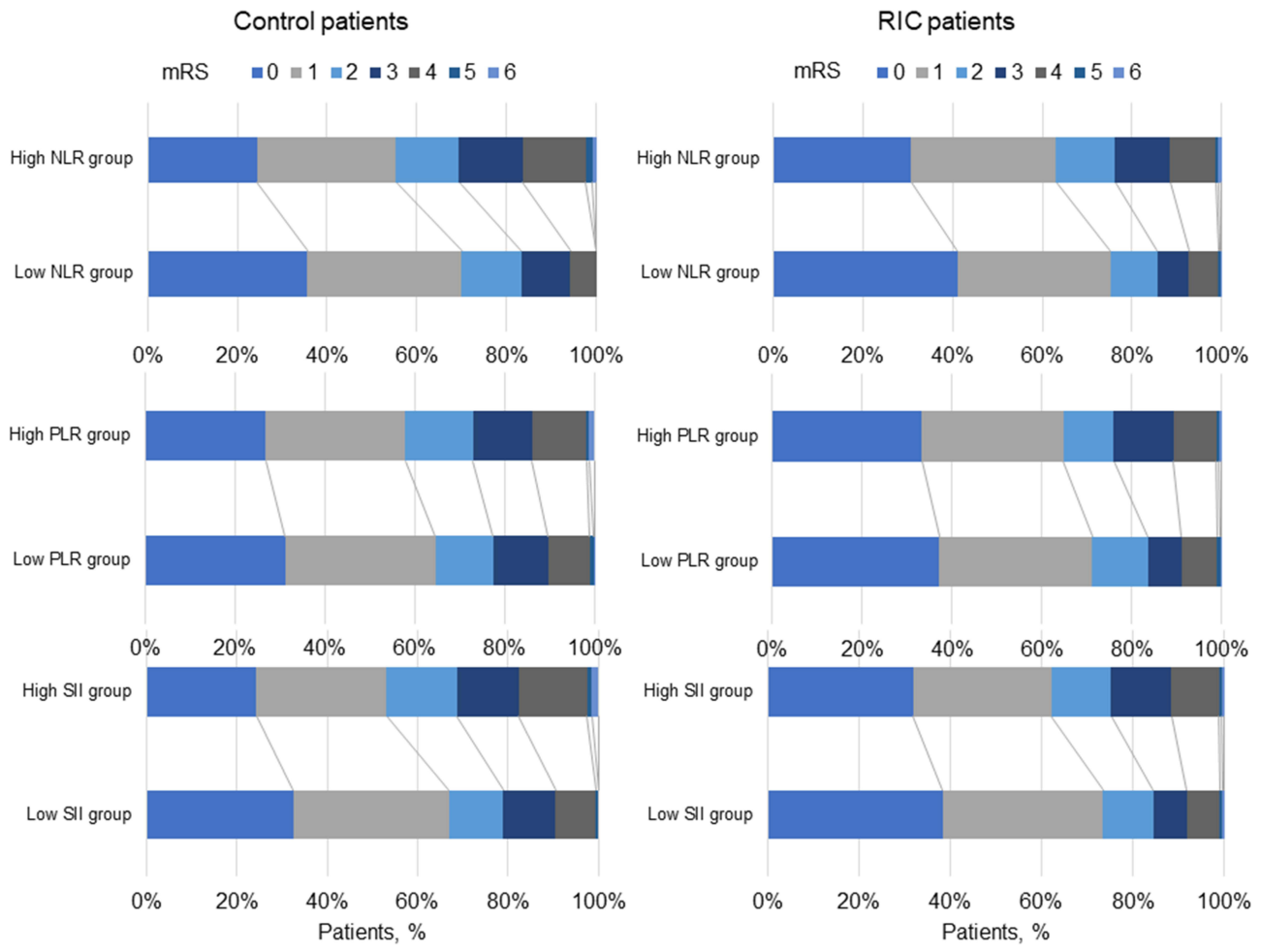

Figure 1 Distribution of modified Rankin Scale scores at 90 days among groups.

