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Lymphocyte-to-Monocyte Ratio Is an Independent Predictor for Neurological Deterioration and 90-Day Mortality in Spontaneous Intracerebral Hemorrhage

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Statistical Analysis C
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Background: Lymphocyte-to-monocyte ratio (LMR) is an independent predictive factor of clinical outcome of acute ischemic stroke and cancer, but the predictive effect of LMR in spontaneous intracerebral hemorrhage (ICH) is unknown. Thus, the aim of this study was to explore the impact of peripheral LMR on the neurological deterioration (ND) during the initial week after spontaneous ICH onset, as well as 90-day mortality.

Material/Method: The clinical data of 558 consecutive patients with ICH were retrospectively analyzed. LMR is calculated by absolute lymphocyte count divided by absolute monocyte count.

Results: Of these patients, 166 patients experienced ND during the first week after admission and 72 patients died within 90 days. Multivariate analysis indicated that white blood cells (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), neutrophil-to-lymphocyte ratio (NLR), LMR were significantly associated with ND during the initial week after ICH onset and also were associated with 90-day mortality. Moreover, NLR and LMR showed a higher predictive ability in ND during the initial week after ICH onset than 90-day mortality in receiver operating characteristic analysis. The best cut-off points of NLR and LMR in predicting ND and 90-day mortality were 10.24 and 2.21 and 16.81 and 2.19, respectively.

Conclusions: Our results suggest that LMR on admission is a predictive factor for ND during the initial week after ICH onset, as well as 90-day mortality.

MeSH Keywords: Intracranial Hemorrhage, Hypertensive • Lymphocyte Activation • Mortality

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Background

Spontaneous intracerebral hemorrhage (ICH) is a common vascular disease with high rates of mortality and disability in the central nervous system (CNS) [1]. Despite the rapid development of medical technology, no treatment protocols with definitive effect have been confirmed [1]. Most patients with ICH will suffer from neurological deterioration (ND), which is a common complication in patients with CNS disease and is related to long l in-hospital stay and poor clinical outcomes [2]. Thus, it is important to identify risk factors for prognosis of patients with ICH and this may also improve the clinical outcome.

Some studies have indicated that 25% of patients with ICH experienced ND following admission, and ND was primarily evaluated by use of the National Institutes of Health Stroke Scale (NIHSS) or Glasgow Coma Scale (GCS) [3]. Hematoma expansion is a key to improving the development of ND and factors, including spot sign, larger hematomas, and hemorrhage into the ventricles of the brain, and these are associated with hematoma growth, which may also indirectly contribute to the development of ND [4]. However, there have been few studies on the association between ND and peripheral immune and inflammation biomarkers, such as neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR). Immune and inflammatory reactions play an important role in ICH-induced brain injury [5]. Systemic inflammatory response syndrome can result from many critical conditions, including ICH. The peripheral neutrophil count, lymphocytes, and monocytes were reported to be associated with secondary injury in ICH [6–15] and these biomarkers of immune and inflammation in peripheral blood have been demonstrated to be associated with long-term prognosis in patients with acute ICH. For example, inflammatory biomarkers including leukocyte count, absolute monocyte count (AMC), absolute lymphocyte count (ALC), and NLR were reported to be predictive factors for 30-day mortality in patients with ICH [6–15]. LMR was calculated by absolute lymphocyte count divided by absolute monocyte count and has been reported to be associated with peripheral immune and inflammation function [16,17]. Previous studies indicated that LMR is an independent predictor of overall survival in patients with cancers and acute ischemic stroke [16,17], but there are no studies on the relationship between LMR and ND and mortality in patients with ICH. Therefore, the primary aim of this study was to explore the association between LMR and ND during the initial week after ICH onset. We also evaluated the impact of LMR on 90-day mortality in these patients.

Material and Methods

Study design and patient enrolment

We retrospectively analyzed the clinical data of consecutive patients hospitalized at our hospital from January 2010 to January 2017 for stroke syndrome resulting from ICH who experienced admission routine blood sampling and brain computed tomographic (CT) scan within 24 h from symptom onset. All patients with supratentorial ICH were confirmed by brain CT scans within 24 h after symptom onset. We excluded patients who received surgery and immunomodulatory treatment before admission, including biological agents, methotrexate, corticosteroids, and azathioprine. In addition, we also excluded patients with aneurysm, hepatitis, arteriovenous malformation, heart failure, seizure, chronic obstructive pulmonary disease, hemorrhage following brain tumor, and isolated intraventricular hemorrhage.

Data collection

Data on demographics, lifestyle risk factors, medical history, total white blood cells (WBC), absolute neutrophil count (ANC), AMC, and absolute lymphocyte count (ALC) were collected. NIHSS and GCS at admission also were evaluated. NLR is calculated by absolute lymphocyte count divided by absolute neutrophil count, and LMR is calculated as ALC over AMC.

Blood pressure (BP) measurements and BP variability (BPV) definition

Noninvasive BP monitoring was performed at admission and subsequently at an interval of 4 h during the first 72 h after stroke symptoms. BP readings were using to calculate the minimum, mean, and maximum values of systolic and diastolic BP for each patient. BPV was defined as the maximum – minimum values, standard deviation (SD), and the coefficient of variation (CV; SD×100/mean).

