

Predictive ability of admission neutrophil to lymphocyte ratio on short-term outcome in patients with spontaneous cerebellar hemorrhage

Fan Zhang, MD, PhD^{a,b}, Yanming Ren, MD, PhD^a, Yan Shi, MD^c, Wei Fu, MD, PhD^a, Chuanyuan Tao, MD, PhD^a, Xi Li, MD^a, Mu Yang, MD, PhD^{a,d,e}, Chao You, MD, PhD^{f,*}, Tao Xin, MD, PhD^{a,*}

Abstract

As one of the prototypical intracranial hemorrhage (ICH), spontaneous cerebellar hemorrhage (SCH) is treated with different strategies by comparing with supratentorial hemorrhage (SH). Additionally, SCH patients usually suffer from worse prognosis than patients with other types of ICH. It is well documented that the unique anatomic structures of posterior cranial fossa lead to a higher risk for brainstem compression and/or brain edema in SCH patients. Recently, neutrophil to lymphocyte ratio (NLR) was reported to possess an excellent predictive ability for the prognosis of patients with ICH, and most of those cases are SH. Thus, the potential association between NLR and the prognosis of SCH patients remains to be elucidated. Here, we aim to assess the predictive role of admission NLR and other available inflammatory parameters for the outcomes of patients with SCH.

All patients with acute SCH admitting to West China Hospital from February 2010 to October 2017 were retrospectively enrolled. According to the absolute neutrophil count, absolute lymphocyte count, white blood count and absolute monocyte count extracted from electronic medical records, NLR was calculated. The multivariable logistic regression analysis was applied to analyze the associations between disease outcome and laboratory biomarkers. The comparisons of predictive powers of each biomarker were assessed by receiver operating curves (ROCs). The spearman analyses and multiple linear analyses were also conducted to identify the independent predictors for admission NLR.

Admission NLR independently associated with 30-day status (odds ratio [OR] 1.785, 95% confidence interval [CI] 1.463–2.666, $P < .01$) and exhibited a better predictive value (AUC 0.751, 95% CI 0.659–0.830, $P < .001$) with the best predictive cutoff point of 7.04 in 62 patients with unfavorable outcomes. Moreover, absolute neutrophil count, absolute lymphocyte count, presence of intraventricular hemorrhage (IVH) and Glasgow coma scale (GCS) score were also correlated with admission NLR, respectively.

Admission NLR is a potential marker to independently predict the 30 days functional outcome of SCH patients. Based on our results, systemic inflammation in admission might be considered as an important player in participating the pathological process of patients with SCH.

Abbreviations: ALC = absolute lymphocyte count, AMC = absolute lymphocyte count, ANC = absolute neutrophil count, AUC = area under the curve, CI = confidence interval, CT = computed tomography, GCS = Glasgow coma scale, GOS = Glasgow outcome scale, ICH = intracranial hemorrhage or intracerebral hemorrhage, IVH = intraventricular hemorrhage, NLR = neutrophil to lymphocyte ratio, OR = odds ratio, ROC = receiver operating curve, SAH = subarachnoid hemorrhage, SH = supratentorial hemorrhage, WBC = white blood count.

Keywords: biomarker, cerebellar hemorrhage, inflammation, neutrophil to lymphocyte ratio, outcome

Editor: Anwen Shao.

FZ, MY, YS, and CT conceived and coordinated the study, designed, performed and analyzed the experiments, and wrote the paper. CT, YR, WF, XL, TX, and FZ carried out the data collection and data analysis. CY, MY, and TX revised the paper. All authors reviewed the results and approved the final version of the manuscript.

Zhang F is supported by Sichuan University postdoctoral grant (2017SCU12048), West China Hospital postdoctoral grant (2018HXBH031), China postdoctoral science foundation grant (2018M633373) and Sichuan Health commission grant (18PJ425), Yang M is Catherine Bushnell fellow (2015). This study was also supported by Sichuan province science and technology grant (2015SZ0051) and West China hospital 135 academic excellence grant (2016102).

The authors have no conflicts of interest to disclose.

^a Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, China, ^b Department of Pathology, Case Western Reserve University, OH, ^c Department of Intensive Care Unit, Chengdu First People's Hospital, Chengdu, China, ^d Alan Edwards Centre for Research on Pain, ^e Department of Neurology and Neurosurgery, McGill University, Montreal, Canada, ^f Department of Neurosurgery, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China.

* Correspondence: Tao Xin, Sichuan University West China Hospital, Chengdu, Sichuan, China (e-mail: drxintao@yeah.net); Chao You, Sichuan University West China Hospital, Chengdu, Sichuan, China (e-mail: doctoryouchao@163.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2019) 98:25(e16120)

Received: 14 July 2018 / Received in final form: 4 May 2019 / Accepted: 27 May 2019

<http://dx.doi.org/10.1097/MD.00000000000016120>

1. Introduction

Intracerebral hemorrhage (ICH) accounts for 10% to 15% of all strokes in the Caucasian population,^[1,2] as well as affects 20% to 30% of Chinese population^[3,4] with high morbidity and mortality. Increasing evidences revealed that inflammatory responses play a critical role in secondary brain injury after ictus of ICH.^[5-9] And more recently, neutrophil to lymphocyte ratio (NLR) was identified as a novel inflammatory marker for predicting the prognosis of ICH patients at 1 month^[10] and 3 months.^[11,12] However, most of the cases that involved in current studies were supratentorial hemorrhage (SH).^[10-14] And the relationship between systemic inflammatory status and spontaneous cerebellar hemorrhage (SCH) has not been fully understood, yet.