Table 3 Efficacy of RIC Based on Inflammatory Indicators

		RIC Group	Control Group	Treatment Effect Metric	Unadjusted Treatment Effect, 95% (CI)	P value	Adjusted Treatment Effect, 95% (CI)	P value	P for Interaction
mRS 2–6	**NLR high (884)**	155/417 (37.2%)	210/467 (45.0%)	OR	0.724 (0.553, 0.948)	0.019	0.620 (0.460, 0.834)	0.002	0.484
	NLR low (795)	95/382 (24.9%)	124/413 (30.0%)	OR	0.771 (0.564, 1.055)	0.104	0.730 (0.522, 1.020)	0.065	
	PLR high (639)	108/307 (35.2%)	140/332 (42.2%)	OR	0.774 (0.541, 1.025)	0.070	0.670 (0.472, 0.951)	0.025	0.946
	PLR low (1040)	142/492 (28.9%)	194/548 (35.4%)	OR	0.740 (0.570,0.962)	0.025	0.670 (0.504, 0.892)	0.006	
	SII high (693)	127/335 (37.9%)	168/358 (46.9%)	OR	0.691 (0.510, 0.935)	0.017	0.610 (0.436, 0.854)	0.004	0.536
	SII low (986)	123/464 (26.5%)	166/522 (31.8%)	OR	0.774 (0.587, 1.020)	0.069	0.708 (0.526, 0.953)	0.023	
Change in NIHSS at day 12 from baseline	**NLR high**	4 (2, 6)	3 (1, 5)	MD	−0.417 (−0.887, 0.053)	0.082	−0.396 (−0.857, 0.064)	0.092	
	NLR low	4 (2, 6)	4 (2, 6)	MD	−0.143 (−0.557, 0.271)	0.499	−0.100 (−0.496, 0.295)	0.620	
	PLR high	4 (2, 6)	4 (1, 5)	MD	−0.240 (−0.803, 0.324)	0.404	−0.253 (−0.807, 0.301)	0.370	
	PLR low	4 (2, 6)	4 (2, 5)	MD	−0.324 (−0.700, 0.051)	0.091	−0.283 (−0.645, 0.080)	0.126	
	SII high	4 (2, 6)	3 (1, 5)	MD	−0.149 (−0.696, 0.398)	0.594	−0.188 (−0.728, 0.352)	0.496	
	SII low	4 (2, 6)	4 (2, 6)	MD	−0.398 (−0.774, −0.021)	0.038	−0.339 (−0.697, 0.020)	0.064	

Notes: Adjusted for key prognostic covariates (age, sex, premorbid function [pre-stroke mRS score, 0 or 1], baseline NIHSS score, history of stroke, history of TIA, and OTT).
Abbreviations: RIC, remote ischemic conditioning; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

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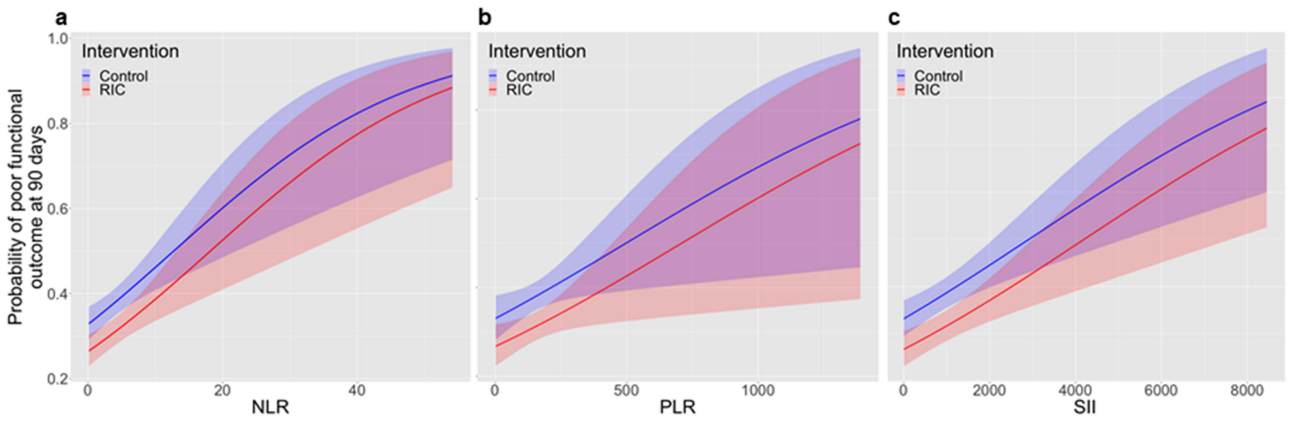

Figure 2 Probability of poor outcome according to inflammatory indicators in RIC and control groups. (**a**) Probability of NLR. (**b**) Probability of PLR. (**c**) Probability of SII.