ND evaluation and 90-day mortality

According to previous research [18], ND is determined by GCS or NIHSS score, which means that if the NIHSS score increased by 4 points or greater or if GCS decreased by 2 points or greater, or death occurred from the time of admission to 7 days post-hemorrhage, the patient may suffer from ND. Mortality at 90 days was documented by telephone interview or outpatient visit.

Infection assessment

Infection was microbiologically assessed using urine, sputum, and blood samples obtained during hospitalization.

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Only patients with infection symptoms such as hyperpyrexia, shivers, and expectoration received the diagnostic exam. The time of infection from stroke onset was also recorded.

Statistical analysis

Continuous variables are expressed as mean ±SD or median (interquartile range), while the categorical variables are presented as number or percent. For comparison analysis, the *t* test or Mann-Whitney test were performed for continuous variables, while the chi-squared test was used for categorical variables. Logistic regression models were used to evaluate the distribution of WBC, ALC, ANC, AMC, NLR, and LMR in patients with and without ND. Logistic regression modeling was also performed to assess the distribution of WBC, ALC, ANC, AMC, NLR, and LMR in patients with and without 90-day mortality. Variables with p value <0.05 indicated by comparison analysis were included in multivariate analysis and adjusted by sex, age, admission GCS, hematoma location, baseline volume, and intraventricular extension of ICH. In addition, receiver operating characteristic (ROC) analysis was performed to assess the ability of WBC, ALC, ANC, AMC, NLR, and LMR to predict ND and 90-day mortality. All p values were 2-sided, and p≤0.05 was considered as statistically significant. Statistical software used for analysis was SPSS version 17.0.

Results

There are 558 patients with ICH included in this study, with a mean age at admission of 57.6 years (range: 28–79). Of these patients, 166 patients experienced ND during the first week after admission. Table 1 summarizes the comparison data of patients with and without ND. Patients with ND tended to be older and smokers, and had higher systolic BP and systolic BP variability, higher diastolic BP and diastolic BP variability, higher frequency of hematoma growth, larger hematoma volume, lower GCS, higher NIHSS score, higher WBC, higher ANC, higher AMC, higher NLR, and lower ALC and LMR at admission compared to patients without ND (Table 1).

In univariate logistic regression, WBC (OR: 1.132; 95%CI: 1.086–1.179, p≤0.001), ANC (OR: 1.166; 95%CI: 1.116–1.219, p≤0.001), ALC (OR: 0.216; 95%CI: 0.144–0.325, p≤0.001), NLR (OR: 1.143; 95%CI: 1.110–1.176, p≤0.001) and LMR (OR: 0.677; 95%CI: 0.599–0.765, p≤0.001) were significantly associated with ND (Table 2). These variables remained statistically significant when they were adjusted by age, sex, initial GCS, mean systolic and diastolic BP, systolic and diastolic BP variability, BP-lowering strategy, types of BP-lowering agents, unhealthy lifestyle including smoking and drinking, baseline ICH volume, time from stroke onset to blood sample, presence of intraventricular hemorrhage, hematoma location, hematoma expansion, and presence of spot sign and infection (all p values ≤0.001).

The results of ROC analysis showed that the area under the curves for WBC, ANC, ALC, AMC, NLR, and LMR in predicting ND were 0.659 (95%CI: 0.611–0.706, p≤0.001), 0.687 (95%CI: 0.641–0.732, p≤0.001), 0.738 (95%CI: 0.692–0.783, p≤0.001), 0.584 (95%: 0.534–0.634, p=0.002), 0.792(95%CI: 0.752–0.833, p≤0.001), and 0.726 (95%CI: 0.680–0.772, p≤0.001), respectively (Table 3). The best cut-offs of WBC, ANC, ALC, AMC, NLR, and LMR in predicting ND were 11.13, 8.45, 1.03, 0.53, 10.24, and 2.21, respectively (Figure 1).

There are 72 patients who died during the first 90 days. Patients who died had higher systolic BP, higher diastolic BP, larger hematoma volume, lower GCS, higher NIHSS score, higher WBC, higher ANC, higher NLR, and lower ALC and LMR at admission compared to patients who survived the first 90 days (Table 4). In univariate logistic regression, WBC (OR: 1.083; 95%CI: 1.033–1.136, p=0.001), ANC (OR: 1.099; 95%CI: 1.045–1.155, p≤0.001), ALC (OR: 0.555; 95%CI: 0.359–0.858, p=0.008), NLR (OR: 1.143; 95%CI: 1.074–1.102, p≤0.001), and LMR (OR: 0.758; 95%CI: 0.648-0.886, p=0.001) were significantly associated with 90-day mortality (Table 5). Furthermore, all of these factors were associated with 90-day mortality after being adjusted by age, sex, initial GCS, mean systolic and diastolic BP, systolic and diastolic BP variability, BP-lowering strategy, types of BP-lowering agents, unhealthy lifestyle including smoking and drinking, baseline ICH volume, time from stroke onset to blood sample, presence of intraventricular hemorrhage, hematoma location and hematoma expansion, presence of spot sign, presence of infection, and ND (all p value ≤0.001, Table 5).

