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ORIGINAL RESEARCH

Association of a High Neutrophil-to-Lymphocyte Ratio with Hyperdense Artery Sign and Unfavorable Short-Term Outcomes in Patients with Acute Ischemic Stroke

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Purpose: Immune–inflammatory processes are involved in all the stages of stroke. This study investigated the association of the neutrophil-to-lymphocyte ratio (NLR) with the hyperdense artery sign (HAS) observed on brain computed tomography (CT) and with clinical features in patients with acute ischemic stroke.

Methods: We retrospectively enrolled 2903 inpatients with acute ischemic stroke from May 2010 to May 2019. Data collected included imaging studies, risk factors, laboratory parameters, and clinical features during hospitalization.

Results: The HAS was identified in 6% of the 2903 patients and 66% of the 236 patients with acute middle cerebral artery occlusion. Patients with the HAS had a higher NLR. HAS prevalence was higher in men and patients with cardioembolism. The NLR exhibited positive linear correlations with age, glucose and creatinine levels, length of hospital stay, initial National Institutes of Health Stroke Scale (NIHSS) scores, and mRS scores at discharge. The NLR was significantly higher in patients with large-artery atherosclerosis and cardioembolism and was the highest in patients with other determined etiology. Multivariate analysis revealed that an initial NIHSS score of ≥10 and an NLR of >3.5 were significant positive factors, whereas diabetes mellitus and age > 72 years were significant negative factors for the HAS, with a predictive performance of 0.893. An initial NIHSS score of ≥5, positive HAS, age > 75 years, diabetes mellitus, an NLR of >3.5, female sex, a white blood cell count of $>8 \times 10^3$/mL, and elevated troponin I were significant predictors of unfavorable outcomes, with a predictive performance of 0.886.

Conclusion: An NLR of >3.5 enabled an efficient prediction of CT HAS. In addition to conventional risk factors and laboratory parameters, both an NLR of >3.5 and CT HAS enabled improved prediction of unfavorable stroke outcomes.

Keywords: acute ischemic stroke, hyperdense artery sign, neutrophil-to-lymphocyte ratio, NIHSS, unfavorable outcome

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Introduction

Stroke was the fourth leading cause of death in Taiwan from 2000 to 2020 and the leading cause of prolonged disability in older adults. Conventional risk factors for vascular diseases, including old age, hypertension, diabetes mellitus, and heart disease, are prominent comorbidities of stroke. Most studies have emphasized the correlation of these comorbidities with stroke and clinical outcomes. The clinical

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feature of initial stroke severity has been reported to be a strong predictor of functional outcomes.[1,2] In addition, laboratory parameters measured during acute stroke, such as the hemoglobin level,[3] blood urea nitrogen-to-creatinine ratio,[4] and troponin I level,[5] provide valuable information in the investigation of clinical outcomes after stroke. Atherosclerosis is a chronic inflammatory process that occurs in the arterial wall.[6] Immunity and inflammation are considered the crucial elements of stroke pathobiology. Immune–inflammatory processes are involved in all the stages of acute stroke, including initial artery occlusion, brain parenchymal damage, subsequent tissue repair, and infectious complications.[7] Innate and adaptive are the two main types of immune systems. Innate immunity refers to immune responses present at birth and provides the 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 -specific responses to invasion. The neutrophil-to-lymphocyte ratio (NLR) can reflect the balance between innate and adaptive immunity.[9] A higher NLR has been reported to be associated with poor outcomes in patients with acute stroke and patients with various types of cancer.[10–13]

The hyperdense artery sign (HAS), caused by the fresh thromboembolic material within the artery, is an early direct sign observed on noncontrast computed tomography (CT) that indicates acute large intracranial artery occlusion. The HAS has been observed in 69% of patients with acute middle cerebral artery (MCA) occlusion within 24 hours and is associated with severe initial neurological deficits, large infarction territory, and poor functional outcomes despite thrombolytic therapy.[14,15] In the present study, we investigated the association of the NLR with the HAS and clinical outcomes in patients with acute ischemic stroke.

Patients and Methods

Study Population and Data Collection

The stroke registry database was retrospectively reviewed to identify patients who received stroke treatment in a neurological ward from May 2010 to May 2019. The inclusion criteria were 1) a diagnosis of acute ischemic stroke confirmed by clinical presentation and 2) evidence of an ischemic lesion or the absence of a corresponding intracranial lesion other than infarction according to brain CT or magnetic resonance imaging. Information on sex; age; history of hypertension, diabetes mellitus, hyperlipidemia, heart disease, and prior stroke; smoking status; alcohol consumption; cancer diagnosis; presence of uremia; and length of stay (LOS) in hospital was recorded for analysis. Laboratory data obtained on arrival at the emergency department included the complete blood count with white blood cell differentials as well as platelet, glucose, creatinine, and troponin I levels. The NLR was calculated as the ratio of the neutrophil count to the lymphocyte count. An abnormal elevation in troponin I levels was defined as a blood troponin I level of >0.01 μg/L. Fasting cholesterol and triglyceride levels were recorded in the morning after admission to the ward. For patients admitted to the ward for transient ischemic attack (TIA) during the same period, the NLR was also collected for comparison.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval for this study was provided by the Institutional Review Board of Taipei Tzu Chi Hospital, New Taipei City (approval no. 09-X-025). Informed written consent was waived because the study was a retrospective data analysis. All data collected and analyzed in this retrospective study were derived from clinical records without any intervention or influence on clinical treatment. To fully protect patient privacy and rights, only clinical data of observations were used for publication, and personal information will not be disclosed to any other third party without the patient's consent.

