Correlation between Immune-Inflammatory Markers and Clinical Features in Patients with Acute Ischemic Stroke

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Abstract

Objective: Chronic inflammatory processes involving the vascular wall may induce atherosclerosis. Immune-inflammatory processes proceed throughout all stages of acute stroke. We investigated the association of three immune-inflammatory markers, namely systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and neutrophil count (NC), with prehospital delay and clinical features in patients with acute ischemic stroke.

Methods: We retrospectively enrolled 2543 inpatients admitted within 4 days of symptom onset from May 2010 to February 2020. Patients were stratified into three groups: Group A, comprising 161 patients with tissue plasminogen activator (tPA) treatment; Group B, comprising 415 patients who were eligible for tPA treatment; and Group C, comprising all 2543 patients.

Results: The levels of all three immune-inflammatory markers had positive linear correlations with onset-to-emergency room time, initial National Institutes of Health Stroke Scale (NIHSS) scores, and discharge modified Rankin Scale scores. In Group B, levels of follow-up, but not initial, immune-inflammatory markers were higher in patients with unfavorable outcomes. Common significant predictors of in-hospital complications and unfavorable outcomes were age > 72 years, female sex, NIHSS > 4, diabetes mellitus, and all three immune-inflammatory markers. When combined with other predictors, NC > 7.2×10^3/mL achieved optimal predictive performance (0.794) for in-hospital complications, and SII > 651, NLR > 2.9, and NC > 7.2×10^3/mL had equal predictive performance up to 0.859 for unfavorable outcomes.

Conclusions: Immune-inflammatory markers dynamically increased from symptom onset of acute ischemic stroke in patients eligible for thrombolytic therapy. Higher levels of immune-inflammatory markers suggest more in-hospital complications and unfavorable short-term outcomes.

Keywords: acute ischemic stroke, neutrophil count, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, unfavorable outcome.

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INTRODUCTION

Inflammation is part of the immune response that can occur throughout the body. Chronic inflammatory processes involving the vascular wall may induce atherosclerosis, and further arterial occlusion may

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cause an acute ischemic stroke. Immune-inflammatory processes proceed throughout all stages of acute ischemic stroke and may thus influence the outcomes of a stroke [1]. Neutrophils and lymphocytes are two main white blood cells of the immune-inflammatory system and can conveniently be surveyed during regular laboratory studies [2]. Platelets also participate in modulating the immune-inflammatory system [3]. Ratios of cell measurements, such as the neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII), which is derived from platelet, neutrophil, and lymphocyte counts, suitably reflect the balance between innate and adaptive immunity [4,5]. Higher neutrophil count (NC) and NLR have been reported to be associated with poor outcomes among patients with acute stroke and patients with various types of cancer [6-8]. SII, a novel immune-inflammatory ratio developed by Hu et al., was found to be a powerful indicator of poor outcomes among patients with hepatocellular carcinoma [5]. Higher SII is associated with deterioration in cancer, endocarditis, coronary artery disease, and dementia [4,9-11]. To the best of our knowledge, correlation of SII and acute stroke has never been reported in English literature.

Theoretically, higher severity of brain damage causes a greater immune-inflammatory response, and this immune-inflammatory response intensifies gradually from symptom onset during acute ischemic stroke. The correlations of the interval between symptom onset and arrival in the emergency room [ER] [onset-to-ER time] with the levels of immune-inflammatory markers have seldom been explored. Previous studies have found a dynamic increase of neutrophils and NLR before and 24 hours after tissue plasminogen activator (tPA) treatment; and the post-tPA, but not admission NLR, was an independent negative predictor of favorable outcome in patients with acute ischemic stroke [12,13]. However, no comparisons between patients with and without tPA treatment were available. Whether dynamic increase of immune-inflammatory markers also predicts unfavorable outcomes in patients eligible for evaluation of thrombolytic therapy but not received tPA treatment is not known. In the present study, we investigated the association of three immune-inflammatory markers, namely SII, NLR, and NC, with the time interval from symptom onset, the impact of thrombolytic therapy, and clinical features in patients with acute ischemic stroke.

MATERIAL AND METHODS

We retrospectively reviewed all the registered inpatients with acute ischemic stroke during the period from May 2010 to February 2020. To investigate the early stage of the immune-inflammatory response, only patients who were admitted within 4 days of symptom onset were enrolled. Diagnosis of acute ischemic stroke was confirmed by clinical presentation and proof of an ischemic lesion or absence of a corresponding intracranial lesion other than infarction by using brain computed tomography or magnetic resonance imaging. Sex, age, history of hypertension, diabetes mellitus, hyperlipidemia, heart disease, previous stroke, smoking status, alcohol consumption, cancer, uremia, and length of stay (LOS) in hospital were recorded for analysis. We collected the duration of prehospital delay of all patients (i.e. onset-to-ER time). Initial stroke severity was assessed at admission according to the National Institutes of Health Stroke Scale (NIHSS) but was assessed in the ER for patients eligible for tPA treatment. Urinary tract infection, pneumonia, gastrointestinal bleeding, and seizure were registered as in-hospital stroke complications. Functional outcomes were evaluated using the modified Rankin Scale (mRS) at discharge. An mRS score > 2 was considered to indicate an unfavorable outcome.