The ROC results showed that the area under the curves for WBC, ANC, ALC, AMC, NLR, and LMR in predicting 90-day mortality were 0.605 (95%CI: 0.537–0.674, p=0.004), 0.623 (95%CI: 0.558–0.639, p=0.001), 0.631 (95%CI: 0.558–0.704, p≤0.001), 0.575 (95%: 0.508–0.642, p=0.041), 0.669 (95%CI: 0.600–0.738, p≤0.001), and 0.648 (95%CI: 0.580–0.716, p≤0.001), respectively. The best cut-offs of WBC, ANC, ALC, AMC, NLR, and LMR in predicting 90-day mortality were 7.83, 6.24, 1.03, 0.55, 16.81, and 2.19, respectively (Table 6, Figure 1).

Furthermore, we also evaluated the association between above blood markers and infections in patients with ICH. There were 89 patients who had infections after admission. Of these patients, 43 were diagnosed with pneumonia, 26 patients had urinary tract infection, and 20 patients had sepsis. The mean time from infection to stroke onset was 14.45±3.56 days. Patients with infections had higher WBC, higher ANC, higher NLR, and lower ALC and LMR compared to patients without infections (all p value ≤0.001, Table 7).

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Table 1. Baseline characteristics and neurological deterioration.

Variable	ND (166)	Non-ND (392)	P value
Sex (Male/Female)	102/64	266/126	0.454
Age	59.32±14.48	55.88±16.67	0.016
Diabetes mellitus	42/124	84/308	0.317
Hyperlipidemia	38/128	70/322	0.169
Smoking	51/115	81/311	0.011
Mean SBP (mmHg)	184.76±20.82	177.92±19.32	<0.001
Mean SBP (mmHg)	109.82±14.41	104.31±11.87	<0.001
SBP CV	11.5 (4.0)	9.8 (3.8)	0.012
DBP CV	11.3 (4.1)	8.7 (4.3)	0.001
SBP SD	16.75 (5.32)	12.89 (4.38)	<0.001
DBP SD	9.36 (2.96)	7.33 (1.89)	<0.001
SBP mum-min	56.23 (18.25)	42.32 (17.22)	<0.001
DBP mun-min	32.15 (9.11)	26.65 (6.54)	<0.001
BP lowering strategy (intensive/conservative)	85/81	173/219	0.126
BP lowering agents			
CCB (Yes/No)	57/109	136/256	0.935
ACEI (Yes/No)	66/100	154/238	0.917
Beta blocker (Yes/No)	18/148	56/336	0.273
ARB(Yes/No)	31/135	61/331	0.881
Diureticum (Yes/No)	50/116	120/272	0.908
NIHSS	13.51±4.67	8.56±3.42	<0.001
GCS	11.25±2.14	11.87±2.41	0.012
Hematoma volume	19.21±9.91	15.60±9.59	<0.001
Spot Sign (Yes/No)	59/107	64/328	<0.001
Hematoma growth (Yes/No)	75/91	63/329	<0.001
Hematoma location			
Lobar (Yes/No)	62/104	142/250	0.801
Basal ganglia region (Yes/No)	74/92	168/224	0.295
Thalamus	30/136	74/318	0.823
Intraventricular extension (Yes/No)	22/144	27/365	<0.001
Blood sampling time (h)	13.5±3.3	14.3±4.1	0.806
WBC	13.39±5.24	10.67±4.15	<0.001
ALC	0.93±0.53	1.44±0.75	<0.001
ANC	11.82±4.85	8.77±4.01	<0.001
AMC	0.69±1.07	0.62±0.39	<0.001
NLR	15.98±8.83	8.03±6.44	<0.001
LMR	2.06±1.95	3.49±2.37	<0.001

SBP – systolic blood pressure; DBP – diastolic blood pressure; ND – neurological deterioration; NIHSS – National Institute of Health Stroke Scale; GCS – Glasgow Coma Scale; CV – coefficient of variation; SD – standard deviation; CCB – calcium channel blocker; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor inhibitor; WBC – white blood cells; ANC – absolute neutrophil count; AMC – absolute monocyte count; ALC – absolute lymphocyte count; NLR – neutrophil-to-lymphocyte ratio; LMR – lymphocyte-to-monocyte ratio.

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Table 2. The relationship between NLR, LMR, and neurological deterioration.

Variables	Unadjusted		Adjusted	
	OR (95%CI)	p Value	OR (95%CI)	p Value
WBC	1.132 (1.086–1.179)	<0.001	1.126 (1.074–1.180)	<0.001
ALC	0.216 (0.144–0.325)	<0.001	0.210 (0.134–0.328)	<0.001
ANC	1.166 (1.116–1.219)	<0.001	1.162 (1.105–1.223)	<0.001
AMC	0.910 (0.730–1.135)	0.403	0.994 (0.756–1.307)	0.965
NLR	1.143 (1.110–1.176)	<0.001	1.142 (1.107–1.179)	<0.001
LMR	0.677 (0.599–0.765)	<0.001	0.664 (0.597–0.760)	<0.001

Adjusted by age, sex, initial GCS, systolic and diastolic BP, systolic and diastolic BP variability, BP-lowering strategy, types of BP-lowering agents, unhealthy lifestyle including smoking and drinking, baseline ICH volume, time from stroke onset to blood sample, presence of intraventricular hemorrhage, hematoma location, hematoma expansion, and presence of spot sign and infection.