Stroke Severity and Clinical Features

Stroke severity was assessed when patients presented to the emergency department after symptom onset according to the National Institutes of Health Stroke Scale (NIHSS). We classified the etiology of ischemic stroke according to the Trial of ORG 10,172 in Acute Stroke Treatment (TOAST) categories, namely large-artery atherosclerosis, small-vessel occlusion, cardioembolism, other determined etiology, and undetermined etiology.[16] Urinary tract infection, pneumonia, gastrointestinal bleeding, and seizure were registered as in-hospital stroke complications. Functional outcomes were evaluated using the NIHSS, Barthel index, and modified Rankin Scale (mRS) at discharge. An mRS score of >2 was considered to indicate an unfavorable outcome.

Identification of Acute Artery Occlusion and HAS

All patients underwent noncontrast 4-mm slice brain CT when they presented to the emergency department. All CT scans were reviewed by a stroke neurologist. The initial CT scan results were compared with results of follow-up magnetic resonance angiography (MRA) or CT angiography. Acute artery occlusion was defined as the presence of 1) a large area of infarction without a visible appropriate artery on MRA or CTA in association with prominent corresponding clinical neurologic deficits and 2) a large area of infarction with severe cerebral edema on follow-up brain CT in patients who did not undergo angiography. Given that the HAS most commonly occurred in acute MCA occlusion, patients who had acute MCA occlusion with and without HASs were selected for further comparisons. A hyperdense MCA sign was defined as an MCA denser than its contralateral counterpart. We measured and recorded the highest CT Hounsfield units (HU) of arteries on both the affected side (with HAS) and the contralateral side (without HAS). In addition, we calculated the HU ratio between the affected and contralateral sides. Nonvisualization of an appropriate artery with a small area of infarction corresponding to minor clinical symptoms was considered as arterial occlusion from chronic stenosis and was excluded during the selection of patients with acute MCA occlusion.

Statistical Analysis

Continuous variables are presented as the 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 the two-sample *t*-test or analysis of variance as appropriate. Significant predictors in the univariate analysis that were continuous variables were converted into dichotomous variables, with the optimal cutoff level determined according to the Youden index by using the receiver operating characteristic (ROC) curve for HAS and unfavorable outcomes. The variables were then added to a multiple logistic regression model to identify significant factors associated with HAS and unfavorable outcomes. In addition, we compared the predictive performance of the variables by using the C-statistic for HAS and unfavorable outcomes. A p value of <0.05 was considered to indicate a significant result. All statistical analyses were performed using SPSS (version 24; SPSS Inc, Chicago, IL, USA).

Results

During the study period, 2903 patients with acute ischemic stroke and 457 patients with TIA were enrolled. Of all patients with acute ischemic stroke, 2036 (70%) had valid data of troponin I levels because troponin I was not routinely measured in the emergency department in patients with acute stroke during that period. The average age of patients with acute ischemic infarct and those with TIA was 71.0 ± 13.5 and 70.5 ± 13.2 years, respectively. Of all 2903 patients, the HAS was identified in 172 (6%). The HU ranged from 42 to 74 (mean value = 59 ± 5) for the affected MCA with the HAS and from 30 to 46 (mean value = 38 ± 4) for the normal contralateral MCA; the mean MCA HU ratio was 1.6 ± 0.2. Table 1 compares the clinical features between 2903 patients with and without the HAS. Patients with the HAS were older than those without the HAS. Patients with the HAS had a higher NLR, initial NIHSS score, discharge NIHSS score, and mRS score as well as longer LOS in hospital; however, they had a lower platelet count, triglyceride level, and Barthel index score. They also had higher rates of large-artery atherosclerosis, cardioembolism, heart disease, atrial fibrillation, elevated troponin I, in-hospital complications, receipt of thrombolytic therapy, but lower rates of diabetes mellitus, hyperlipidemia, and prior stroke.

Acute artery occlusion was found in 252 patients; among those, 236 patients had acute MCA or terminal ICA occlusion. The HAS occurred in the first segment of the MCA (M1) in 142 patients, in the distal branch of the MCA (M2) in 12 patients, in the terminal internal carotid artery in 2 patients, in the basilar artery in 14 patients, in the vertebral artery in 1 patient, and in the posterior cerebral artery in 1 patient (Figure 1). Twelve patients had the HAS on the initial brain CT; however, no corresponding artery occlusion was found on follow-up MRA. Of these 12 patients, 2 patients who were classified to have large-artery atherosclerosis received thrombolytic therapy; of the remaining 10 patients who were classified to have cardioembolism, only 5 patients received thrombolytic therapy. Table 2 shows a comparison of clinical features between 236 patients who had acute MCA occlusion with and without the HAS. Of 236 patients, 156 (66%) with acute MCA occlusion exhibited the HAS. The occurrence of the HAS was higher in men than in women. In addition, HAS occurrence was higher in patients with cardioembolism. Patients with the HAS had lower white blood cell and

Table 1 Comparison of Clinical Features in 2903 Patients with and without Hyperdense Artery Sign

