High levels of immuno-inflammatory markers predicts unfavorable short-term outcomes in patients with acute ischemic stroke

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Research

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Abstract

Background Atherosclerosis is a chronic inflammatory process that occurs in the arterial wall. This immuno-inflammatory process plays a role throughout all stages of stroke. Neutrophils, lymphocytes, and platelets are crucial blood cells for innate and adaptive immunity. This study investigated the associations of four types of immuno-inflammatory markers, namely the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and neutrophil count (NC), with clinical outcomes in patients with acute ischemic stroke. Methods In this retrospective study, we enrolled 2903 inpatients with acute ischemic stroke from May 2010 to May 2019. Data included risk factors, laboratory parameters, and clinical features during hospitalization. The National Institutes of Health Stroke Scale (NIHSS), and modified Rankin Scale (mRS) were used to assess stroke severity and outcomes. Results All four immuno-inflammatory markers exhibited positive linear correlations with age, glucose, creatinine, length of hospital stay, NIHSS score on admission, and mRS score at discharge. The levels of the four immuno-inflammatory markers were significantly higher in patients with large-artery atherosclerosis and cardioembolism and were highest in patients with other determined etiology. Patients with levels of immuno-inflammatory markers higher than their cutoff values for unfavorable outcomes also exhibited higher rates of cancer history (except for SII and NC), uremia (except for NC), elevated troponin I, and in-hospital complications. Multivariate analysis including SII revealed that admission NIHSS score ≥ 5, age > 75 years, SII > 724, diabetes mellitus, female sex, elevated troponin I, heart disease, and prior stroke were significant predictors for unfavorable outcomes. These significant predictors were retained after replacing SII > 724 with NLR > 143, PLR > 3.5, or NC > 6 × 10 3 /mL, except for prior stroke. For a basic model comprising seven significant predictors of unfavorable outcomes, the C-statistic was 0.860. The addition of SII, NLR, and PLR to the basic model resulted in a significant improvement in the prediction performance to 0.864, 0.863, and 0.863, respectively. Conclusions Immuno-inflammatory markers provide more useful information than conventional risk factors and other laboratory parameters for the prediction of stroke outcomes. SII > 724 is the most appropriate marker when combined with other predictors.

Introduction

Stroke was the fourth leading cause of death in Taiwan from 2000 to 2020, and it is the leading cause of prolonged disability among older adults. Traditional risk factors for vascular diseases, such as old age, hypertension, diabetes mellitus, and heart disease, are prominent comorbidities of stroke. Most previous studies have emphasized the correlation of these comorbidities with stroke and clinical outcomes. The clinical feature of initial stroke severity has been reported to be a strong predictor of functional outcomes [1, 2]. Laboratory parameters during acute stroke, such as hemoglobin level [3], blood urea nitrogen-to-creatinine ratio [4], and troponin I level [5], also provide valuable information when investigating clinical outcomes after stroke. Atherosclerosis is a chronic inflammatory process that occurs in the arterial wall [6]. Immunity and inflammation have been recognized as crucial elements of the pathobiology of stroke.

Immuno-inflammatory processes play roles throughout all stages of acute stroke, including initial arterial occlusion, brain parenchymal damage, subsequent tissue repair, and infectious complications [7].

Innate and adaptive systems are two main types of immune systems. Innate immunity refers to the immune responses present at birth, and this provides first rapid defense against invasion. Innate immunity is mainly provided by neutrophils, monocytes, macrophages, natural killer cells, and complement systems [8]. Adaptive immunity, also known as acquired immunity, is provided by lymphocytes, which deliver antigen-dependent and antigen-specific responses to invasion. Recent studies have suggested that platelets not only mediate hemostasis and thrombosis but also participate in immuno-inflammatory responses by promoting innate effector cell functions and enhancing adaptive immune responses [9, 10]. To clarify the associations between immuno-inflammatory responses and outcomes of acute stroke, several clinical studies have investigated neutrophils, lymphocytes, and platelets. Detection of a single cellular line may be insufficient to recognize the status and complexity of the immune system. Moreover, a single blood cell test can be influenced by conditions such as overhydration, dehydration, and the treatment of blood specimens [11]. Ratios of cell measurements, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), are considered suitable for reflecting the balance between innate and adaptive immunity [12]. Higher neutrophil count (NC), NLR, and PLR have been reported to be associated with poor outcomes among patients with acute stroke and patients with various types of cancer [11, 13–16]. Hu et al. developed a novel systemic immune-inflammation index (SII) based on platelet, neutrophil, and lymphocyte counts, and they found that SII was a powerful indicator of poor outcomes among patients with hepatocellular carcinoma [17]. Similarly, other studies have reported that higher SII is associated with deterioration in cancer, endocarditis, and dementia [12, 18, 19]. However, the correlation of SII with stroke outcomes has rarely been explored. In the present study, we aimed to investigate the association of four immuno-inflammatory markers, namely SII, NLR, PLR, and NC, with clinical outcomes in patients with acute ischemic stroke. We also compared the predictive performance of these four markers.