Table 3. The ability of NLR and LMR in predicting neurological deterioration.

Variables	Area under the curve (95%CI)	p Value	Cut-off	Specificity	Sensitivity
WBC	0.659 (0.611–0.706)	<0.001	11.13	62.70%	61.27%
ALC	0.738 (0.692–0.783)	<0.001	1.03	71.40%	67.50%
ANC	0.687 (0.641–0.732)	<0.001	8.45	78.30%	54.10%
AMC	0.584 (0.534–0.634)	0.002	0.59	48.20%	67.30%
NLR	0.792 (0.752–0.833)	<0.001	10.24	71.10%	75.00%
LMR	0.726 (0.680–0.772)	<0.001	2.21	63.80%	75.90%

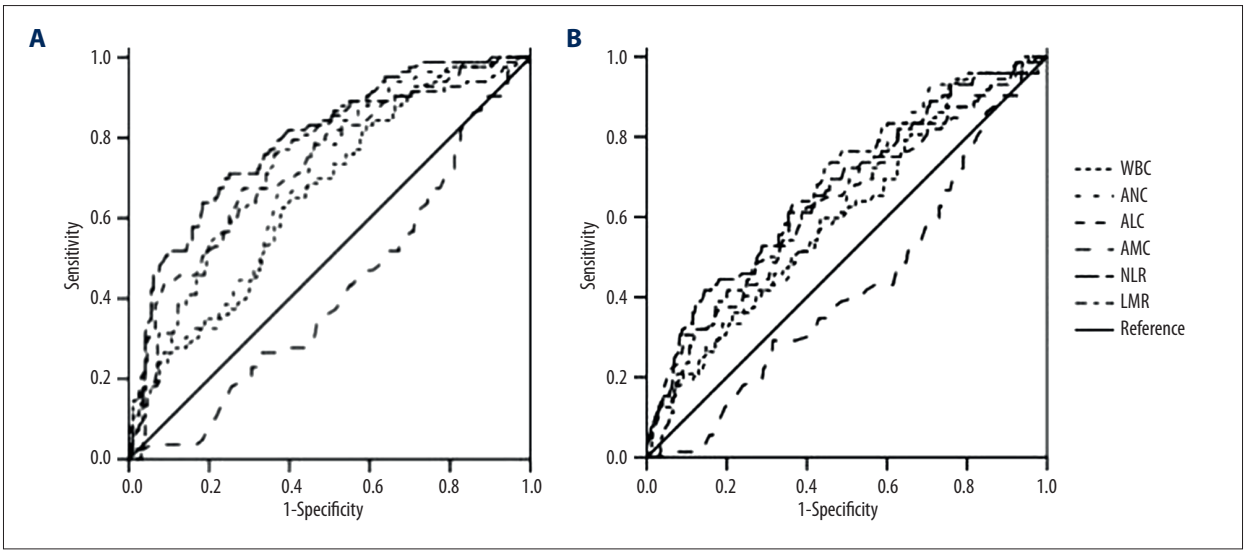

Figure 1. The ability of NLR and LMR to predict neurological deterioration and 90-day mortality.

Discussion

The aim of this study was to identify risk factors for ND and 90-day mortality in patients with ICH. Our main results showed that higher WBC, higher ANC, higher NLR, lower ALC, and LMR on admission were predictive factors for ND during the initial week after ICH onset and 90-day mortality. To the best of our knowledge, the present study is the first to evaluate the relationship between LMR and ND and 90-day mortality in patients with ICH.

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Table 4. Baseline characteristics and 90-day mortality.