Characteristics	Total (n = 2903)	Hyperdense Artery Sign		
		Y (n = 172)	N (n = 2731)	*P* value
Mean age (years)	71.0±13.6	73.9±12.8	70.8±13.6	0.004
Female sex	1258 (43%)	80 (47%)	1178 (43%)	0.384
TOAST classification				<0.001
Small-vessel occlusion	1361 (47%)	0 (0%)	1361 (50%)	
Large-artery atherosclerosis	936 (32%)	98 (57%)	846 (31%)	
Cardioembolism	463 (16%)	73 (42%	390 (14%)	
Other determined etiology	43 (2%)	1 (1%)	42 (2%)	
Undetermined etiology	100 (3%)	0 (0%)	92 (3%)	
Hemoglobin (g/dL)	13.6±2.1	13.8±2.1	13.6±2.1	0.128
White blood cells ($\times 10^3$/mL)	8.0±2.8	8.3±2.8	8.0±2.8	0.166
Neutrophil-to-lymphocyte ratio	4.5±5.6	5.5±6.2	4.1±5.5	0.001
Platelet ($\times 10^9$/L)	212±70	198±84	213±69	0.006
Glucose (mg/dL)	166±80	156±60	166±81	0.117
Creatinine (mg/dL)	1.36±1.17	1.3±0.8	1.4±1.2	0.394
Cholesterol (mg/dL)	170±43	171±45	170±43	0.833
Triglyceride (mg/dL)	123±96	102±103	124±96	0.004
Hypertension	2112 (73%)	126 (73%)	1986 (73%)	0.929
Diabetes Mellitus	980 (36%)	44 (26%)	990 (36%)	0.005
Hyperlipidemia	564 (19%)	21 (12%)	543 (20%)	0.013
Heart disease	867 (30%)	93 (54%)	774 (28%)	<0.001
Prior stroke	730 (25%)	30 (17%)	700 (26%)	0.018
Current smoker	603 (21%)	32 (19%)	571 (21%)	0.499
Alcohol consumption	230 (8%)	14 (8%)	216 (8%)	>0.999
History of cancer	199 (7%)	18 (10%)	181 (7%)	0.061
Uremia	82 (3%)	4 (2%)	78 (3%)	>0.999
Atrial fibrillation	537 (18%)	79 (46%)	458 (17%)	<0.001
Elevated troponin I	231/2036 (11%)	24/90 (27%)	207/1946 (11%)	<0.001
Initial NIHSS score	8±8	20±8	7±7	<0.001
Thrombolytic therapy	138 (5%)	35 (20%)	103 (4%)	<0.001
In-hospital complications	444 (16%)	81 (47%)	363 (13%)	<0.001
Length of stay (days)	15±14	24±17	14±13	<0.001
Discharge NIHSS score	7±10	22±13	6±9	<0.001
Barthel index score at discharge	65±37	17±28	68±35	<0.001
Modified Rankin Scale at discharge	2.7±1.7	4.7±1.2	2.6±1.7	<0.001
Modified Rankin Scale >2 at discharge	1479 (51%)	158 (92%)	1321 (48%)	<0.001

Notes: Data are expressed as the mean ± standard deviation or n (%); Two-sample *t* or Chi-square test.
Abbreviation: NIHSS, National Institute of Health Stroke Scale.

platelet counts as well as lower diabetes mellitus and prior stroke rates.

We compared the NLR among the five groups categorized according to the TOAST classification and patients with TIA (Table 3). Patients with cardioembolism were older and had the highest initial NIHSS scores, whereas patients with small-vessel disease had the lowest initial NIHSS scores. No difference was observed in the NLR between patients with TIA and those with a small-vessel disease or between those with large-artery atherosclerosis and those with cardioembolism. The NLR was significantly higher in patients with large-artery atherosclerosis, cardioembolism, and other determined etiology than in other patients ($p < 0.001$). The highest NLR was observed in patients with other determined etiology. Table 4 shows the correlation of the NLR with the measured variables and clinical features. The NLR exhibited linear correlations with the measured

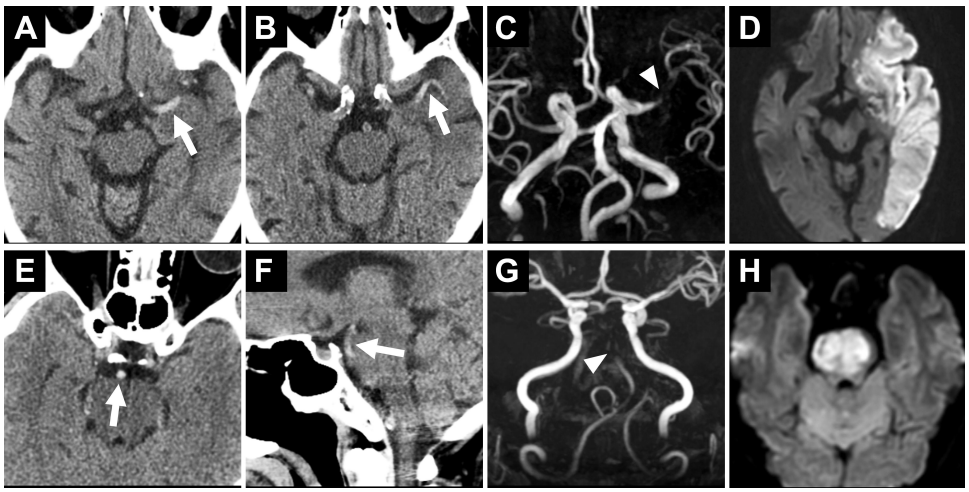

Figure 1 (**A**–**D**) An 82-year-old woman had hyperdense artery sign (HAS; arrows) with the highest Hounsfield units (HU) of 62 showing acute occlusion of the left middle cerebral artery (arrowhead) on MR angiography and a large area of infarction. (**E**–**H**) A 62-year-old man had HAS (arrows) with the highest HU of 66 showing acute occlusion of the basilar artery (arrowhead) on MR angiography and a large area of brainstem infarction.