Laboratory data obtained on arrival in the ER included a full blood count with white blood cell differentials and platelet. Three immune-inflammatory markers, namely SII, NLR, and NC, were obtained for analysis (initial markers). The NLR was calculated as the ratio of NC to lymphocyte count. SII was calculated as the platelet count multiplied by the NLR. Given a delay between blood-draw time and arrival time in the ER was usually present, such delay could be minimized in patients eligible for tPA treatment through a code stroke. In such situation, onset-to-ER time could be considered as an appropriate time of blood-draw. The first follow-up full blood count studies within one week of admission were also collected for comparison (follow-up markers).

The chi-square test and Fisher's exact test were used for categorical comparisons. Group comparisons of continuous variables were performed using two-sample

t tests. Linear regression tests were used to analyze the associations between variables. Paired-t tests were used to compare the initial and follow-up immune-inflammatory markers. Continuous variables that were significant predictors of in-hospital complications and unfavorable outcomes in the univariate analyses were converted into dichotomous variables, with the optimal cutoff level determined according to the Youden index by using a receiver operating characteristic (ROC) curve. The variables were then added to a multiple logistic regression model to identify the significant factors associated with in-hospital complications and unfavorable outcomes. We used the C-statistic to analyze the predictive performance of all the significant variables for both in-hospital complications and unfavorable outcomes. A p value less than 0.05 was considered indicative of a significant result. All statistical analyses were performed using SPSS version 24 (SPSS Inc., Chicago, IL, USA). The ROC curves were compared using MedCalc version 18 (MedCalc Software, Mariakerke, Belgium). This study was approved by the Institutional Review Board of Taipei Tzu Chi Hospital (09-X-025).

RESULTS

During the study period, 3641 patients with acute ischemic stroke were registered. After excluding patients without information of symptom onset time (n = 112), those who presented 4 days after symptom onset (n = 389), and those with incomplete laboratory data or

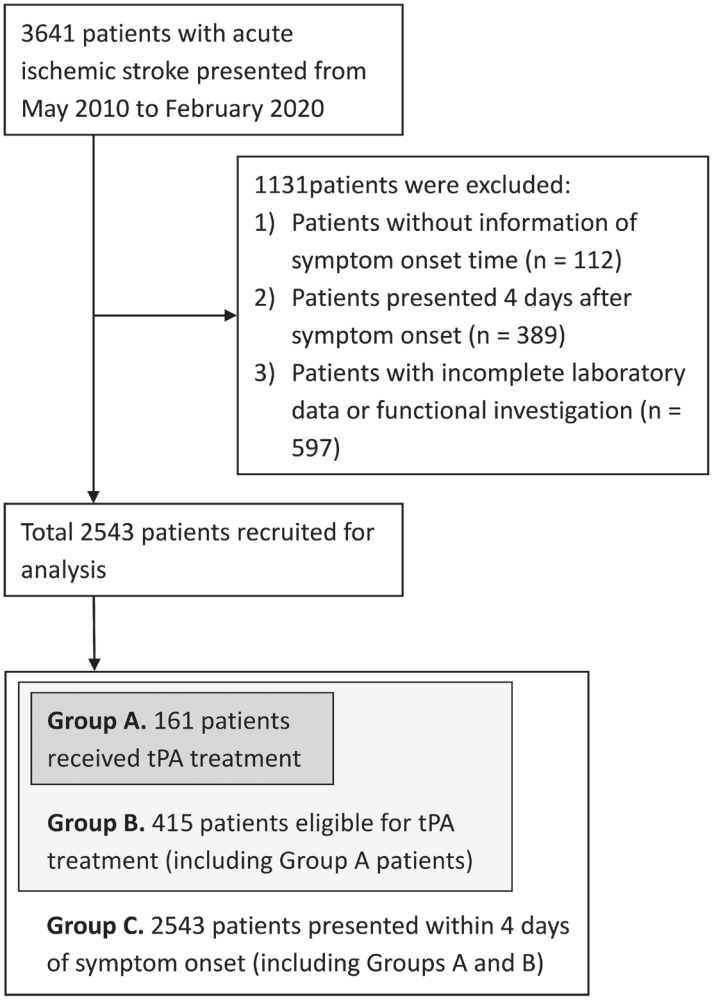

Figure 1. Flowchart of patient enrollment. tPA, tissue plasminogen activator.

Table 1. Baseline characteristics of patients in different groups.