Variable	90-day mortality		P value
	Death (72)	Survival (486)	
Sex (Male/Female)	52/20	316/170	0.229
Age	57.46±15.11	58.42±14.89	0.611
Diabetes mellitus (Yes/No)	26/46	100/386	0.005
Hyperlipidemia (Yes/No)	19/53	89/397	0.105
Smoking (Yes/No)	25/47	107/379	0.018
Mean SBP (mmHg)	185.14±23.60	176.19±19.36	0.044
Mean DBP (mmHg)	90.52±15.91	86.12±12.21	0.002
SBP CV	11.8 (4.1)	10.1 (3.7)	0.028
DBP CV	10.3 (4.0)	8.3 (4.2)	0.001
SBP SD	15.97 (5.52)	13.19 (4.08)	<0.001
DBP SD	9.06 (2.23)	7.01 (1.22)	<0.001
SBP mum-min	50.12 (16.12)	39.12 (18.11)	<0.001
DBP mun-min	31.22 (8.99)	26.22 (5.34)	<0.001
BP lowering strategy (intensive/conservative)	29/43	229/257	0.277
BP lowering agents			
CCB	24/48	169/317	0.810
ACEI	26/46	194/292	0.537
Beta blocker	11/61	63/423	0.589
ARB	12/60	74/412	0.752
Diureticum	21/51	149/337	0.797
NIHSS	12.37±4.31	7.41±4.11	<0.001
GCS	11.94±2.31	12.83±2.33	0.003
Hematoma volume	20.91±10.21	16.32±8.89	0.003
Spot Sign (Yes/No)	26/46	97/389	0.002
Hematoma growth (Yes/No)	41/31	95/391	<0.001
Hematoma location involvement			
Lobar (Yes/No)	25/47	179/307	0.729
Basal ganglia region (Yes/No)	29/43	213/273	0.571
Thalamus (Yes/No)	18/54	86/400	0.137
Intraventricular extension (Yes/No)	18/54	40/446	<0.001
Blood sampling time(h)	14.1±3.5	14.4±4.5	0.843
WBC	13.22±5.43	11.22±4.49	0.004
ALC	1.08±0.73	1.32±0.73	0.008
ANC	11.55±5.13	9.40±4.33	<0.001
AMC	0.62±0.36	0.68±0.98	0.599
NLR	15.44±10.80	9.65±7.33	<0.001
LMR	2.15±1.68	3.20±2.40	<0.001

SBP – systolic blood pressure; DBP – diastolic blood pressure; ND – neurological deterioration; NIHSS – National Institute of Health Stroke Scale; GCS – Glasgow Coma Scale; CV – coefficient of variation; SD – standard deviation; CCB – calcium channel blocker; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin II receptor inhibitor; WBC – white blood cells; ANC – absolute neutrophil count; AMC – absolute monocyte count; ALC – absolute lymphocyte count; NLR – neutrophil-to-lymphocyte ratio; LMR – lymphocyte-to-monocyte ratio.

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Table 5. The relationship between NLR, LMR and 90-day mortality.

Variables	Unadjusted		Adjusted	
	OR (95%CI)	p Value	OR (95%CI)	p Value
WBC	1.083 (1.033–1.136)	0.001	1.084 (1.026–1.146)	0.004
ALC	0.555 (0.359–0.858)	0.008	0.635 (0.411–0.981)	0.041
ANC	1.099 (1.045–1.155)	<0.001	1.096 (1.033–1.162)	0.002
AMC	0.919 (0.671–1.259)	0.601	1.083 (0.746–1.572)	0.676
NLR	1.074 (1.046–1.102)	<0.001	1.061 (1.030–1.094)	<0.001
LMR	0.758 (0.648–0.886)	0.001	0.765 (0.641–0.912)	0.003

Adjusted by age, sex, initial GCS, systolic and diastolic BP, systolic and diastolic BP variability, BP lowering strategy, types of BP-lowering agents, unhealthy lifestyle including smoking and drinking, baseline ICH volume, time from stroke onset to blood sample, presence of intraventricular hemorrhage, hematoma location and hematoma expansion, presence of spot sign, presence of infection, and ND.

Table 6. The ability of NLR and LMR in predicting 90-day mortality.

Variables	AUC (95%CI)	p Value	Cut-off	Specificity	Sensitivity
WBC	0.605 (0.537–0.674)	0.004	7.83	24.50%	93.10%
ALC	0.631 (0.558–0.704)	<0.001	1.03	63.90%	63.40%
ANC	0.623 (0.558–0.639)	0.001	6.24	29.10%	93.10%
AMC	0.575 (0.508–0.642)	0.041	0.55	61.50%	56.90%
NLR	0.669 (0.600–0.738)	<0.001	16.81	85.60%	41.70%
LMR	0.648(0.580–0.716)	<0.001	2.19	72.20%	55.60%

Table 7. The relationship of LMR, NLR associated with infections.

Variable	Infection (89)	Non-infection (469)	P value
WBC	13.74±5.32	10.83±4.28	<0.001
ALC	0.97±0.68	1.38±0.72	<0.001
ANC	11.13±4.81	8.96±4.14	<0.001
AMC	0.65±0.38	0.67±1.03	0.859
NLR	16.10±8.42	8.76±7.22	<0.001
LMR	2.03±2.04	3.37±2.34	<0.001

Our results are in line with previous publications which indicated that elevated WBC, ANC, and NLR and lower ALC were associated with ND [19] and 90-day mortality [9–17], which suggests that immune and inflammatory response play an important role in the pathological process following ICH [5]. The pathophysiological process after ICH is involved with leukocyte infiltration and release of various inflammatory mediators, contributing to neuron death or apoptosis, which results in a poor outcome in patients with ICH [20–22]. The present study primarily explained the role of LMR in ICH from 2 aspects: lymphocytes and monocytes.