variables; moreover, it demonstrated positive correlations with the glucose level, creatinine level, age, LOS in hospital, initial and discharge NIHSS scores, and mRS at discharge and negative correlations with the hemoglobin level, cholesterol level, triglyceride level, and Barthel index at discharge. Furthermore, the NLR was higher in patients with elevated troponin I, cancer history, atrial fibrillation, acute MCA occlusion, positive HAS, in-hospital complications, and discharge mRS score of >2 but lower in patients with hyperlipidemia.

Table 5 presents the correlations of clinical features with the HAS and unfavorable outcomes. The univariate analyses of continuous variables revealed that old age, high NLR, initial NIHSS score, long LOS in hospital, low platelet count, and low triglyceride level were significantly associated with the HAS. The univariate analyses of dichotomous variables revealed that elevated troponin I, heart disease, atrial fibrillation, thrombolytic therapy, and in-hospital complications were significantly positively associated with the HAS, whereas diabetes mellitus, hyperlipidemia, and prior stroke were negatively correlated with the HAS. The findings of the univariate analysis of continuous variables revealed that old age; high white blood cell count, NLR, and creatinine level; initial NIHSS score; long LOS in hospital; and low hemoglobin, cholesterol, and triglyceride levels were significantly associated with unfavorable outcomes. The findings of the univariate analysis of dichotomous variables revealed that female sex, elevated troponin I, hypertension, diabetes mellitus, heart disease, prior stroke, cancer history, uremia, atrial fibrillation, thrombolytic therapy, in-hospital complications, and a positive HAS was significantly positively associated with unfavorable outcomes. However, hyperlipidemia, smoking status, and alcohol consumption were negatively correlated with favorable outcomes.

Through the ROC curve analysis, we identified cutoff points for the NLR and other continuous variables to indicate the HAS and unfavorable outcomes (ie, an mRS score of >2). The cutoff point of the NLR for the HAS was 3.5, which was identified to be the same cutoff point for unfavorable outcomes. The cutoff points of age and the initial NIHSS score were >72 years and ≥10 for HAS, respectively, and >75 years and ≥5 for unfavorable outcomes, respectively. Table 6 presents the results of the multiple regression analysis of the effect of the main significant factors listed in Table 5 on the HAS. An initial NIHSS score of ≥10 (odds ratio [OR]: 144.226; 95% confidence interval [CI]: 19.623–99.673; $p < 0.001$) and an NLR of >3.5 (OR: 2.146; 95% CI: 1.303–3.534; $p = 0.003$) were significant positive predictors of the HAS, whereas age > 72 years and diabetes mellitus were significant negative predictors of the HAS. The C-statistics of the regression model for the detection of the HAS comprising the aforementioned four significant factors was 0.893 (95% CI: 0.874–0.912; $p < 0.001$; Figure 2A). Table 7 presents the results of the regression analysis for the effect of the main significant factors listed in Table 5 on unfavorable outcomes. Initial NIHSS score ≥ 5 (OR: 12.354; 95% CI: 9.715–15.709; $p < 0.001$), positive HAS (OR: 3.420; 95% CI: 1.727–6.772; $p < 0.001$), age > 75 years (OR: 2.590; 95% CI: 1.989–3.374; $p < 0.001$), diabetes mellitus (OR: 1.653; 95% CI: 1.273–2.146;

Table 2 Comparison of Clinical Features Between 236 Patients Who Had Acute Middle Cerebral Artery Occlusion with Positive and Negative Hyperdense Artery Sign

Characteristics	Positive Hyperdense Sign (n = 156)	Negative Hyperdense Sign (n = 80)	*P* value
Mean age (years)	74.6±12.8	75.5±13.5	0.626
Female sex	75 (48%)	56 (70%)	0.002
TOAST classification			0.002
Large-artery atherosclerosis	84 (54%)	52 (65%)	
Cardioembolism	72 (46%)	23 (29%)	
Other determined etiology	0 (0%)	1 (1%)	
Undetermined etiology	0 (0%)	4 (5%)	
Hemoglobin (g/dL)	13.7±2.1	13.2±1.9	0.083
White blood cells ($\times 10^3$/mL)	8.1±2.6	9.3±3.6	0.005
Neutrophil-to-lymphocyte ratio	5.2±5.2	7.1±12.6	0.097
Platelet ($\times 10^9$/L)	192±64	215±68	0.012
Glucose (mg/dL)	156±62	170±75	0.157
Creatinine (mg/dL)	1.3±0.8	1.4±1.1	0.347
Cholesterol (mg/dL)	172±46	165±36	0.367
Triglyceride (mg/dL)	103±107	103±64	0.971
Hypertension	113 (72%)	62 (78%)	0.436
Diabetes Mellitus	42 (27%)	35 (44%)	0.012
Hyperlipidemia	20 (13%)	10 (13%)	>0.999
Heart disease	89 (57%)	35 (44%)	0.056
Prior stroke	26 (17%)	23 (29%)	0.028
Current smoker	30 (19%)	10 (13%)	0.206
Alcohol consumption	11 (7%)	3 (4%)	0.393
History of cancer	16 (10%)	6 (8%)	0.638
Uremia	3 (2%)	2 (3%)	>0.999
Atrial fibrillation	78 (50%)	34 (43%)	0.335
NIHSS score on admission	20±7	20±8	0.983
In-hospital complications	72 (46%)	31 (39%)	0.332
Length of stay (days)	24±17	23±15	0.545
Discharge NIHSS score	22±13	21±13	0.956
Barthel index score at discharge	18±28	18±28	0.836
Modified Rankin Scale at discharge	4.7±1.2	4.7±1.1	0.981
Modified Rankin Scale >2 at discharge	143 (92%)	76 (95%)	0.433