	Group A (n = 161) [a]	Group B (n = 415) [b]	Group C (n = 2543) [c]
Mean age (years)	67.2±11.7	71.1±13.8	70.8±13.5
Female sex	55 (34%)	159 (38%)	1074 (42%)
Onset-to-ER time (min)	64±42	94±66	1409±1460
Initial NIHSS score	13±6	12±6	7±7
Discharge NIHSS score	8±9	10±11	6±8
Discharge mRS score	2.8±1.8	3.2±1.7	2.6±1.6
Hospital LOS	18±15	18±15	15±13
SII	557±514	635±610	861±1256
NLR	2.6±1.9	3.3±4.9	4.0±5.3
NC ($\times 10^3$/mL)	4.9±1.9	5.1±2.1	5.5±2.6

ER: emergency room, LOS: length of stay, mRS: modified Rankin Scale, NC: neutrophil count, NIHSS: National Institutes of Health Stroke Scale, NLR: neutrophil-to-lymphocyte ratio, SII: systemic immune-inflammation index

[a] Patients who received tissue plasminogen activator treatment; [b] Patients who were eligible for tissue plasminogen activator treatment; [c] Patients who presented within 4 days of symptom onset.

Data are expressed as mean ± standard deviation or n (%).

functional evaluation (n = 597), we enrolled 2543 patients in the analysis. Enrollees were stratified into three groups. Group A comprised 161 patients who received intravenous tPA treatment. Group B comprised 415 patients who were eligible for tPA treatment (i.e., patients who presented to the ER within 4 hours of symptom onset with an initial NIHSS score between 4 and 25). Thus, Group B included the patients from Group A and an additional 254 patients who did not meet the criteria for thrombolytic therapy and did not receive tPA treatment. Group C comprised all 2543 patients who presented to the ER within 4 days of symptom onset (Fig. 1). Follow-up full blood count studies within 1 week of hospitalization were available for 130 of the 161 patients (81%) who received tPA treatment and for 192 of the 254 patients (76%) without tPA treatment in Group B.

Table 1 lists the basic characteristics of patients in the three groups. The average SII, NLR, and NC values for all 2543 patients (Group C) were 861 ± 1256, 4.0 ± 5.3, and 5.5 ± 2.6 × 10^3/mL, respectively. The onset-to-ER time was shortest and the levels of the three immune-inflammatory markers were lowest in patients in Group A.

Table 2 presents the correlation between three immune-inflammatory markers and onset-to-ER time in different groups; furthermore, the correlation between the markers and initial stroke severity as well as functional outcomes in patients in Group C are also presented. In all three groups, the levels of all the immune-inflammatory markers had positive linear correlations with onset-to-ER time, except for NC in Group A. Among patients in Group C, all three immune-inflammatory marker levels also exhibited a positive linear correlation with initial NIHSS, discharge mRS, and LOS in hospital ($p < 0.001$). Initial NIHSS scores were positively correlated with discharge mRS and hospital LOS ($p < 0.001$), whereas the onset-to-ER times had negative linear correlations with initial NIHSS, discharge mRS, and LOS in hospital ($p < 0.001$).

Relative to patients who received tPA treatment, patients without tPA treatment in Group B were older, had longer onset-to-ER times, lower initial NIHSS scores, lower percentages of hemorrhagic transformation, and higher percentages of unfavorable outcomes (Table 3). Initial SII and NLR values were higher in patients who did not receive tPA treatment. No differences were observed in follow-up immune-inflammatory markers between patients with and without tPA treatment. In Group A (those who received tPA treatment), patients with unfavorable outcomes were older, had higher initial NIHSS scores, and higher percentages of hemorrhagic transformation than did patients with favorable outcomes. Paired-t tests revealed that levels of all three immune-inflammatory markers elevated significantly during follow-up studies as compared with levels of initial studies ($p < 0.001$) (Fig. 2). The levels of follow-up, but not the initial, immune-

Table 2. Linear correlation of immune-inflammatory markers with timing of symptom onset, initial stroke severity, and short-term outcome.

	SII		NLR		NC ($\times 10^3$/mL)		Initial NIHSS		Onset-to-ER time	
	coefficient	R^2	coefficient	R^2	coefficient	R^2	coefficient	R^2	coefficient	R^2
Group A (n = 161) [a]										
Onset-to-ER time (min)	0.016	0.038*	4.877	0.049*	3.153	0.002	-0.029	0.004*	-	-
Group B (n = 415) [b]										
Onset-to-ER time (min)	0.023	0.045**	0.377	0.032**	4.352	0.021*	-1.98	0.037**	-	-
Group C (n = 2543) [c]										
Onset-to-ER time (min)	0.055	0.002*	13.194	0.002*	20.546	0.003*	-39.865	0.037**	-	-
Initial NIHSS	0.001	0.023**	0.24	0.032**	0.445	0.027**	-	-	-0.001	0.037**
Discharge mRS	0.0002	0.017**	0.05	0.026**	0.093	0.022**	0.15	0.436**	-0.000	0.009**
Hospital LOS (days)	0.001	0.006**	0.266	0.011**	0.704	0.019**	0.925	0.246**	-0.001	0.01**

ER: emergency room, LOS: length of stay, mRS: modified Rankin Scale, NC: neutrophil count, NIHSS: National Institutes of Health Stroke Scale, NLR: neutrophil-to-lymphocyte ratio, SII: systemic immune-inflammation index

*$p < 0.05$; **$p < 0.001$

[a] Patients who received tissue plasminogen activator treatment; [b] Patients who were eligible for tissue plasminogen activator treatment; [c] Patients who presented within 4 days of symptom onset.