Materials & Methods

Study Population and Data Collection

The stroke registry database was retrospectively reviewed to identify patients who were treated for stroke in a neurological ward from May 2010 to May 2019. Inclusion criteria were 1) diagnosis of acute ischemic stroke confirmed by clinical presentation and 2) proof of an ischemic lesion or absence of a corresponding intracranial lesion other than infarction according to brain computed tomography or magnetic resonance imaging. Sex, age, history of hypertension, diabetes mellitus, hyperlipidemia, heart disease, prior stroke, smoking status, alcohol consumption, cancer, uremia, and length of stay (LOS) in hospital were recorded for analysis. Laboratory data obtained on arrival in the emergency department included full blood count with white blood cell differentials as well as platelet, glucose, creatinine, and troponin I levels. Abnormal elevation of troponin I was defined as a blood troponin I level > 0.01 μg/L;

troponin I level was registered as 0.01 μg/L if the patient had a value of ≤ 0.01 μg/L. Fasting cholesterol and triglyceride were recorded during the morning after admission to the ward.

Stroke Severity and Clinical Features

Stroke severity was assessed on admission according to the National Institutes of Health Stroke Scale (NIHSS). We classified the etiology of ischemic stroke according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) categories, namely large-artery atherosclerosis, small-vessel occlusion, cardioembolism, other determined etiology, and undetermined etiology [20]. Urinary tract infection, pneumonia, gastrointestinal bleeding, and seizure were registered as in-hospital stroke complications. Functional outcomes were evaluated using the NIHSS, the Barthel index and the modified Rankin Scale (mRS) at discharge. An mRS score > 2 was considered to indicate an unfavorable outcome.

Definition of Immuno-inflammatory Markers

Four immuno-inflammatory markers, namely SII, NLR, PLR, and NC, were obtained for analysis. The NLR and PLR were calculated as the ratio of neutrophil count to lymphocyte count and the ratio of platelet count to lymphocyte count, respectively. SII was calculated as the platelet count multiplied by the NLR. For patients admitted to the ward with transient ischemic attack (TIA) during the same period, these immuno-inflammatory markers were also collected for comparison.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation. 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 or analysis of variance as appropriate. Significant predictors in the univariate analyses that were continuous variables were converted into dichotomous variables, with the optimal cutoff level determined according to the Youden index by using receiver operating characteristic (ROC) curve for unfavorable outcomes. The variables were then added to a multiple logistic regression model to identify the significant factors associated with unfavorable outcomes. We compared the predictive performance of the variables by using the C-statistic for unfavorable outcomes. A *p* value of less than 0.05 was considered to indicate a significant result. All statistical analyses were performed with SPSS (Version 24, SPSS Inc, Chicago, IL, USA). The ROC curves were compared using the MedCalc software package (version 18, Mariakerke, Belgium). This study was approved by the Institutional Review Board of Taipei Tzu Chi Hospital (09-X-025).

Results

During the study period, 2903 patients with acute ischemic stroke and 457 patients with TIA were enrolled. Of the 2903 patients with acute ischemic stroke, 2036 patients (70%) had valid data concerning troponin I levels because troponin I was not routinely measured in the emergency department for patients with acute stroke during that period. The average age of patients with acute ischemic infarct and patients

with TIA were 71.0 ± 13.5 and 70.5 ± 13.2 years, respectively. Table 1 shows the clinical characteristics of the 2903 patients with acute ischemic stroke and the sex differences for these characteristics. The average values of SII, NLR, PLR, and NC were 892 ± 1354, 4.2 ± 56, 145 ± 119, and 5.6 ± 2.6 × 10^3/mL, respectively. Female patients tended to be older than their male counterparts; they had higher platelet count, SII, PLR, cholesterol, LOS in hospital, NIHSS on admission, and mRS at discharge; and they had higher rates of heart disease, history of cancer, and in-hospital complications. Male patients had higher levels of hemoglobin, creatinine, and triglyceride than their female counterparts, as well as higher rates of prior stroke, smoking, and alcohol consumption. Table 2 shows correlations of the four immuno-inflammatory markers with the measured variables. All of the immuno-inflammatory markers exhibited similar linear correlations with the measured variables, including positive correlations with age, glucose level, creatinine level, LOS in hospital, NIHSS on admission, NIHSS at discharge, and mRS at discharge; negative correlations were observed with hemoglobin level, triglyceride level (except for NC), and Barthel index at discharge. By using ROC curve analysis, we identified cutoff points for the immuno-inflammatory markers to indicate unfavorable outcomes (i.e., mRS >2). The cutoff points for SII, NLR, PLR, and NC were 724, 3.5, 143, and 6 × 10^3/mL, respectively. Patients with SII, NLR, PLR, and NC higher than cutoff values also had higher rates of history of cancer (except for SII and NC), uremia (except for NC), elevated troponin I level, in-hospital complications, and unfavorable outcomes (Table 2).

We compared the levels of the four immuno-inflammatory markers in the five groups categorized according to the TOAST classifications and patients with TIA; this comparison revealed the same results (Table 3). Patients with cardioembolism tended to be older and the highest initial NIHSS scores, whereas patients with small-vessel disease had the lowest initial NIHSS scores. No difference was observed in the levels of the four immuno-inflammatory markers between patients with TIA and those with small-vessel disease, or between those with large-artery atherosclerosis and those with cardioembolism. Levels of the four markers were significantly higher in patients with large-artery atherosclerosis, cardioembolism, and other determined etiology compared with other patients ($p \leq 0.002$). The highest levels of these markers were observed in patients with other determined etiology.