Notes: Data are expressed as the mean ± standard deviation or n (%); Two-sample *t* or Fisher's exact test.
Abbreviation: NIHSS, National Institute of Health Stroke Scale.

Table 3 Mean Values of the Neutrophil-to-Lymphocyte Ratio in Different Groups of TOAST Classification and Transient Ischemic Attack

TOAST Classification	Mean Age (Years)	Initial NIHSS Score	NLR
Transient ischemic attack (n = 475)	71.0±13.5	–	3.8±5.9
Small-vessel occlusion (n = 1361)	68.8±13.5	4.4±4.0	3.5±3.4
Large-artery atherosclerosis (n = 936)	71.8±13.4	9.8±8.7	4.6±5.9
Cardioembolism (n = 463)	76.2±11.9	12.1±10.0	5.1±7.9
Other determined etiology (n = 43)	67.2±17.0	8.4±8.3	6.9±14.0
Undetermined etiology (n = 100)	69.9±14.1	8.8±8.8	4.5±6.2
P value	<0.001	<0.001	<0.001

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; TOAST, Trial of ORG 10,172 in Acute Stroke Treatment.

Table 4 Correlation Analyses of Neutrophil-to-Lymphocyte Ratio with Measured Variables and Clinical Features in 2903 Patients with Acute Ischemic Stroke

Neutrophil-to-Lymphocyte Ratio				Neutrophil-to-Lymphocyte Ratio			
Variables	**Coefficient**	R^2	P^a	**Variables**	**Y**	**N**	P^b
Age	0.224	0.008	<0.001	Female gender	4.3±6.8	4.1±4.4	0.228
Hemoglobin (g/dL)	−0.026	0.005	<0.001	Elevated troponin I	6.6±11.5	3.8±4.0	<0.001
Platelet ($\times 10^9$/L)	0.091	0.000	0.697	Hypertension	4.2±5.4	4.2±5.9	0.974
Glucose (mg/dL)	1.524	0.012	<0.001	Diabetes mellitus	4.4±6.0	4.1±5.3	0.125
Creatinine (mg/dL)	0.015	0.005	<0.001	Hyperlipidemia	3.3±2.5	4.4±6.1	<0.001
Cholesterol (mg/dL)	−0.527	0.005	<0.001	Heart disease	4.3±4.7	4.1±5.9	0.354
Triglyceride (mg/dL)	−1.274	0.005	<0.001	Prior stroke	4.0±4.8	4.3±5.8	0.312
LOS in hospital (days)	0.264	0.012	<0.001	Current smoker	3.9±4.8	4.3±5.7	0.109
Initial NIHSS score	0.29	0.043	<0.001	Alcohol consumption	3.8±3.4	4.2±5.7	0.245
Discharge NIHSS score	0.37	0.042	<0.001	Cancer history	5.2±9.7	4.2±5.1	0.008
BI at discharge	−1.434	0.047	<0.001	Uremia	5.3±3.4	4.2±5.6	0.059
mRS at discharge	0.063	0.042	<0.001	Atrial fibrillation	5.0±6.7	4.0±5.3	<0.001
				Hyperdense artery sign	5.5±6.2	4.1±5.5	0.001
				Acute MCA occlusion	6.1±8.9	4.0±5.1	<0.001
				In-hospital complications	6.5±10.9	3.8±3.7	<0.001
				mRS > 2	5.1±7.3	3.3±2.5	<0.001

Notes: [a]Linear regression test; [b]Two-sample *t*-test. Data are expressed as mean ± standard deviation.
Abbreviations: BI, Barthel index; LOS, length of stay; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.

$p < 0.001$), NLR > 3.5 (OR: 1.512; 95% CI: 1.169–1.954; $p = 0.002$), female sex (OR: 1.497; 95% CI: 1.133–1.978; $p = 0.005$), white blood cell count > 8×10^3/mL (OR: 1.446; 95% CI: 1.120–1.866; $p = 0.005$), and elevated troponin I level (OR: 1.694; 95% CI: 1.139–2.521; $p = 0.009$) were the significant predictors of unfavorable outcomes. The C-statistics of the regression model for the detection of unfavorable outcomes comprising the aforementioned eight significant factors was 0.886 (95% CI: 0.874–0.898; $p < 0.001$; Figure 2B).