Lymphocytes, a subtype of leukocytes, are the main immune regulatory cells, which play a defensive role in the invasion of diseases. Some studies with animal models also indicated that lymphocytes were involved in the pathology following ICH [23], which suggested that lymphocytes have a role in the pathological changes after ICH. Patients with stroke may experience lymphopenia or decreasing absolute lymphocyte count, a phenomenon of immunodepression, which might result from activation of the hypothalamic-pituitary-adrenal system, sympathetic nervous system, and parasympathetic nervous system, via the secretion and release of acetylcholine,

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catecholamines, and cortisol, which may lead to lymphocyte apoptosis [24]. Some studies suggested that higher ALC can up-regulate the anti-inflammatory cytokine interleukin (IL)-10 and suppress inflammatory cytokines including tumor necrosis factor (TNF)-α and IL-6, resulting in a neuroprotective effect [25,26]. In addition, there are studies demonstrating that decreased lymphocyte count was associated with infection in patients with ICH [27], which is consistent with our result. Therefore, not only the length of hospital stay was prolonged in patients with decreased lymphocytes, but also the clinical course was aggravated by infection owing to the suppression of lymphocyte in defensive effect [28]. NLR calculated from neutrophil and lymphocyte is a biomarker conveying important information about inflammatory and immune status in the vascular bed [29]. Increased neutrophils and reduced lymphocytes are involved in secondary injury after ICH, so NLR combined with the above 2 is an independent predictor of ND and 90-day mortality.

Monocyte was another important immunoregulator involved with secondary injury following ICH [30]. Migration of monocytes into the hemorrhagic brain via monocyte chemoattractant protein-1 and its receptor chemokine receptor 2 which were elevated after ICH [31]. TNF-α, IL-6, and IL-1b secreted from monocyte exerted a pro-inflammatory effect on brain lesions after stroke onset [32]. Furthermore, evidence suggests that monocytes migrate into the lesion following ICH and meditated by infiltrated neutrophil and Toll-like receptors, adhere to the vascular endothelial and destroy the blood–brain barrier and then aggravate the brain edema [33]. In addition, monocytes promote neuronal death and vascular injury and increase the expression of Toll-like receptor 2, 4 pro-inflammatory molecules, and inducible nitric oxide synthase, leading to secondary brain damage by combining with vascular endothelial chemotactic protein, all of which also promote and aggravate brain edema [34,35] and then the development of ND. Previous studies indicated that increased monocyte was associated with ND and long-term clinical outcome in patients with ICH [36,37], while monocytes were unrelated to ND and 90-day mortality. However, the peripheral LMR was a predictive factor for ND and 90-day mortality.

As far as we know, this is the first study to evaluate the relationship of LMR with short- and long-term clinical outcome in patients with ICH. Although previous studies assessed the correlation of NLR with ND [19] and long-term mortality [9–11,13,15,16], the importance of LMR in ICH remains unclear. In the present study, the association of LMR with ND and 90-day mortality may be explained by the following. On the one hand, just like NLR, LMR is a biomarker reflecting the inflammatory and immune status caused by ICH. The inflammatory response following ICH is meditated by lymphocytes and monocytes, leading to secondary brain injury including white matter damage, blood–brain barrier breakdown, and brain edema [24–28,31–35], which may have a critical role in the development of ND and 90-day mortality. On the other hand, immunosuppression caused by ICH may led to some post-stroke complications such as pneumonia, which promotes patient mortality [27]. As a result, LMR as well as NLR were combined in an index reflecting both the proinflammatory status and immunosuppression and predicted ND and poor clinical outcome in the present study.

We also found that BPV, including CV, SD, and maximum -minimum values, were significantly higher in patients with ND and 90-day mortality, which was consistent with previously published studies [38,39]. Lattanzi et al. [38]. performed a retrospective study with 138 patients of ICH and suggested that BPV during 72 hours after stroke onset was independently associated with poor clinical outcome at 3-month. The mechanism of poor clinical outcome mediated by BPV may include the following aspects. Recurrent sudden rises or falls in BP may contribute to the arterial bleeding and hematoma enlargement [39,40] which were the risk factors for patients with ICH. In addition, fluctuation of BP may have an affect brain perfusion and blood flow, therefore aggravating the secondary brain injury [41]. The evidence presented above shows that stabilization of BPV during the first 72 h after stroke onset can improve the clinical outcome of patients with ICH.

Besides LMR, BPV, and spot sign, many other factors are meditated secondary brain injury following spontaneous ICH, such as hyperglycemia, ficolin-1, and glycosylated hemoglobin [42–44], indicating that the pathophysiological processes involved in secondary-induced damage are associated with metabolic, hemodynamic, and pharmacological factors. Therefore, it is important to perform multidimensional modeling to predict treatment complications and prognosis in patients with ICH. A multidimensional model could involve immunological, imaging, serological, genetic, clinical, and proteomic information of patients [45]. This multidimensional model may be used to identify patients at high risk and customize treatment strategies, thus comprehensively improving the clinical outcome. However, it is difficult to predict clinical outcome based on multidimensional models due to the heterogeneity and complexity of all the potentially involved determinants [45]. In the near future, artificial intelligence with a large-scale stroke database based on multiple hospitals and centers may build this model [45].