Univariate analyses of continuous variables revealed that older age; higher levels of white blood cell counts, SII, NLR, PLR, NC, and creatinine; longer LOS in hospital; higher NIHSS on admission; and lower levels of hemoglobin, cholesterol, and triglyceride were significantly associated with unfavorable outcomes (Table 4). Univariate analyses of dichotomous variables revealed that female sex, hypertension, diabetes mellitus, heart disease, prior stroke, history of cancer, uremia, elevated troponin I level, and in-hospital complications were significant positive predictors of unfavorable outcomes. However, hyperlipidemia, smoking status, and alcohol consumption were positive predictors of favorable outcomes.

Table 5 presents the regression analysis for the effect of the main significant factors in Table 4 on unfavorable outcomes; the optimal cutoff values for age (75 years) and admission NIHSS score (5) were determined according to the ROC curve. The four immuno-inflammatory markers were included separately in each analysis. Multivariate logistic regression analysis including SII revealed that admission

NIHSS score ≥ 5 (odds ratio [OR]: 13.934; 95% confidence interval [CI]: 11.001–17.648; $p < 0.001$), age > 75 years (OR: 2.650; 95% CI: 2.067–3.399; $p < 0.001$), SII > 724 (OR: 1.808; 95% CI: 1.422–2.297; $p < 0.001$), diabetes mellitus (OR: 1.561; 95% CI: 1.214–2.008; $p < 0.001$), elevated troponin I level (OR: 1.875; 95% CI: 1.272–2.765; $p = 0.002$), female sex (OR: 1.403; 95% CI: 1.088–1.809; $p = 0.009$), heart disease (OR: 1.340; 95% CI: 1.038–1.729; $p = 0.0258$), and prior stroke (OR: 1.316; 95% CI: 1.008–1.717; $p = 0.043$) were significant predictors of unfavorable outcomes. These same significant predictors were identified in multivariate logistic regression analyses when SII was replaced with NLR (OD: 1.761; 95% CI: 1.382–2.243; $p < 0.001$), PLR (OD: 1.600; 95% CI: 1.254–2.041; $p < 0.001$), and NC (OR: 1.769; 95% CI: 1.378–2.272; $p < 0.001$), except for prior stroke.

The C-statistics of the regression models for the detection of unfavorable outcomes are shown in Table 6 for each predictor. We established a basic model comprising the seven significant predictors of admission NIHSS ≥ 5, age > 75 years, diabetes mellitus, elevated troponin I level, female sex, heart disease, and prior stroke. The C-statistic for this basic model was 0.860 (Figure 1). The addition of SII to the basic model resulted in a significant improvement in the C-statistic from 0.860 to 0.864 ($p = 0.038$; Table 6). The addition of NLR or PLR to the basic model also resulted in significant improvements of the C-statistic from 0.860 to 0.863 ($p = 0.042$ and 0.048 for NLR and PLR, respectively). Including NC in the basic model improved the C-statistic from 0.860 to 0.861, but the difference was not significant. The simultaneous addition of all four immuno-inflammatory markers to the basic model resulted in a significant improvement of the C-statistic to 0.864 ($p = 0.032$); the addition of all markers did not result in a stronger predictive performance than addition of SII alone.

Discussion

Sex differences in the risk factor distribution, severity, and outcomes of ischemic stroke are multifactorial and related to genetics, environmental factors, and social influences [21–23]. Previous studies have revealed that older women with higher stroke severity at stroke onset have higher platelet counts, higher prevalence of cardioembolism, and more unfavorable clinical outcomes. Similar results were observed in the present study. Furthermore, we found that women had higher SII and PLR, as well as higher rates of cancer history, elevated troponin I level, and in-hospital complications. No differences in NLR and NC were observed between male and female patients, possibly due to absence of platelet count in these markers. Recent studies have revealed that risk of stroke not only increases after a new cancer diagnosis but also increases with time in almost all cancer survivors [24, 25]. Cancer and related therapies may cause coagulopathies, such as nonbacterial thrombotic endocarditis, alterations in platelet and endothelial function, and radiation-induced atherosclerosis. Elevated troponin I level during acute stroke is a strong independent predictor for both unfavorable outcomes and in-hospital mortality. The mechanisms of elevated troponin I level during acute stroke include ischemic myocardial injury, neurogenic heart syndrome through increased sympathetic activity causing cardiomyopathy, and other systemic conditions such as infection, sepsis, renal failure, and pulmonary embolism [5].