OR, 1.570; 95% CI, 1.258–1.961; P = 0.000), the RIC group (adjusted OR, 1.462; 95% CI, 1.051–2.035; P = 0.024), and the control group (adjusted OR, 1.699; 95% CI, 1.253–2.304; P = 0.001). Similar results were found in the high vs low SII subgroup in all patients (adjusted OR, 1.551; 95% CI, 1.244–1.934; P = 0.000), the RIC group (adjusted OR, 1.471; 95% CI, 1.061–2.039; P = 0.021), and the control group (adjusted OR, 1.678; 95% CI, 1.238–2.273; P = 0.001). A significant decrease in NIHSS scores between baseline and 12 days after randomization was found in the low vs high NLR subgroup of overall patients (adjusted MD, 0.669; 95% CI, 0.357–0.980; P = 0.000), the RIC group (adjusted MD, 0.534; 95% CI, 0.071–0.996; P = 0.024), and the control group (adjusted MD, 0.756; 95% CI, 0.337–1.176; P = 0.000). Similar results were found in the low vs high SII subgroup of all patients (adjusted MD, 0.497; 95% CI, 0.182–0.812; P = 0.002) and the RIC group (adjusted MD, 0.635; 95% CI, 0.172–1.098; P = 0.007). However, these changes were not observed in PLR group.

Table 4 Efficacy of Inflammatory Indicators Based on Intervention

		Treatment effect Metric	Overall patients (1679)		RIC group (799)		Control group (880)	
			Adjusted Treatment effect, 95% (CI)	P value	Adjusted Treatment effect, 95% (CI)	P value	Adjusted Treatment Effect, 95% (CI)	P value
mRS 2–6	**NLR**	OR	1.570 (1.258, 1.961)	0.000	1.462 (1.051, 2.035)	0.024	1.699 (1.253, 2.304)	0.001
	PLR	OR	1.221 (0.977, 1.527)	0.079	1.231 (0.885, 1.711)	0.216	1.251 (0.920, 1.701)	0.154
	SII	OR	1.551 (1.244, 1.934)	0.000	1.471 (1.061, 2.039)	0.021	1.678 (1.238, 2.273)	0.001
Change in NIHSS at day 12 from baseline	**NLR**	MD	0.669 (0.357, 0.980)	0.000	0.534 (0.071, 0.996)	0.024	0.756 (0.337, 1.176)	0.000
	PLR	MD	0.239 (−0.080, 0.557)	0.142	0.266 (−0.203, 0.735)	0.266	0.204 (−0.227, 0.634)	0.354
	SII	MD	0.497 (0.182, 0.812)	0.002	0.635 (0.172, 1.098)	0.007	0.390 (−0.037, 0.817)	0.074

Notes: Adjusted for key prognostic covariates (age, sex, premorbid function [pre-stroke mRS score, 0 or 1], baseline NIHSS score, history of stroke, history of TIA, and time from symptom onset to RIC treatment).
Abbreviations: RIC, remote ischemic conditioning; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

Discussion

In this secondary analysis of RICAMIS, we divided patients with acute moderate ischemic stroke into high and low NLR, PLR, and SII groups according to cut-off values, intending to explore the effect of inflammation level on the clinical outcome of RIC treatment and more accurately identify the optimal patients for RIC treatment. The results showed that (1) compared with the control group, the likelihood of poor functional outcome was lower in the RIC group, regardless of the inflammation level; (2) more benefit from RIC was identified in patients with high vs low NLR, while a similar trend was observed in the high vs low SII group; (3) there was no interaction effect of inflammatory indicators on RIC treatment efficacy; and (4) inflammatory indicators were independently associated with poor outcomes. Collectively, these findings suggest that inflammatory indicators may not affect the neuroprotective effect of RIC treatment but that patients with a high inflammatory status may benefit more from RIC treatment.