Table 3. Correlation of clinical features and immune-inflammatory markers with outcomes in patients eligible for tPA treatment [a].

	Patients received tPA treatment				Patients not received tPA treatment				P value
	mRS ≦ 2 (n = 69)	mRS > 2 (n = 92)	P value	Total (n = 161)	mRS ≦ 2 (n = 69)	mRS > 2 (n = 185)	P value	Total (n = 254)	
Age (years)	65±12	69±11	0.043	67±12	67±13	76±14	<0.001	74±15	<0.001
Female sex	14 (20%)	41 (45%)	0.001	55 (34%)	24 (35%)	80 (43%)	0.252	104 (41%)	0.179
Onset-to-ER time (min)	71±43	59±42	0.089	65±43	108±71	115±71	0.479	113±71	<0.001
Initial NIHSS	10±5	15±6	<0.001	13±6	6±4	13±6	<0.001	11±6	0.015
Initial SII	598±553	526±482	0.382	554±510	638±439	705±728	0.472	687±662	0.031
Initial NLR	2.5±1.6	2.6±2.2	0.861	2.6±1.9	3.0±2.4	4.0±6.9	0.252	3.7±6.1	0.020
Initial NC ($\times 10^3$/mL)	4.9±2.0	4.8±1.8	0.107	4.9±1.9	5.0±2.5	5.2±2.3	0.444	5.2±2.3	0.140
Follow-up SII	773±564	1438±1572	0.005	1380±1462	674±475	1414±1237	0.009	1309±1188	0.696
Follow-up NLR	3.6±2.3	7.5±6.7	<0.001	6.8±5.8	3.4±1.8	7.8±5.9	0.001	7.2±5.8	0.651
Follow-up NC ($\times 10^3$/mL)	5.5±2.4	7.5±3.3	<0.001	7.0±3.0	5.2±2.0	7.9±3.3	<0.001	7.6±3.3	0.234
Hemorrhagic transformation	4 (6%)	23 (25%)	0.001	27 (17%)	0 (0%)	9 (5%)	0.062	9 (4%)	<0.001
Modified Rankin Scale > 2	-	-	-	92 (57%)	-	-	-	185 (73%)	0.001

ER: emergency room, mRS: modified Rankin Scale, NC: neutrophil count, NIHSS: National Institutes of Health Stroke Scale, NLR: neutrophil-to-lymphocyte ratio, SII: systemic immune-inflammation index, tPA: tissue plasminogen activator

[a] Presented to ER within 4 hours of symptom onset with NIHSS score between 4 and 25.

Data are expressed as mean ± standard deviation or n (%); two-sample t test or chi-square test was conducted.

inflammatory markers were higher in patients with unfavorable outcomes. Similar results between favorable and unfavorable outcomes were observed among patients without tPA treatment in Group B.

Univariate analyses of continuous variables revealed that older age; shorter onset-to-ER time; higher initial NIHSS score; higher initial SII, NLR, and NC values; and longer LOS in hospital were significantly associated with both in-hospital complications and unfavorable outcomes (Table 4). Univariate analyses of dichotomous variables