Atherosclerosis is the primary underlying pathological process in coronary and cerebral arterial diseases; it is considered as a chronic inflammation that causes large and medium arterial thromboses [26]. The innate and adaptive immune mechanisms are both involved in the prothrombotic progression of atherosclerotic change. When acute ischemic stroke occurs during arterial occlusion, the inflammatory response following the release of danger signals from damaged brain tissue leads to an activation of immune system. Innate immunity, including neutrophils, monocytes, macrophages, platelet, and dendritic cells, is rapidly activated with the production of various cytokines. This is followed by activation of the adaptive immunity, namely lymphocytes, which exerts an immunosuppressive effect that promotes intercurrent infections (i.e., stroke-induced immunodepression) [7]. These immunological changes may last for weeks and may increase the risk of respiratory or urinary tract infections, particular among patients with severe stroke, thus affecting clinical outcomes [27]. Neutrophils, which are secretory and phagocytic cells, migrate to the intraparenchymal perivascular areas within several hours after cerebral ischemia and participate in the early destruction of the blood–brain barrier [28]. Higher NC indicates a larger area of ischemia and more severe brain damage. Lymphocytes, which mainly comprise humoral immune response B cells and cellular immunity T cells, accumulate in the brain 3–6 days after stroke and are considered as having a regulatory function by inducing neuroprotection. Persistent lymphopenia after stroke, caused by the redistribution of lymphocytes to the lymphatic organs and increased catecholamine and cortisol levels, indicates prolonged brain damage with a higher stress response, and this is associated with unfavorable long-term prognosis [29]. In addition to promoting the progression of atherosclerosis, platelets release mediators to boost inflammation after stroke and result in the release of neutrophils and lymphocytes into the vessel wall. For patients with cancer, neutrophils and platelets have also been observed to promote cancer cell proliferation, invasion, immune evasion, and metastasis through multiple mechanisms. Therefore, elevated levels of inflammatory markers are considered to indicate a substantial tumor burden and an ongoing chronic inflammatory process [30].

In the present study we found that all four immuno-inflammatory markers were positively correlated with age, glucose level, creatinine level, NIHSS on admission, LOS in hospital, and mRS at discharge. Patients whose immuno-inflammatory markers were higher than the cutoff values for unfavorable outcomes also exhibited higher rates of uremia, elevated troponin I level, and in-hospital complications. Higher NLR and PLR have been reported in patients with type 2 diabetes mellitus and hyperglycemia, respectively [31, 32]. Although previous studies have suggested that these immuno-inflammatory markers were increased among patients with various cancers, we did not identify any differences among stroke patients with and without a history of cancer, possibly because these cancers were inactive or cured. Cholesterol level had an inverse correlation with age and immuno-inflammatory markers, and it was lower in patients with unfavorable outcomes. This result was similar to that revealed by Fang et al., who identified that high total cholesterol was significantly and independently predictive of lower NIHSS and less severe stroke [13]. Older adults tending to have diets with low lipid content or experiencing malnutrition due to chewing disorders may explain this finding. Higher immuno-inflammatory markers indicated a higher severity of stroke and a less favorable immune status, which resulted in more in-hospital complications, such as pneumonia and urinary tract infections, and prolonged LOS in hospital. The levels of immuno-

inflammatory markers varied between the etiologies of stroke according to TOAST classification. Patients with TIA and small-vessel disease had the lowest levels of these markers; this was due to the minor level of stroke severity and the small extent of brain tissue damage from small-artery occlusion. Notably, patients with other determined etiology of stroke, who tended to be younger and have minor degrees of stroke severity relative to those with large-artery atherosclerosis and cardioembolism, exhibited the highest levels of immuno-inflammatory markers. These results differ slightly from those of Gökhan et al., who revealed that NLR was lowest among patients with TIA and highest among those with large-artery occlusion [29]. Other determined etiology in the TOAST classification was classified as rare stroke type in the study by Gökhan et al., and no patient was assigned to the rare stroke subtype. In the present study, 43 patients were assigned to the other determined etiology group. Most of these patients had prominent immunological, hematological, or systemic disorders associated with acute stroke. Therefore, immuno-inflammatory markers were considerably higher in these patients.

Several concomitant comorbidities, clinical features, and laboratory parameters were associated with unfavorable short-term outcomes during univariate analyses. Significant predictors of unfavorable outcomes in the multivariate analyses were NIHSS on admission ≥ 5, age > 75 years, diabetes mellitus, elevated troponin I level, female sex, heart disease, prior stroke, and the four immuno-inflammatory markers (SII > 724, NLR > 3.5, PLR > 143, and NC > 6×10^3/mL). Among these, NIHSS on admission ≥ 5 had the highest OR for unfavorable outcomes (13.4–14.2), followed by age > 75 years (2.5–2.8), and the four immuno-inflammatory markers (1.6–1.8). The predictive performance for unfavorable outcomes was similar when using SII, NLR, and PLR, whereas the performance of NC was slightly weaker. Because the four markers were derived from white blood cell counts with or without platelet counts, which are essential laboratory data during acute stroke and common routine examinations, we can choose one as a reference marker for the prediction of unfavorable outcomes. SII > 724 is the most appropriate marker because this provided the optimal predictive performance of 0.864 when combined with the other seven predictors.