To date, no study explored the effect of inflammatory indicators on the neuroprotective efficacy of RIC. In this study, the proportion of patients with poor functional outcomes was significantly lower in the RIC subgroup than that in the control subgroup, regardless of the level of inflammation. Importantly, a greater benefit of RIC treatment was observed in patients with high versus low inflammation levels. This finding implies that anti-inflammation may be an important mechanism underlying RIC neuroprotection, which is also supported by previous studies. For example, modulation of nuclear factor kappa-B (NF-κB), a key transcription factor for inflammatory cytokines, is believed to be involved in the initiation of protective signaling following the application of the RIC protocol on the upper arm.[12,24] Other studies have indicated that extracellular vehicles and small particles containing both proinflammatory and anti-inflammatory factors are proposed as potential carriers of the protective effects of RIC.[25–28] Additionally, some animal and human studies have shown that RIC can induce an immune response and modulate immune cell activation. For example, RIC was found to shift circulating monocytes to a proinflammatory subset, which contributes to a reduction in infarct volume, brain swelling, and improvement of functional recovery in chronic stroke patients.[29] RIC has also been shown to alter the levels of immune cell populations and circulating cytokines, including proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and IL-6.[15,30] These findings suggest that significant alterations in the immune system contribute to the neuroprotective effects of RIC against cerebral ischemia. In the current study, the improved probability of poor functional outcomes in the RIC vs control groups was numerically greater in the high vs low inflammation group. Although a greater benefit of RIC was identified in patients with a high inflammation status, we did not find an interaction effect of an intervention (RIC or control) by different inflammation statuses for clinical outcomes, which suggested that inflammatory indicators may not affect the neuroprotective effect of RIC treatment.

Previous clinical studies have shown that NLR, PLR, and SII were associated with functional outcomes of acute ischemic stroke.[19,20,22,23,31–35] Consistent with these studies, the NLR and SII were found to be independently associated with poor outcomes in overall, RIC, or control patients. However, we did not find an association between the PLR and poor clinical outcomes. In the past few years, several studies have explored the association between the PLR and prognosis in patients with ischemic stroke. Some studies have reported that a higher PLR was linked to worse outcomes after stroke,[17,31] while others[20,32,36] did not find the connection between PLR and clinical outcomes. A meta-analysis of eight studies showed no statistically significant relationship between PLR and poor functional outcomes in stroke patients, especially in patients with a baseline NIHSS score of ≥8,[37] which was consistent with the population in our study (patients with NIHSS scores of 6–16). In addition, a recent study found that PLR at 24 h after thrombolysis, but not on admission, was associated with poor outcomes.[36] These findings suggest that PLR on admission may not be a suitable biomarker for predicting clinical outcomes of acute ischemic stroke.[20]

As a secondary analysis of RICAMIS, for the first time, we explored the effect of inflammatory indicators on efficacy of RIC treatment. These results suggest a greater benefit of RIC treatment in patients with high inflammation levels, although inflammation did not affect the efficacy of RIC because their interactions were not identified. However, our study had some limitations that need to be addressed. First, the imbalanced sample size between groups and the relatively small sample size in each group may limit the statistical power. Second, the lack of dynamic changes in NLR, PLR, and SII in this study will affect our understanding of the association between inflammation and RIC efficacy. Third, the generalizability of the findings may be limited to the Chinese population, and needs to be validated in other cohorts,

particularly in non-Chinese populations. Finally, our results should be interpreted with caution due to the exploratory nature of this secondary analysis. Therefore, our findings need to be confirmed by further studies.

Conclusion

This post hoc exploratory analysis of the RICAMIS trial suggested that inflammatory indicators such as NLR, PLR, and SII may not affect the efficacy of RIC treatment in patients with acute moderate ischemic stroke, although a lower probability of poor outcome at 90 days was identified in patients with a high vs low inflammatory status. In addition, these inflammatory indicators were independently associated with functional outcomes in patients regardless of whether they received RIC or not.

Data Sharing Statement

These data are available upon request.

Ethics Approval

This study was approved by the ethics committee of the General Hospital of Northern Theater Command and was in compliance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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