Discussion

Atherosclerosis, the primary underlying pathological process in coronary and cerebral arterial diseases, is characterized by chronic inflammation that causes large and medium arterial thromboses.[17] When an acute ischemic stroke occurs during artery occlusion, the inflammatory response following the release of danger signals from the damaged brain tissue leads to the activation of the immune system. Innate immunity, including neutrophils, monocytes, macrophages, platelets, and dendritic cells, is rapidly activated with the production of various cytokines. This is followed by the activation of the adaptive immunity involving lymphocytes, which exert an immunosuppressive effect that promotes intercurrent infections (ie, stroke-induced immunodepression).[7] These immunological changes may last for weeks and may increase the risk of respiratory or urinary tract infections, particularly in patients with severe stroke, thus affecting clinical outcomes.[18] Neutrophils, which are secretory and phagocytic cells, migrate to intraparenchymal perivascular areas within several hours after cerebral ischemia and participate in the early destruction of the blood–brain barrier.[19] Lymphocytes accumulate in the brain 3–6 days after stroke and are considered to exhibit a regulatory function by inducing neuroprotection. Persistent lymphopenia after stroke, caused by the redistribution of lymphocytes to lymphatic organs and increased catecholamine and cortisol levels, indicates prolonged brain damage with a high-stress response, which is associated with unfavorable long-term prognosis.[20]

The HAS is subjectively recognized on noncontrast CT when the artery appears denser than its contralateral counterpart or the surrounding brain density and can be seen within 90 minutes of acute artery occlusion.[21] The high attenuation of a thrombus is due to the extrusion of plasma in the thrombus with a subsequent increase in the local hematocrit level, which causes a higher range of 47–61 HU than that of 40–43 HU observed for nonoccluded blood in noncontrast CT.[22,23] Red thrombi, usually from acute or cardioembolic clots, are richer in erythrocytes and cause a higher HU, whereas white thrombi, usually from nonacute atherosclerotic clots, are richer in platelets and fibrin and cause a lower HU.[24] The presence of the HAS has been reported to predict a poor thrombolytic effect but

Table 5 Univariate Analysis of Factors Affecting Hyperdense Artery Sign and Predictors of Unfavorable Outcomes (mRS Score > 2) in 2903 Patients with Acute Ischemic Stroke

Variables	Hyperdense Artery Sign			Unfavorable Outcomes		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age (years)	1.018	1.006–1.030	0.004	1.051	1.044–1.057	<0.001
Female sex	1.146	0.842–1.562	0.386	1.802	1.553–2.091	<0.001
Hemoglobin (g/dL)	1.061	0.983–1.145	0.128	0.837	0.807–0.869	<0.001
White blood cells (× 10^3 mL)	1.000	1.000–1.000	0.166	1.000	1.000–1.000	<0.001
Neutrophil-to-lymphocyte ratio	1.026	1.008–1.043	0.003	1.140	1.111–1.174	<0.001
Platelet (10^9/L)	0.996	0.994–0.999	0.005	0.999	0.998–1.000	0.067
Glucose (mg/dL)	0.998	0.996–1.000	0.117	1.001	1.000–1.002	0.155
Creatinine (mg/dL)	0.934	0.799–1.093	0.396	1.168	1.088–1.254	<0.001
Cholesterol (mg/dL)	1.000	0.997–1.004	0.833	0.997	0.995–0.999	<0.001
Triglyceride (mg/dL)	0.995	0.992–0.998	0.001	0.998	0.997–0.998	<0.001
Elevated troponin I	4.216	3.073–5.784	<0.001	3.896	2.897–5.241	<0.001
Hypertension	1.028	0.726–1.455	0.879	1.267	1.076–1.492	0.005
Diabetes Mellitus	0.605	0.425–0.859	0.005	1.378	1.183–1.606	<0.001
Hyperlipidemia	0.560	0.352–0.893	0.015	0.640	0.532–0.771	<0.001
Heart disease	2.976	2.180–4.063	<0.001	1.789	1.522–2.104	<0.001
Prior stroke	0.613	0.410–0.917	0.017	1.490	1.258–1.766	<0.001
Current smoker	0.865	0.582–1.283	0.471	0.471	0.391–0.567	<0.001
Alcohol consumption	1.032	0.587–1.813	0.914	0.560	0.424–0.739	<0.001
History of cancer	1.647	0.988–2.745	0.056	1.985	1.465–2.689	<0.001
Uremia	0.810	0.293–2.239	0.684	2.874	1.741–4.745	<0.001
Atrial fibrillation	4.216	3.073–5.784	<0.001	2.460	2.015–3.002	<0.001
Initial NIHSS score	1.157	1.138–1.177	<0.001	1.451	1.405–1.498	<0.001
Thrombolytic therapy	6.518	4.282–9.923	<0.001	1.528	1.077–2.168	0.018
In-hospital complications	5.962	4.334–8.203	<0.001	21.183	14.141–31.733	<0.001
Length of stay (days)	1.037	1.028–1.045	<0.001	1.164	0.149–1.178	<0.001
Positive hyperdense artery sign	-	-	-	13.074	7.391–23.127	<0.001

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

Table 6 Multivariate Logistic Regression of Factors Affecting Hyperdense Artery Sign in 2903 Patients with Acute Ischemic Stroke

Variables	Odds ratio	95% Confidence Interval	*P* value
Age > 72 (years)	0.505	0.297–0.858	0.012
Neutrophil-to-lymphocyte ratio > 3.5	2.146	1.303–3.534	0.003
Platelet < 185 (×10^9/L)	1.042	0.525–2.068	0.906
Triglyceride <106 (mg/dL)	1.077	0.614–1.892	0.795
Elevated troponin I	1.020	0.586–1.776	0.943
Diabetes mellitus	0.341	0.185–0.630	<0.001
Hyperlipidemia	1.362	0.692–2.681	0.371
Heart disease	1.575	0.889–2.788	0.119
Prior stroke	0.811	0.467–1.408	0.456
Atrial fibrillation	1.732	0.980–3.061	0.059
Initial NIHSS score ≥ 10	44.226	19.623–99.673	<0.001