The results of this study should be interpreted prudently. To begin with, this was a retrospective study and lacks prospective and multi-center studies using specific blood sampling analyses. Times of blood collection varied following admission, so it is difficult to assess the dynamic changes of NLR and LMR during the hospital stay. Thus, the relationships of NLR associated with ND and 90-day mortality are unclear. Furthermore, patients who underwent surgery were excluded in the present study, which may have contributed to selection bias. Finally, NLR

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and LMR can be affected by many factors, including chronic or acute systemic inflammation, unhealthy lifestyle, and concomitant conditions such as pneumonia, hypertension, diabetes, hepatitis, and heart failure. In the present study, we excluded patients with pneumonia, hepatitis, and heart failure, while unhealthy lifestyle including smoking and drinking and concomitant conditions such as hypertension and diabetes were identified as confounding factors adjusting for NLR and LMR. Therefore, further studies based on LMR and NLR should clearly define the exclusion and inclusion criteria.

Conclusions

Our results indicate that LMR upon admission is a simple, inexpensive, and immediately obtainable biomarker useful in predicting ND and 90-day mortality in patients with ICH. This reliable and easy-to-use predictor could contribute to clinical treatment strategy design in patients with ICH. Further studies should be performed to investigate the relevant inflammation and immune pathways to find new targets for ND and 90-day mortality and to improve the clinical outcome.

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Conflicts of interest

None.

References:

1. Feigin VL, Lawes CM, Bennett DA et al: Stroke epidemiology: A review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol, 2003; 2: 43–53
2. Kwan J, Hand P: Early neurological deterioration in acute stroke: clinical characteristics and impact on outcome. QJM, 2006; 99: 625–33
3. Qureshi AI, Safdar K, Weil J et al: Predictors of early deterioration and mortality in Black Americans with spontaneous intracerebral hemorrhage. Stroke, 1995; 26: 1764–67
4. Ovesen C, Christensen AF, Havsteen I et al: Prediction and prognostication of neurological deterioration in patients with acute ICH: A hospital-based cohort study. BMJ Open, 2015; 5(7): e008563
5. Xi G, Keep RF, Hoff JT: Mechanisms of brain injury after intracerebral haemorrhage. Lancet Neurol, 2006; 5: 53–63
6. Kazui S, Naritomi H, Yamamoto H et al: Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. Stroke, 1996; 27: 1783–87
7. Leira R, Dávalos A, Silva Y et al: Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. Neurology, 2004; 63: 461–67
8. Sansing LH, Harris TH, Kasner SE et al: Neutrophil depletion diminishes monocyte infiltration and improves functional outcome after experimental intracerebral hemorrhage. Acta Neurochir Suppl, 2011; 111: 173–78
9. Wang F, Wang L, Jiang TT et al: Neutrophil-to-lymphocyte ratio is an independent predictor of 30-day mortality of intracerebral hemorrhage patients: A validation cohort study. Neurotox Res, 2018 [Epub ahead of print]
10. Wang F, Xu F, Quan Y et al: Early increase of neutrophil-to-lymphocyte ratio predicts 30-day mortality in patients with spontaneous intracerebral hemorrhage. CNS Neurosci Ther, 2018 [Epub ahead of print]
11. Lattanzi S, Cagnetti C, Rinaldi C et al: Neutrophil-to-lymphocyte ratio and outcome prediction in acute intracerebral hemorrhage. J Neurol Sci, 2018; 387: 98–102
12. Walsh KB, Sekar P, Langefeld CD et al: Monocyte count and 30-day case fatality in intracerebral hemorrhage. Stroke, 2015; 46: 2302–4
13. Wang F, Hu S, Ding Y et al: Neutrophil-to-lymphocyte ratio and 30-day mortality in patients with acute intracerebral hemorrhage. J Stroke Cerebrovasc Dis, 2016; 25: 182–87
14. Agnihotri S, Czap A, Staff I et al: Peripheral leukocyte counts and outcomes after intracerebral hemorrhage. J Neuroinflammation, 2011; 8: 160
15. Lattanzi S, Cagnetti C, Provinciali L et al: Neutrophil-to-lymphocyte ratio predicts the outcome of acute intracerebral hemorrhage. Stroke, 2016; 47: 1654–57
16. Ho CL, Lu CS, Chen JH et al: Neutrophil/lymphocyte ratio, lymphocyte/monocyte ratio, and absolute lymphocyte count/absolute monocyte count prognostic score in diffuse large B-cell lymphoma: Useful prognostic tools in the rituximab era. Medicine (Baltimore), 2015; 94(24): e993
17. Ren H, Han L, Liu H et al: Decreased lymphocyte-to-monocyte ratio predicts poor prognosis of acute ischemic stroke treated with thrombolysis. Med Sci Monit, 2017; 23: 5826–33
18. Lord AS, Gilmore E, Choi HA, Mayer SA, VISTA-ICH Collaboration: Time course and predictors of neurological deterioration after intracerebral hemorrhage. Stroke, 2015; 46: 647–52
19. Lattanzi S, Cagnetti C, Provinciali L et al: Neutrophil-to-lymphocyte ratio and neurological deterioration following acute cerebral hemorrhage. Oncotarget, 2017; 8(34): 57489–94
20. Sansing LH, Harris TH, Kasner SE et al: Neutrophil depletion diminishes monocyte infiltration and improves functional outcome after experimental intracerebral hemorrhage. Acta Neurochir Suppl, 2011; 111: 173–78
21. Tapia-Perez JH, Karagianis D, Zilke R et al: Assessment of systemic cellular inflammatory response after spontaneous intracerebral hemorrhage. Clin Neurol Neurosurg, 2016; 150: 72–79
22. Mracsko E, Javidi E, Na SY et al: Leukocyte invasion of the brain after experimental intracerebral hemorrhage in mice. Stroke, 2014; 45: 2107–14
23. Rolland WB, Lekic T, Krafft PR et al: Fingolimod reduces cerebral lymphocyte infiltration in experimental models of rodent intracerebral hemorrhage. Exp Neurol, 2013; 241: 45–55
24. Gu L, Jian Z, Stary C et al: T Cells and cerebral ischemic stroke. Neurochem Res, 2015; 40: 1786-91
25. Liesz A, Suri-Payer E, Veltkamp C et al: Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke. Nat Med, 2009; 15: 192–99
26. Li P, Mao L, Zhou G et al: Adoptive regulatory T-cell therapy preserves systemic immune homeostasis after cerebral ischemia. Stroke, 2013; 44: 3509–15
27. Moxon-Emre I, Schlichter LC: Neutrophil depletion reduces blood–brain barrier breakdown, axon injury, and inflammation after intracerebral hemorrhage. J Neuropathol Exp Neurol, 2011; 70(3): 218–35
28. Westendorp WF, Nederkoorn PJ, Vermeij JD et al: Post-stroke infection: A systematic review and meta-analysis. BMC Neurol, 2011; 11: 110
29. Tamhane UU, Aneja S, Montgomery D et al: Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol, 2008; 102: 653–57
30. Mracsko E, Veltkamp R: Neuroinflammation after intracerebral hemorrhage. Front Cell Neurosci, 2014; 8: 388
31. Yao Y, Tsirka SE: Chemokines and their receptors in intracerebral hemorrhage. Transl Stroke Res, 2012; 3: 70–79
32. Boyette LB, Macedo C, Hadi K et al: Phenotype, function, and differentiation potential of human monocyte subsets. PLoS One, 2017; 12: e0176460
33. Sansing LH, Harris TH, Kasner SE et al: Neutrophil depletion diminishes monocyte infiltration and improves functional outcome after experimental intracerebral hemorrhage. Acta Neurochirurgica, 2011; 111: 173–78

