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

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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 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.

8283
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, higherANC, 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%: 0.580–0.716, p≤0.001) were significantly associated with 90-day mortality (Table 5). 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).
## Table 1. Baseline characteristics and neurological deterioration.

| Variable                                | ND (166)       | Non-ND (192)   | P value |
|-----------------------------------------|----------------|----------------|---------|
| Sex (Male/Female)                       | 102/64         | 266/126        | 0.454   |
| Age                                     | 59.3±14.48     | 55.8±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)                         | 184.7±20.82    | 177.9±19.32    | <0.001  |
| Mean DBP (mmHg)                         | 104.3±11.87    | 109.8±14.41    | <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                                  | 16.7 (5.32)    | 12.8 (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)                   | 18/138         | 56/336         | 0.273   |
| ARB (Yes/No)                            | 31/135         | 61/331         | 0.881   |
| Diureticum (Yes/No)                     | 50/116         | 120/272        | 0.908   |
| NIHSS                                   | 13.5±4.67      | 15.6±9.59      | <0.001  |
| GCS                                     | 11.25±2.14     | 11.87±4.24     | 0.012   |
| Hematoma volume                         | 19.2±9.91      | 15.6±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±2.1       | 0.806   |
| WBC                                     | 13.3±5.24      | 10.6±4.15      | <0.001  |
| ALC                                     | 0.93±0.53      | 1.44±0.75      | <0.001  |
| ANC                                     | 11.8±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.
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.

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

| Variables | Unadjusted | OR (95%CI) | p Value | Adjusted | 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)           | >0.05   | 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.
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)            | 19/53            | 89/397 | 0.105 |
| Smoking (Yes/No)                      | 25/47            | 107/379 | 0.018 |
| Mean SBP (mmHg)                       | 185.14±23.60     | 176.19±19.04 | 0.004 |
| 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)       | 9.7 (3.8) | 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 mum-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                                   | 11/60            | 71/876 | 0.922 |
| Diureticium                           | 21/51            | 149/337 | 0.797 |
| NIHSS                                 | 12.37±4.31       | 7.41±4.11 | <0.001 |
| GCS                                   | 11.94±2.31       | 12.85±3.33 | 0.003 |
| Hematoma volume                       | 20.91±10.21      | 16.32±8.89 | 0.003 |
| Spot Sign (Yes/No)                    | 26/46            | 97/389 | 0.002 |
| 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.
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.

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

| Variables | Unadjusted OR (95%CI) | p Value | Adjusted 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   |
| LMR       | 1.074 (1.046–1.102)   | <0.001  | 1.061 (1.030–1.094) | <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 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%      |
| LMR       | 0.669 (0.600–0.738) | <0.001  | 16.81   | 85.60%      | 41.70%      |

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

| Variable | Infection (89) WBC | Non-infection (469) WBC | P value |
|----------|--------------------|-------------------------|---------|
| WBC      | 13.74±5.32         | 10.83±4.28              | <0.001  |
| ALC      | 0.87±0.68          | 0.97±0.68               | <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.
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 chemotactic protein-1 and its receptor chemokine receptor 2 which were elevated after ICH [31]. TNF-α, IL-6, and IL-1β 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 mediated 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 mediated 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 pro-inflammatory 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 mediated 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
and LMR can be affected by many factors, including chronic or acute systemic inflammation, unhealthy lifestyle, and comorbid 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.

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