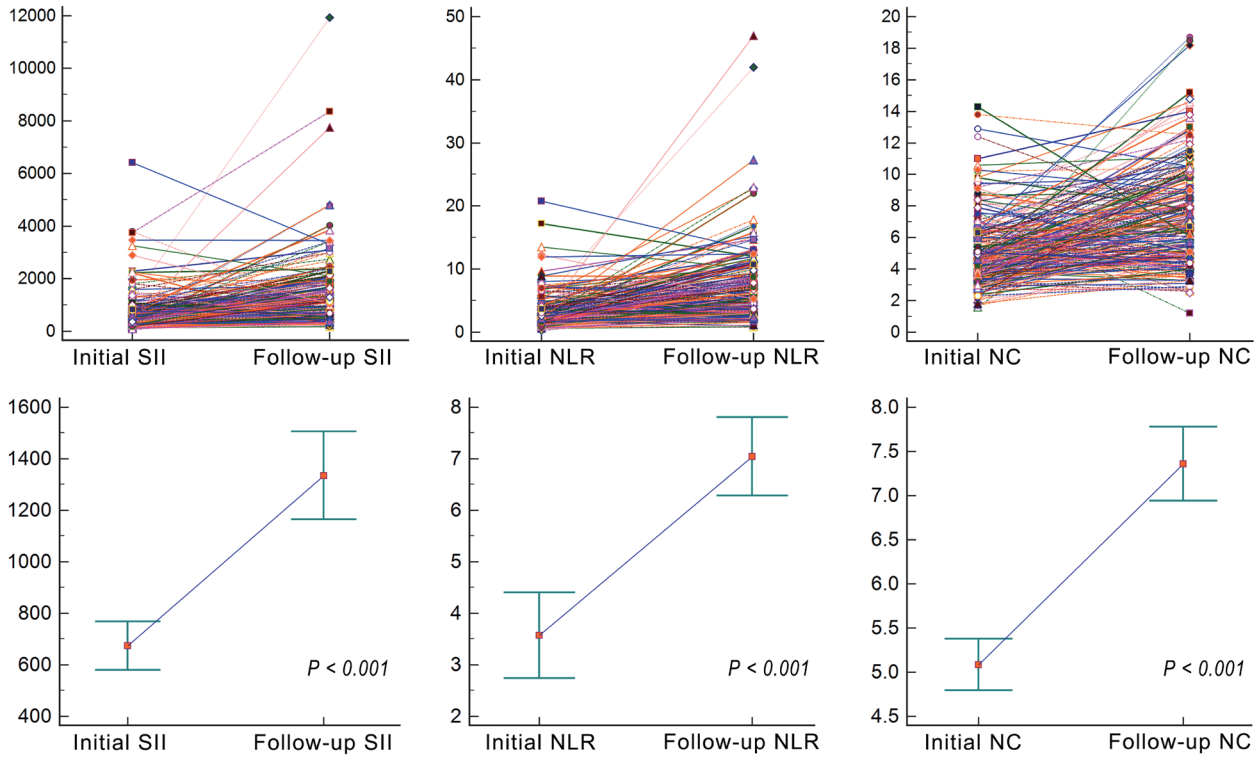

Figure 2. Paired comparisons of initial and follow-up immune-inflammatory markers in 415 patients eligible for thrombolytic therapy. NC, neutrophil count; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammatory index.

revealed that female sex, hypertension, diabetes mellitus, heart disease, and previous stroke were significant positive predictors of both in-hospital complications and unfavorable outcomes. History of cancer and uremia were also positive predictors of unfavorable outcomes. However, smoking and alcohol consumption were negative predictors of both in-hospital complications and unfavorable outcomes, and hyperlipidemia was a negative predictor of unfavorable outcomes.

Table 5 presents the results of the multiple logistic regression analysis for the effect of the main significant factors in Table 4 on in-hospital complications and unfavorable outcomes. The optimal cutoff values for age (72 years), initial NIHSS score (4), SII (651), NLR (2.9), and NC (7.2×10^3/mL) were determined according to the ROC curve associated with unfavorable outcomes. The three immune-inflammatory markers were included separately in each analysis. Six factors were found to significantly influence in-hospital complications, namely age > 72 years, female sex, initial NIHSS score > 4, diabetes mellitus, heart disease, and SII > 651. Eight significant predictors of unfavorable outcomes were identified, namely age > 72 years, female sex, initial NIHSS score > 4, diabetes mellitus, previous stroke, being a current smoker, uremia, and SII > 651. Being a current smoker was a negative predictor of unfavorable outcomes. These significant predictors for in-hospital complications and unfavorable outcomes were identical when SII > 651 was replaced with NLR > 2.9 and NC > 7.2×10^3/mL, except for heart disease for in-hospital complication with NC.

For C-statistics analysis of in-hospital complications, we established a model (Model 1) comprising the five significant predictors of in-hospital complications, namely age > 72 years, female sex, initial NIHSS score > 4, diabetes mellitus, and heart disease. The C-statistic of

Table 4. Univariate analysis of actors influencing in-hospital complications and predictors of unfavorable outcomes (mRS > 2) in 2543 patients who presented within 4 days of symptom onset.