This study had several limitations. First, this was a retrospective study. We did not have sufficient sequential data during hospitalization for a dynamic comparison of immuno-inflammatory markers. A dynamic increase in NLR has been reported to predict 3-month mortality or major disability among patients receiving intravenous thrombolytic treatment [33]. Second, we did not investigate the association between infarct volume and the immuno-inflammatory markers. However, the TOAST classifications may partly reflect the infarct size. Third, because we did not perform a follow-up study after discharge, only short-term outcomes at discharge were available. A prospective study with serial immuno-inflammatory markers and long-term outcomes may provide more prognostic relevance for acute ischemic stroke. Notwithstanding these limitations, the results extend the current understanding of the implications of immuno-inflammatory markers among patients with acute ischemic stroke.

Conclusion

Initial stroke severity (NIHSS on admission ≥ 5) and age (age > 75 years) are the two most significant predictors of unfavorable outcome among patients with acute ischemic stroke. Immuno-inflammatory markers including SII, NLR, PLR, and NC provide improved prediction of stroke outcomes compared with conventional risk factors and laboratory parameters. SII > 724 is the most appropriate marker because it provided the optimum predictive performance of up to 0.864 when combined with other predictors.

Abbreviations

CI: confidence interval; LOS: length of stay; mRS: modified Rankin Scale; NC: neutrophil count; NIHSS: National Institutes of Health Stroke Scale; NLR: neutrophil-to-lymphocyte ratio; OD: odds ratio; PLR: platelet-to-lymphocyte ratio; ROC: receiver operating characteristic; SII: systemic immune-inflammation index; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; TIA: transient ischemic attack

Declarations

Acknowledgements

Not applicable.

Authors' contributions

PA, GC, PJ, CL, FY, CY, AT, and YC participated in taking care of patients and acquisition of data. SK designed the study, conducted data analysis, drafted the initial manuscript, prepared the tables, and revised the manuscript. All authors have contributed to manuscript revision, read, and approved the submitted version.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

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

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Correlation of clinical features with sex in 2903 patients with acute ischemic stroke

Characteristics	Total (n = 2093)	Gender		
		Men (n = 1645)	Women (n = 1258)	*P* value
Mean age (years)	71.0±13.6	68.5±13.6	74.2±12.8	<0.001
Hemoglobin (g/dL)	13.6±2.1	14.2±2.0	12.7±1.9	<0.001
Platelet (10^9/L)	212±70	204±66	223±74	<0.001
White blood cells (x10^3/mL)	8.0±2.8	8.1±2.7	8.0±3.0	0.265
Neutrophil counts (x10^3/mL)	5.6±2.6	5.6±2.5	5.5±2.8	0.459
Systemic immune inflammation index	892±1354	829±862	975±1803	0.004
Neutrophil-to-lymphocyte ratio	4.2±5.6	4.1±4.4	4.3±6.8	0.228
Platelet-to-lymphocyte ratio	145±119	138±81	156±148	<0.001
Troponin I (ug/L)	0.05±0.35	0.04±0.22	0.06±0.47	0.144
Glucose (mg/dL)	166±80	164±77	167±83	0.320
Creatinine (mg/dL)	1.36±1.17	1.45±1.18	1.24±1.16	<0.001
Cholesterol (mg/dL)	170±43	167±42	175±44	<0.001
Triglyceride (mg/dL)	123±96	126±106	119±81	0.042
Length of stay (days)	14.7±13.6	13.8±13.4	16.0±13.8	<0.001
NIHSS score on admission	7.6±7.8	6.8±7.2	8.7±8.4	<0.001
NIHSS score at discharge	7.1±10.1	6.2±9.4	8.4±10.7	<0.001
Barthel index score at discharge	65±37	70±35	59±38	<0.001
modified Rankin Scale at discharge	2.7±1.7	2.5±1.7	3.0±1.7	<0.001
Hypertension	2115 (73%)	1179 (71%)	936 (74%)	0.080
Diabetes Mellitus	980 (36%)	563 (34%)	471 (37%)	0.073
Hyperlipidemia	564 (19%)	316 (19%)	248 (20%)	0.734
Heart disease	867 (30%)	438 (27%)	429 (34%)	<0.001
Prior stroke	730 (25%)	439 (27%)	291 (23%)	0.031
Current smoker	603 (21%)	558 (34%)	45 (4%)	<0.001
Alcohol consumption	230 (8%)	224 (14%)	6 (1%)	<0.001
History of cancer	199 (7%)	92 (6%)	107 (9%)	0.002
Uremia	82 (3%)	40 (2%)	42 (3%)	0.144
Elevated troponin I	231/2036 (11%)	118/1173 (10%)	113/863 (13%)	0.033
In-hospital complications	444 (16%)	204 (12%)	240 (19%)	<0.001
modified Rankin Scale > 2 at discharge	1479 (51%)	734 (45%)	745 (59%)	<0.001

Abbreviations: NIHSS National Institutes of Health Stroke Scale

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

Table 2 Correlation of the four immuno-inflammatory markers with measured variables in 2903 patients