Abbreviation: NIHSS, National Institutes of Health Stroke Scale.

successful recanalization during thrombectomy.[15,25] Several studies have emphasized the precise measurement of thin-slice CT HU values of high attenuation and the bilateral MCA HU ratio to improve the qualitative and quantitative evaluations of sensitivity and specificity as well as the intraobserver and interobserver reliability of

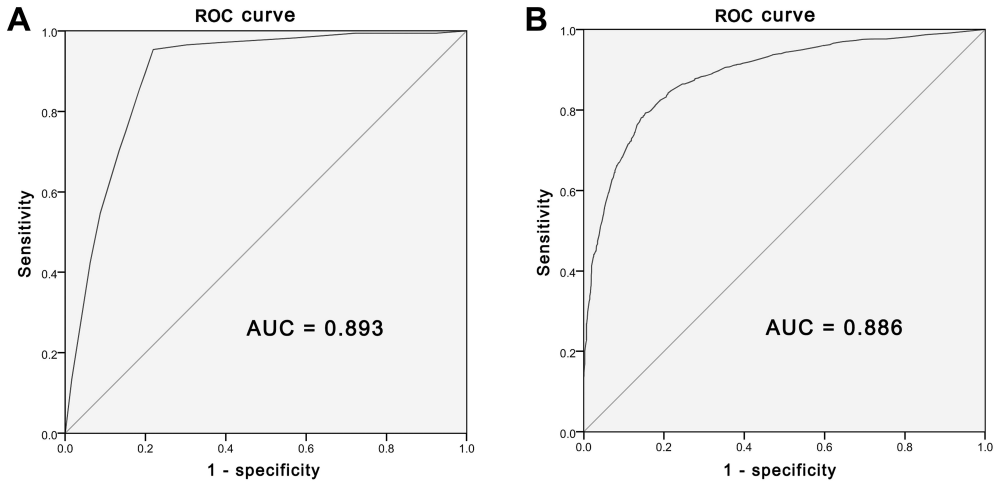

Figure 2 (**A**) C-statistic of the four significant predictors of hyperdense artery sign; predictive performance of 0.893. (**B**) C-statistic of the eight significant predictors of unfavorable outcomes; predictive performance of 0.886.
Abbreviation: AUC, area under the curve.

the HAS. However, the real-life clinical features of acute stroke (such as the NIHSS score) at the emergency department together with positive CT HAS provided a more accurate diagnostic value and guide for decision-making regarding thrombolytic or thrombectomy therapy.[26]

Table 7 Multivariate Logistic Regression of Predictors for Unfavorable Outcomes (mRS Score > 2) in 2903 Patients with Acute Ischemic Stroke

Variables	Odds Ratio	95% Confidence Interval	*P* value
Age > 75 years	2.590	1.989–3.374	<0.001
Female sex	1.497	1.133–1.978	0.005
Hemoglobin < 13.5 (g/dL)	1.115	0.853–1.457	0.425
White blood cells > 8 ($\times 10^3$/mL)	1.446	1.120–1.866	0.005
Neutrophil-to-lymphocyte ratio > 3.5	1.512	1.169–1.954	0.002
Creatinine > 1.1 (mg/dL)	1.147	0.887–1.484	0.294
Cholesterol < 139 (mg/dL)	0.990	0.750–1.306	0.941
Triglyceride < 96 (mg/dL)	1.225	0.947–1.584	0.123
Elevated troponin I	1.694	1.139–2.521	0.009
Hypertension	0.958	0.729–1.259	0.757
Diabetes mellitus	1.653	1.273–2.146	<0.001
Hyperlipidemia	0.887	0.652–1.207	0.444
Heart disease	1.187	0.883–1.594	0.256
Current smoker	0.789	0.561–1.110	0.174
Alcohol consumption	0.959	0.590–1.557	0.865
Prior stroke	1.299	0.994–1.699	0.056
History of cancer	1.354	0.848–2.164	0.205
Uremia	1.689	0.776–3.678	0.187
Atrial fibrillation	1.096	0.765–1.570	0.618
Initial NIHSS score ≥ 5	12.354	9.715–15.709	<0.001
Positive hyperdense artery sign	3.420	1.727–6.772	<0.001

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

In the present study, the HAS was identified in 6% of all patients with acute ischemic stroke and in 66% of patients with acute MCA occlusion. Compared with patients who had an acute ischemic stroke without the HAS, 172 patients with the HAS had higher rates of heart disease, atrial fibrillation, receipt of thrombolytic therapy, in-hospital complications, elevated troponin I levels, long LOS in hospital, poor mRS score on discharge, and high NLR. Similar results were observed in 236 patients who had acute MCA occlusion (with or without the HAS; data not shown). A history of prior stroke typically denotes a chronic atherosclerotic process of intracranial arteries and hence a low probability of an acute large arterial occlusion with the HAS. Among 236 patients with acute MCA occlusion, the HAS was more prevalent in male patients and occurred in patients with the TOAST classification of large-artery atherosclerosis and cardioembolism, with a higher occurrence rate in patients with cardioembolism. Recanalization of the occluded MCA after thrombolytic therapy was observed in two patients with large-artery atherosclerosis and in five patients with cardioembolism who exhibited the HAS on initial CT. Spontaneous recanalization of MCA occlusion occurred in the other five patients with cardioembolism who exhibited the HAS on initial CT but a patent MCA on follow-up MRA. This is compatible with the characteristic that red thrombi from cardioembolism had higher HU on CT and higher potential to break down spontaneously or through thrombolytic therapy.