	In-hospital complications			Unfavorable outcomes		
Variables	OR	95 % CI	P value	OR	95 % CI	P value
Age (years)	1.052	1.041-1.064	<0.001	1.051	1.044-1.058	<0.001
Female sex	1.922	1.506-2.452	<0.001	1.914	1.632-2.246	<0.001
Onset-to-ER time (min)	1.000	1.000-1.000	0.002	1.000	1.000-1.000	<0.001
Initial NIHSS score	1.150	1.133-1.168	<0.001	1.416	1.372-1.463	<0.001
Hypertension	1.348	1.015-1.791	0.039	1.206	1.014-1.434	0.034
Diabetes mellitus	1.418	1.109-1.813	0.005	1.312	1.114-1.546	0.003
Hyperlipidemia	0.883	0.645-1.209	0.438	0.699	0.574-0.852	<0.001
Heart disease	2.061	1.615-2.628	<0.001	1.976	1.672-2.336	<0.001
Previous stroke	1.320	1.010-1.725	0.042	1.987	1.650-2.394	<0.001
Current smoker	0.478	0.333-0.687	<0.001	0.470	0.385-0.572	<0.001
Alcohol consumption	0.491	0.270-0.893	0.019	0.614	0.453-0.832	0.002
Cancer history	1.152	0.719-1.854	0.559	1.578	1.136-2.192	0.007
Uremia	0.690	0.833-3.390	0.139	3.241	1.731-6.068	<0.001
SII	1.000	1.000-1.000	<0.001	1.000	1.000-1.000	<0.001
NLR	1.039	1.020-1.059	<0.001	1.097	1.067-1.127	<0.001
NC ($\times 10^3$/mL)	1.143	1.098-1.188	<0.001	1.098	1.064-1.134	<0.001
tPA treatment	1.374	0.874-2.159	0.169	1.373	0.992-1.900	0.056
Hospital LOS	1.089	1.079-1.100	<0.001	1.171	1.156-1.187	<0.001
In-hospital complications	-	-	-	16.278	10.365-25.563	<0.001

CI: confidence interval, ER: emergency room, mRS: modified Rankin Scale, LOS: length of stay, NC: neutrophil count, NIHSS: National Institutes of Health Stroke Scale, NLR: neutrophil-to lymphocyte ratio, OR: odds ratio, tPA: tissue plasminogen activator, SII: systemic immune-inflammation index

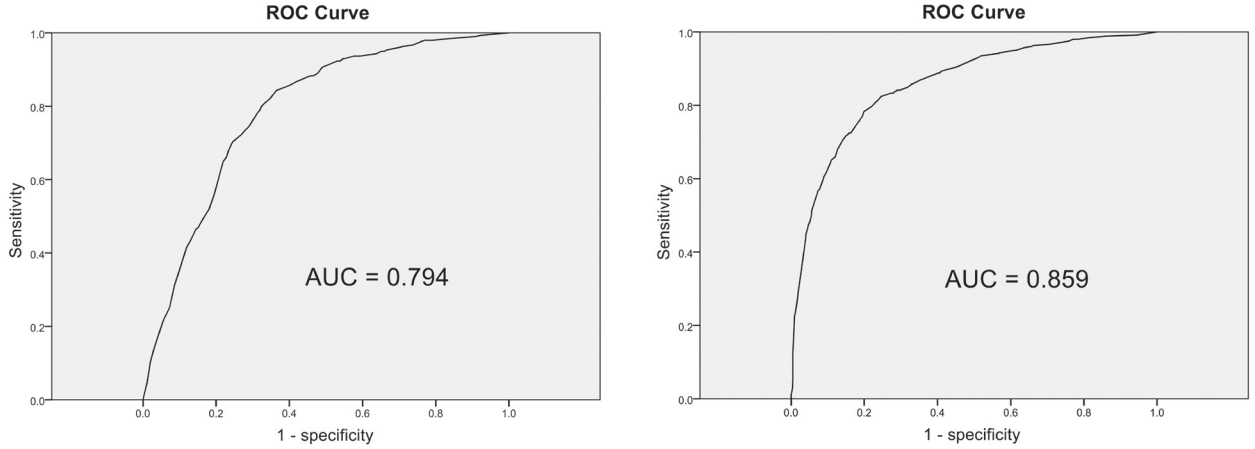

Figure 3. C-statistic of the five significant predictors and neutrophil count > 7.2 × 10^3/mL of in-hospital complications revealed predictive performance of 0.794 (Left). C-statistic of the seven significant predictors plus systemic immune-inflammation index > 651 of unfavorable outcomes revealed predictive performance of 0.859 (Right). AUC, area under the curve.