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

34. Chen Y, Hallenbeck JM, Ruetzler C et al: Overexpression of monocyte chemoattractant protein 1 in the brain exacerbates ischemic brain injury and is associated with recruitment of inflammatory cells. J Cereb Blood Flow Metab, 2003; 23(6): 748–55
35. Urra X, Villamor N, Amaro S et al: Monocyte subtypes predict clinical course and prognosis in human stroke. J Cereb Blood Flow Metab, 2009; 29: 994–1002
36. Adeoye O, Walsh K, Woo JG et al: Peripheral monocyte count is associated with case fatality after intracerebral hemorrhage. J Stroke Cerebrovasc Dis, 2014; 23(2): e107–11
37. Walsh KB, Sekar P, Langefeld CD et al: Monocyte count and 30-day case fatality in intracerebral hemorrhage. Stroke, 2015; 46(8): 2302–4
38. Lattanzi S, Cagnetti C, Provinciali L et al: Blood pressure variability and clinical outcome in patients with acute intracerebral hemorrhage. J Stroke Cerebrovasc Dis, 2015; 24(7): 1493–99
39. Menon RS, Burgess RE, Wing JJ et al: Predictors of highly prevalent brain ischemia in intracerebral hemorrhage. Ann Neurol, 2012; 71: 199–205
40. Rodriguez-Luna D, Piñeiro S, Rubiera M et al: Impact of blood pressure changes and course on hematoma growth in acute intracerebral hemorrhage. Eur J Neurol, 2013; 20: 1277–83
41. Buratti L, Cagnetti C, Balucani C et al: Blood pressure variability and stroke outcome in patients with internal carotid artery occlusion. J Neurol Sci, 2014; 339(1–2): 164–68
42. Saxena A, Anderson CS, Wang X et al: Prognostic significance of hyperglycemia in acute intracerebral hemorrhage: The INTERACT2 study. Stroke, 2016; 47(3): 682–88
43. Lattanzi S, Bartolini M, Provinciali L et al: Glycosylated hemoglobin and functional outcome after acute ischemic stroke. J Stroke Cerebrovasc Dis, 2016; 25(7): 1786–91
44. Zangari R, Zanier ER, Torgano G et al: Early ficolin-1 is a sensitive prognostic marker for functional outcome in ischemic stroke. J Neuroinflammation, 2016; 13: 16
45. Stroke Lattanzi S, Silvestrini M: Stroke outcome prediction: What do we know and where are we going? Eur J Neurol, 2018 [Epub ahead of print]

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]