We found that the NLR was positively correlated with age, glucose levels, creatinine levels, initial NIHSS scores,

LOS in hospital, and mRS scores at discharge. The NLR was higher in patients who had elevated troponin I levels, cancer history, atrial fibrillation, positive HAS, acute MCA occlusion, in-hospital complications, and unfavorable outcomes. Cholesterol, triglyceride, and hemoglobin levels showed an inverse correlation with age and the NLR and were also lower in patients with unfavorable outcomes. This result is similar to that reported by Fang et al, who identified that a high total cholesterol level was significantly and independently predictive of lower NIHSS scores and less severe stroke.[10] The tendency of older adults to have diets with a low lipid content or experience malnutrition due to chewing disorders may explain this finding. A higher NLR indicated a higher stroke severity and less favorable immune status, resulting in more in-hospital complications, such as pneumonia and urinary tract infections, and prolonged LOS in hospital. Patients with TIA and small-vessel disease had the lowest NLR; this was due to the less severity of the stroke 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 lower stroke severity compared with those with large-artery atherosclerosis and cardioembolism exhibited the highest NLR. These results slightly differ from those reported by Gökhan et al, who revealed that the NLR was the highest in those with large-artery occlusion.[20] No patient was assigned to the group of other determined etiology by Gökhan et al. 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, the NLR was considerably higher in these patients.

The NLR was higher not only in patients with acute MCA occlusion but also in those with the HAS. To the best of our knowledge, these findings have not been reported previously. Acute large intracranial artery occlusion indicates a more severe brain tissue damage and inflammatory response. Occlusion of the MCA must be confirmed through contrast-enhanced CT angiography or MRA. However, the HAS provides an immediate clue for the diagnosis of acute large intracranial occlusion through noncontrast CT. Together with the clinical severity of symptoms, physicians can make a quick decision for further treatment. An initial NIHSS score of ≥10 and an NLR of >3.5 were the two most significant factors for predicting the HAS during the hyperacute stage of stroke. Lim et al reported that the HAS had a high sensitivity of 79% for identifying large-vessel occlusion in acute ischemic stroke patients presenting with an NIHSS score of >10.[27]

Studies have suggested that the NLR increases in patients with various cancers.[12,13] In this study, we found that the NLR was increased in patients with elevated troponin I levels. The risk of stroke increases not only after a new cancer diagnosis but also with time in almost all cancer survivors.[28] Cancer and related therapies may cause coagulopathies, such as nonbacterial thrombotic endocarditis, alterations in platelet and endothelial functions, and radiation-induced atherosclerosis. Elevated troponin I levels during acute stroke is a strong independent predictor of both unfavorable outcomes and in-hospital mortality. Mechanisms underlying elevated troponin I levels 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]

Multivariate analyses revealed that the significant predictors of unfavorable outcomes were initial NIHSS score ≥ 5, positive HAS, age > 75 years, diabetes mellitus, NLR > 3.5, female sex, white blood cell count > 8×10^3/mL, and elevated troponin I levels. The predictive performance for unfavorable outcomes of the aforementioned eight factors was up to 0.886. Furthermore, the cutoff point of NLR > 3.5 for the HAS and unfavorable outcomes was the same. Because the NLR was derived from the white blood cell count, which is essential laboratory information during the acute stroke and common routine examinations, the NLR can be selected as a reliable marker for the prediction of both the HAS and unfavorable outcomes.

This study has several limitations. First, this was a retrospective study. We did not have sufficient sequential data during hospitalization for performing a dynamic comparison of the NLR. A dynamic increase in the NLR has been reported to predict 3-month mortality or major disability in patients receiving intravenous thrombolytic treatment.[29] Second, we did not investigate the association between the infarct volume and NLR. However, the TOAST classification may partly reflect the infarct size. Third, we did not perform interobserver reliability in recognizing the HAS. Most previous studies have documented the reliability of interobserver agreement in identifying CT HAS. Fourth, because we did not perform a follow-up study after discharge, and only short-term outcomes at discharge were available. A prospective study examining serial NLR and long-term outcomes may provide more prognostic relevance

for acute ischemic stroke. Regardless of these limitations, the present results extend the current understanding of the implications of the NLR in patients with acute ischemic stroke.

Conclusion

The HAS occurred in 66% of patients with acute MCA occlusion. An initial NIHSS score of ≥10 and an NLR of >3.5 were the two most significant predictors of the HAS. Initial NIHSS score ≥ 5, positive HAS, age > 75 years, diabetes mellitus, NLR > 3.5, female sex, white blood cell count > 8×10^3/mL, and elevated troponin I were the significant predictors of unfavorable outcomes in patients with acute ischemic stroke. An NLR of >3.5 enabled the improved prediction of CT HAS. Both an NLR of >3.5 and CT HAS enabled the efficient prediction of unfavorable stroke outcomes in addition to conventional risk factors and laboratory parameters.

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Disclosure

The authors report no conflicts of interest in this work.

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