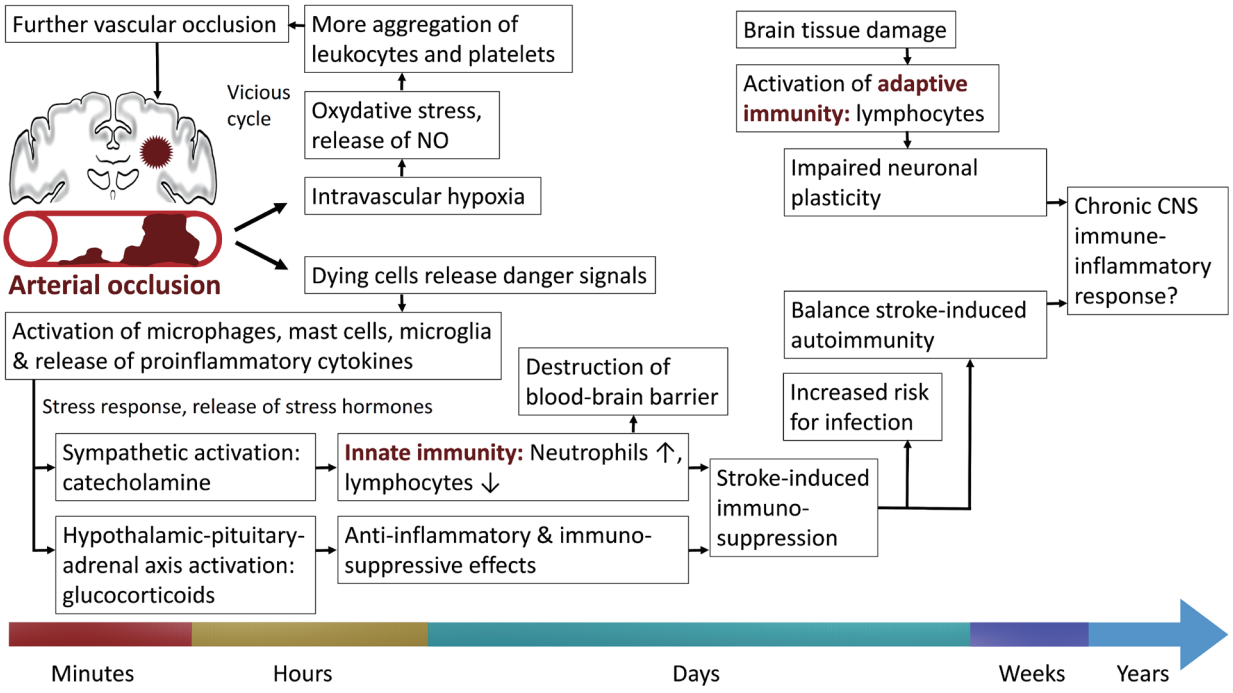

Figure 4. Simplified illustration of immune-inflammatory response after acute ischemic stroke. NO, nitric oxide; CNS, central nervous system.

Model 1 for the detection of in-hospital complications was 0.784. The addition of SII > 651, NLR > 2.9, or NC > 7.2 × 10^3/mL to Model 1 resulted in a significant improvement in the C-statistic from 0.784 to 0.788, 0.787, and 0.794, respectively ($p < 0.05$; Fig. 3). We also established a model (Model 2) comprising the seven significant predictors of unfavorable outcomes, namely age > 72 years, female sex, initial NIHSS score > 4, diabetes mellitus, previous stroke, being a current smoker, and uremia. The C-statistic of Model 2 for the detection of unfavorable outcomes was 0.855. The addition of SII > 651, NLR > 2.9, or NC > 7.2 × 10^3/mL to Model 2 resulted in a significant improvement in the C-statistic from 0.855 to 0.859, 0.858, and 0.859, respectively ($p < 0.05$; Fig. 2).

DISCUSSION

Innate and adaptive systems are the two main branches of the immune system. Innate immunity, comprising neutrophils, monocytes, macrophages, natural killer cells, and complement systems, provides the first line of rapid defense against pathogens. Adaptive immunity, also known as acquired immunity, comprises mainly lymphocytes and is the second line of defense against nonself pathogens. Acute ischemic stroke activates the immune system. Neutrophils migrate to the intraparenchymal perivascular areas within 6–24 hours after cerebral ischemia, producing various cytokines and participating in the early destruction of the blood–brain barrier [14]. Lymphocytes accumulate in the brain 3–6 days after stroke, considerably later than neutrophils, and are considered to have a regulatory function whereby the induce neuroprotection [15,16]. However, adaptive immunity also exerts an immunosuppressive effect that promotes intercurrent infections [1]. In addition to mediating hemostasis and thrombosis, platelets also participate in immune-inflammatory responses by releasing mediators to boost inflammation after stroke and result in the release of neutrophils and lymphocytes into the vessel wall [3]. Activation of microglia, macrophages, and mast cells due to cerebral infarct causes release of proinflammatory cytokines, which in turn induces a release

of stress hormones by activation of both sympathetic and hypothalamic-pituitary-adrenal axis systems [17]. Catecholamine released from sympathetic activation leads to an increase of neutrophils as well as a lymphopenia. Activation of hypothalamic-pituitary-adrenal axis causes transient release of glucocorticoids within several days of acute infarct (Fig. 4). This stress-induced immune alteration also participate in stroke-associated infections. Given the complexity of the immune-inflammatory response, the conversion of detected single blood cell counts into ratios of cell measurement, such as SII and NLR, appears to be more suitable for reflecting the balance between innate and adaptive immunity [11,12].

On the basis of this immune response, changes in peripheral NC would not be prominent during the hyperacute stage of stroke (the stage within several hours of symptom onset). In the present study, we found that levels of all three immune-inflammatory markers were lowest in patients in Group A who had the shortest onset-to-ER time. Although patients in Group B had similar initial NIHSS scores to those of patients in Group A, those in Group B had slightly longer onset-to-ER times. Patients in Group C, who presented within 4 days, obviously had the longest onset-to-ER time and highest level of immune-inflammatory markers. Elevation of neutrophil level occurs several hours after symptom onset and may last for several days. A gradual elevation of lymphocytes could be expected several days after acute stroke and might last for several weeks. However, no relevant data before discharge were available to demonstrate this sequential change of markers in the present study.