Variables	SII			NLR			PLR			Neutrophil counts		
Linear regression test	coefficient	R^2	*P*	coefficient	R^2	*P*	coefficient	R^2	*P*	coefficient	R^2	*P*
Age	0.0004	0.002	0.026	0.224	0.008	<0.001	0.008	0.006	<0.001	-0.381	0.005	<0.001
Hemoglobin	-0.001	0.005	<0.001	-0.026	0.005	<0.001	-0.003	0.027	<0.001	0.089	0.013	<0.001
Glucose	0.007	0.014	<0.001	1.524	0.012	<0.001	0.041	0.004	0.001	5.201	0.029	<0.001
Creatinine	0.0005	0.004	<0.001	0.015	0.005	<0.001	0.001	0.003	0.002	0.036	0.006	<0.001
Cholesterol	-0.001	0.0005	0.260	-0.527	0.005	<0.001	-0.011	0.001	0.121	0.379	0.001	0.246
Triglyceride	-0.003	0.002	0.027	-1.274	0.005	<0.001	-0.052	0.004	<0.001	0.686	0.000	0.334
LOS at hospital	0.001	0.006	<0.001	0.264	0.012	<0.001	0.006	0.003	0.006	0.747	0.021	<0.001
NIHSS on admission	0.001	0.027	0.001	0.29	0.043	<0.001	0.007	0.012	<0.001	0.642	0.046	<0.001
NIHSS at discharge	0.001	0.021	<0.001	0.37	0.042	<0.001	0.008	0.01	<0.001	0.793	0.042	<0.001
BI at discharge	-0.04	0.028	<0.001	-1.434	0.047	<0.001	-0.041	0.018	<0.001	-2.827	0.041	<0.001
mRS at discharge	0.0002	0.025	<0.001	0.063	0.042	<0.001	0.002	0.017	<0.001	0.127	0.038	<0.001

Chi-square test	>724 (n = 1128)	≦724 (n = 1775)	*P*	>3.5 (n = 1102)	≦3.5 (n = 1801)	*P*	>143 (n = 1040)	≦143 (n = 1863)	*P*	>6 x10^3/mL (n = 957)	≦6 x10^3/mL (n = 1946)	*P*
Female sex	512 (45)	746 (42)	0.075	469 (43)	789 (44)	0.509	514 (49)	744 (40)	<0.001	399 (42)	859 (44)	0.217
History of cancer	82 (7)	117 (7)	0.496	95 (9)	104 (6)	0.003	85 (7)	114 (6)	0.036	72 (8)	127 (7)	0.318
Uremia	45 (4)	37 (2)	0.003	51 (5)	31 (2)	<0.001	42 (4)	40 (2)	0.003	33 (3)	49 (3)	0.155
Elevated Troponin I	116/762 (15)	115/1274 (9)	<0.001	117/733 (16)	114/1303 (9)	<0.001	99/706 (14)	132/1330 (10)	0.006	112/655 (17)	119/1381 (9)	<0.001
Complications	232 (21)	212 (12)	<0.001	236 (21)	208 (12)	<0.001	188 (18)	256 (14)	0.002	208 (22)	236 (12)	<0.001
mRS > 2 at discharge	685 (61)	794 (45)	<0.001	691 (63)	788 (44)	<0.001	610 (59)	869 (47)	<0.001	582 (61)	897 (46)	<0.001

Abbreviations: BI Barthel index, *LOS* Length of stay, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *SII* systemic immune-inflammation index

Data are expressed as n (%)

Table 3 Mean values of the four immuno-inflammatory markers in groups divided according to the TOAST classification

TOAST classification	Mean age (years)	NIHSS on admission	SII	NLR	PLR	NC ($\times 10^3$/mL)
Transient ischemic attack (n = 475)	71.0±13.5	-	772±1048	3.8±5.9	142±103	4.9±2.3
Small vessel occlusion (n = 1365)	68.8±13.5	4.5±4.1	771±810	3.5±3.4	139±91	5.2±2.3
Large artery atherosclerosis (n = 935)	71.8±13.4	9.7±8.7	979±1451	4.6±5.9	150±136	6.0±2.8
Cardioembolism (n = 460)	76.2±11.9	12.0±10.0	994±1682	5.0±7.9	150±122	5.6±2.8
Other determined etiology (n = 43)	67.2±17.0	8.4±8.3	1755±4839	6.9±14.0	209±317	6.6±3.8
Undetermined etiology (n = 100)	69.9±14.1	9.7±9.3	903±1088	4.5±6.1	145±119	5.6±2.9
P value	<0.001	<0.001	<0.001	<0.001	0.002	<0.001

Abbreviations: NC neutrophil counts, *NIHSS* National Institutes of Health Stroke Scale, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *SII* systemic immune-inflammation index, *TOAST* Trial of ORG 10172 in Acute Stroke Treatment

Table 4 Univariate analysis of the predictors of unfavorable outcomes (modified Rankin Scale score >2)

Variables	Odds ratio	95 % CI	*P* value
Age (years)	1.051	1.044-1.057	<0.001
Hemoglobin (g/dL)	0.837	0.807-0.869	<0.001
Platelet (10^9/L)	0.999	0.998-1.000	0.067
White blood cells (× 10^3mL)	1.000	1.000-1.000	<0.001
Neutrophil counts (× 10^3mL)	1.134	1.100-1.170	<0.001
Systemic immune inflammation index	1.000	1.000-1.001	<0.001
Neutrophil-to-lymphocyte ratio	1.140	1.109-1.172	<0.001
Platelet-to-lymphocyte ratio	1.003	1.002-1.003	<0.001
Glucose (mg/dL)	1.001	1.000-1.002	0.155
Creatinine (mg/dL)	1.168	1.088-1.254	<0.001
Cholesterol (mg/dL)	0.997	0.995-0.999	<0.001
Triglyceride (mg/dL)	0.998	0.997-0.998	<0.001
Length of stay (days)	1.164	0.149-1.178	<0.001
NIHSS score on admission	1.451	1.405-1.498	<0.001
Female sex	1.802	1.553-2.091	<0.001
Hypertension	1.267	1.076-1.492	0.005
Diabetes Mellitus	1.378	1.183-1.606	<0.001
Hyperlipidemia	0.640	0.532-0.771	<0.001
Heart disease	1.789	1.522-2.104	<0.001
Prior stroke	1.490	1.258-1.766	<0.001
Current smoker	0.471	0.391-0.567	<0.001
Alcohol consumption	0.560	0.424-0.739	<0.001
History of cancer	1.985	1.465-2.689	<0.001
Uremia	2.874	1.741-4.745	<0.001
Elevated Troponin I	3.896	2.897-5.241	<0.001
In-hospital complications	21.183	14.141-31.733	<0.001

Abbreviations: NIHSS National Institutes of Health Stroke Scale

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

Table 5 Logistic model of the influence of factors along with the immuno-inflammatory markers on unfavorable outcomes

Variables	Unfavorable outcome (mRS > 2) with SII		Unfavorable outcome (mRS > 2) with NLR		Unfavorable outcome (mRS > 2) with PLR		Unfavorable outcome (mRS > 2) with NC	
	OD (95% CI)	*P* value	OD (95% CI)	*P* value	OD (95% CI)	*P* value	OD (95% CI)	*P* value
Age > 75 years	2.650 (2.067-3.399)	<0.001	2.539 (1.979-3.257)	<0.001	2.578 (2.011-3.304)	<0.001	2.783 (2.167-3.574)	<0.001
Female sex	1.403 (1.088-1.809)	0.009	1.459 (131.1-1.882)	0.004	1.363 (1.058-1.757)	0.017	1.427 (1.107-1.839)	0.006
Hypertension	0.989 (0.757-1.293)	0.938	0.986 (0.754-1.289)	0.918	1.029 (0.787-1.345)	0.835	0.964 (0.737-1.261)	0.789
Diabetes mellitus	1.561 (1.214-2.008)	<0.001	1.586 (1.233-2.040)	<0.001	1.600 (1.245-2.056)	<0.001	1.566 (1.217-2.014)	<0.001
Hyperlipidemia	0.846 (0.626-1.142)	0.275	0.871 (0.645-1.175)	0.366	0.847 (0.628-1.142)	0.276	0.835 (0.619-1.127)	0.239
Heart disease	1.340 (1.038-1.729)	0.025	1.301 (1.009-1.678)	0.043	1.328 (1.030-1.712)	0.029	1.316 (1.020-1.698)	0.035
Prior stroke	1.316 (1.008-1.717)	0.043	1.299 (0.996-1.694)	0.054	1.284 (0.985-1.674)	0.065	1.272 (0.975-1.659)	0.076
Current smoker	0.807 (0.577-1.128)	0.209	0.796 (0.570-1.112)	0.182	0.780 (0.559-1.090)	0.146	0.781 (0.559-1.091)	0.147
Alcohol consumption	0.961 (0.598-1.547)	0.871	0.940 (0.583-1.514)	0.799	0.977 (0.608-1.571)	0.925	0.917 (0.569-1.479)	0.723
History of cancer	1.423 (0.894-2.266)	0.137	1.359 (0.853-2.165)	0.197	1.405 (0.886-2.229)	0.149	1.385 (0.871-2.201)	0.168
Uremia	1.757 (0.824-3.742)	0.144	1.723 (0.807-3.682)	0.160	1.782 (0.839-3.786)	0.133	1.922 (0.895-4.128)	0.094
Elevated troponin I	1.875 (1.272-2.765)	0.002	1.872 (1.267-2.767)	0.002	1.943 (1.320-2.862)	<0.001	1.838 (1.247-2.708)	0.002
NIHSS (admission) ≧ 5	13.934 (11.001-17.648)	<0.001	13.863 (10.948-17.553)	<0.001	14.183 (11.199-17.963)	<0.001	13.429 (10.613-16.992)	<0.001
SII > 724	1.808 (1.422-2.297)	<0.001	-		-		-	
NLR > 3.5	-		1.761 (1.382-2.243)	<0.001	-		-	
PLR > 143	-		-		1.600 (1.254-2.041)	<0.001	-	
NC > 6 (× 10^3/mL)	-		-		-		1.769 (1.378-2.272)	<0.001

Abbreviations: CI confidence interval, *mRS* modified Rankin Scale, *NC* neutrophil counts, *NIHSS* National Institutes of Health Stroke Scale, *NLR* neutrophil-to-lymphocyte ratio, *OD* odds ratio, *PLR* platelet-to-lymphocyte ratio, *SII* systemic immune-inflammation index