All three immune-inflammatory markers had positive linear correlations with both onset-to-ER time and initial NIHSS score, indicating an extensive immune-inflammatory response to wide-ranging brain damage. A larger area of cerebral infarct typically causes more severe clinical disability with a higher NIHSS score, longer LOS in hospital, and less favorable discharge outcome. However, an inverse relationship was observed between onset-to ER time and initial NIHSS as well as discharge mRS scores. In general, patients who have an acute stroke and exhibit symptoms of obvious functional disability, such as disturbance of consciousness or dense hemiplegia, are more likely to be identified and tend to be delivered to the ER earlier. The efficacy of thrombolytic and thrombectomy therapy decreases as more time elapses following symptom onset. Intravenous thrombolytic and endovascular thrombectomy therapy have demonstrated promising results in treating patients in the ER during hyperacute stroke. Patients who had received tPA treatment in Group B had higher initial NIHSS scores but exhibited more favorable functional outcomes than did those who did not receive tPA treatment. However, in this study, the overall benefits of early arrival to the ER was not evident because of the small percentage of patients receiving thrombolytic therapy.

Follow-up NLR is reportedly higher in patients who develop hemorrhagic transformation after thrombolysis [18]. A dynamic increase in NLR reportedly predicts 3-month mortality or major disability in patients receiving tPA treatment [19]. In the present study, a dynamic increase of immune-inflammatory markers occurred not only in patients who received tPA treatment but also in patients without tPA treatment, and was higher in both group of patients with unfavorable outcomes. Although levels of initial SII and NLR were higher in patients without tPA treatment, no differences of follow-up levels were observed between patients with and without tPA treatment. These findings might suggest that the immune-inflammatory response after acute stroke might not be altered apparently after thrombolytic therapy. The mechanisms of elevated markers during follow-up studies include an ongoing inflammatory process as a result of the primary stroke, extensive brain damage due to herniation, hemorrhagic transformation of cerebral infarct, and subsequent complications such as pneumonia or urinary tract infections. Each of these factors contributes to unfavorable outcomes.

The factors related to in-hospital complications and unfavorable outcomes were remarkably similar for both the univariate and multivariate analyses. The occurrence of a particular in-hospital complication has a crucial influence on functional outcomes. Pneumonia and urinary tract infection were two most common in-hospital complications. Elevation of immune-inflammatory markers indicates a status of stroke-induced immunosuppression which leads patients to be susceptible to infections. Common significant predictors of in-hospital complications and unfavorable outcomes were age > 72 years, female sex, NIHSS > 4, diabetes mellitus, and all

three immune-inflammatory markers, namely SII > 651, NLR > 2.9, and NC > 7.2 × 10^3/mL. Heart disease was another significant factor of in-hospital complication, and previous stroke, being a current smoker, and uremia were significant factors for unfavorable outcome. Among these risk factors, initial NIHSS > 4 had the highest odds ratio (OR) for in-hospital complications (7.3) and unfavorable outcomes (13.3). The OR of the three immune-inflammatory markers ranged from 1.4 to 2.2 for in-hospital complications and from 1.3 to 1.7 for unfavorable outcomes. It appears that NC > 7.2 × 10^3/mL represents the most appropriate marker for in-hospital complications because it provides optimal predictive performance (0.794) when combined with the other five predictors. SII > 651, NLR > 2.9, and NC > 7.2 × 10^3/mL had equal predictive performance, ranging from 0.858 to 0.859, for unfavorable outcomes when combined with the other seven predictors.

This study had several limitations. First, this was a retrospective study. Not all patients had follow-up studies of immune-inflammatory markers, and the timing of follow-up studies was not consistent for all patients. Second, the criteria for tPA treatment (according to Taiwan Stroke Society guidelines) have been adjusted several times during the past 9 years for aspects such as the severity of NIHSS score and onset-to-ER time. The simple enrollment criteria for the selection of patients in Group B may not have corresponded to actual clinical practice for specific periods between 2010 and 2020. Third, because we did not perform a follow-up study after discharge, only short-term outcomes at discharge were available. Notwithstanding these limitations, the results extend the current understanding of the implications of immune-inflammatory markers in patients with acute ischemic stroke.

CONCLUSION

SII, NLR, and NC exhibit strong correlations with clinical features and outcomes, and patients arriving earlier at the ER had higher NIHSS scores. Immune-inflammatory markers exhibited a dynamic increase starting from symptom onset of acute ischemic stroke in patients eligible for thrombolytic therapy. Higher levels of immune-inflammatory markers suggest more in-hospital complications and unfavorable short-term outcomes.

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Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Taipei Tzu Chi Hospital (09-X-025).

Competing interests

The authors declare that they have no competing interests.

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