Table 6 *C*-statistics of the basic model with various immuno-inflammatory markers for the prediction of unfavorable outcome

Variables	Unfavorable outcome (mRS > 2)	
	C-statistics (95% CI)	*P**
Basic model with 7 predictors [a]	0.860 (0.843-0.876)	-
Plus systemic immune-inflammatory index > 724	0.864 (0.847-0.880)	0.038
Plus neutrophil-to-lymphocyte ratio > 3.5	0.863 (0.847-0.880)	0.042
Plus platelet-to-lymphocyte ratio > 143	0.863 (0.846-0.880)	0.048
Plus neutrophil counts > 6 (× 10^3/mL)	0.861 (0.845-0.879)	0.124
Plus all above four markers	0.864 (0.848-0.881)	0.032

Abbreviations: CI confidence interval

[a] Including National Institute of Health Stroke Scale score ≧ 5, age > 75 years, diabetes mellitus, elevated troponin I level, female sex, heart disease, and prior stroke

*Compared with the basic model

Figures

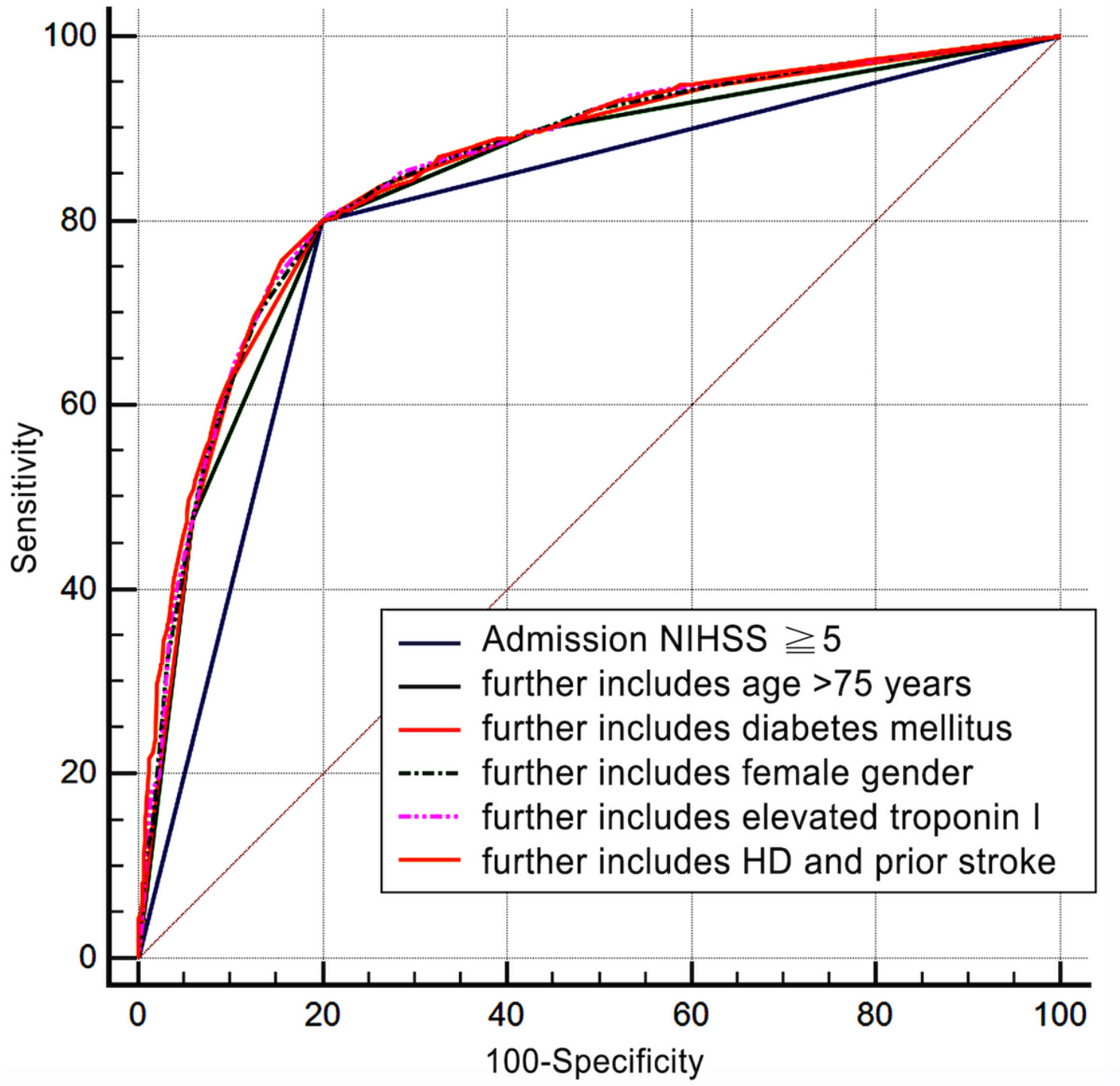

Figure 1

C-statistic of the basic model for the seven significant predictors of unfavorable outcome; predictive performance of 0.860. HD: heart disease

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Datasets2903Pt.xlsx