As the subtype of ICH, SCH patients usually experience much poor prognosis^[15] than patients with other types of ICH. Meanwhile, they also exhibit higher prevalence of specific lethal complications, including brainstem compression and obstructive hydrocephalus, which are the major causes for massive tissue edema.^[16] Due to the well-accepted concepts on the relationship between brain edema and inflammation,^[17] the variation of inflammatory markers on patients with SCH may be different from ICH patients. Furthermore, SCH and ICH were always separately investigated due to distinctive anatomic structure (posterior fossa), different prognosis and surgical indications.^[15,18] Therefore, we aim to evaluate the potential association between inflammation (admission NLR) and short-term prognosis in patients with SCH.

2. Methods

2.1. Patient selection

We screened all the patients with spontaneous cerebellar hemorrhage that visited West China Hospital from February 2010 to October 2017. According to the inclusion criteria, patients were eligible when:

- (1) a diagnosis of spontaneous cerebellar hemorrhage by head computed tomography (CT) scan;
- (2) blood routine examination was conducted within 24 hours after ictus;
- (3) age ≥ 18 years old.

And exclusive criteria included:

- (1) secondary ICH attributed to aneurysm or vascular malformation or trauma or brain tumor;
- (2) clinical evidence of acute or chronic infection;
- (3) missing clinical or radiological data or loss of follow-up;
- (4) systemic inflammation induced by severe systemic diseases, including autoimmune disease, lung cancer, chronic heart disease, chronic obstructive pulmonary disease, uremia, severe renal dysfunction, pneumonia, acute or chronic infectious diseases;
- (5) medication which would directly affect immune condition, such as immunosuppressant drug, immunotherapy or anti-coagulants;
- (6) ischemia or hemorrhagic stroke happened within 6 months.

Protocol used in present study is approved by the Ethic Committee of West China Hospital, and all informed consents were collected from the patients or their guardians. This study was also conducted in accordance with relevant national regulations.

2.2. Clinical data

Baselines of clinical variable were obtained from electronic medical records, including age, gender, the systolic and diastolic blood pressure, smoking history, drinking history, hypertension, diabetes mellitus, and medical history of stroke due to cerebral ischemia or infarction or aneurysm. Results of routine blood tests were also collected, such as white blood cells (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC). Neutrophil to lymphocyte ratio (NLR) was measured as the ratio of the ANC to the ALC on admission. Short-term functional outcome was assessed by 30-day Glasgow outcome scale (GOS) scores by telephone or outpatient visiting. $GOS \leq 3$ was defined as unfavorable outcome including severe disability, persistent vegetative state, as well as death.

2.3. Radiological variables

CT scans were performed within 24 hours after ictus, and 2 neuroradiologists independently reviewed and assessed all the imagine features, including hematoma site, hematoma size, accompanying subarachnoid hemorrhage, intraventricular hemorrhage, cerebral infarction, acute obstructive hydrocephalus, brainstem compression, and fourth ventricle compression. Hematoma volume was calculated by applying ABC/2 method, whereas A is the greatest diameter, B is the greatest perpendicular line to A and C represents sum of thickness of slides of hematoma in the CT scans. Any discrepancy between 2 reviewers was solved by consensus.

2.4. Statistical analysis

All the baselines of clinical characteristic were compared between favorable and unfavorable outcomes, including clinical variables, laboratorial data, and radiological feature. Data were described as the mean \pm standard deviation, median with interquartile range (IQR) or frequency and percentage, respectively. Comparisons between each parameter were analyzed by independent *t* test, Mann-Whitney *U* test, Chi-square test or Fisher exact test, independently. The variables were identified by univariate analysis with a *P* value $< .10$ and then included into multivariable logistic regression model to evaluate association of prognosis and inflammatory biomarkers, as well as NLR. Receiver-operator analysis was applied to estimate the predictive ability of NLR for poor outcome in patients with cerebellar hemorrhage. Statistical significance was considered if *P* $< .05$. All the analyses were conducted by using SPSS 23.0.

3. Results

From February 2010 to October 2017, 107 consecutive patients (72 males and 35 females) with spontaneous cerebellar hemorrhage fulfilling the inclusive criteria were enrolled in this retrospective study (Detail exclusion of patients in Fig. 1). The mean age was 54.74 ± 12.04 years ranging from 32 to 84 years old. The mean baseline hematoma size was 3.12 ± 2.26 ml. Hypertension showed a high prevalence rate in SCH patients (70.1%) while there were 6 patients with diabetes. Subarachnoid hemorrhage (SAH) and intraventricular hemorrhage (IVH) occurred in 33 and 28 patients, respectively. The incidence of unfavorable outcome at day 30 was 57.9%. The features of included patients with or without poor outcome are shown in Table 1.

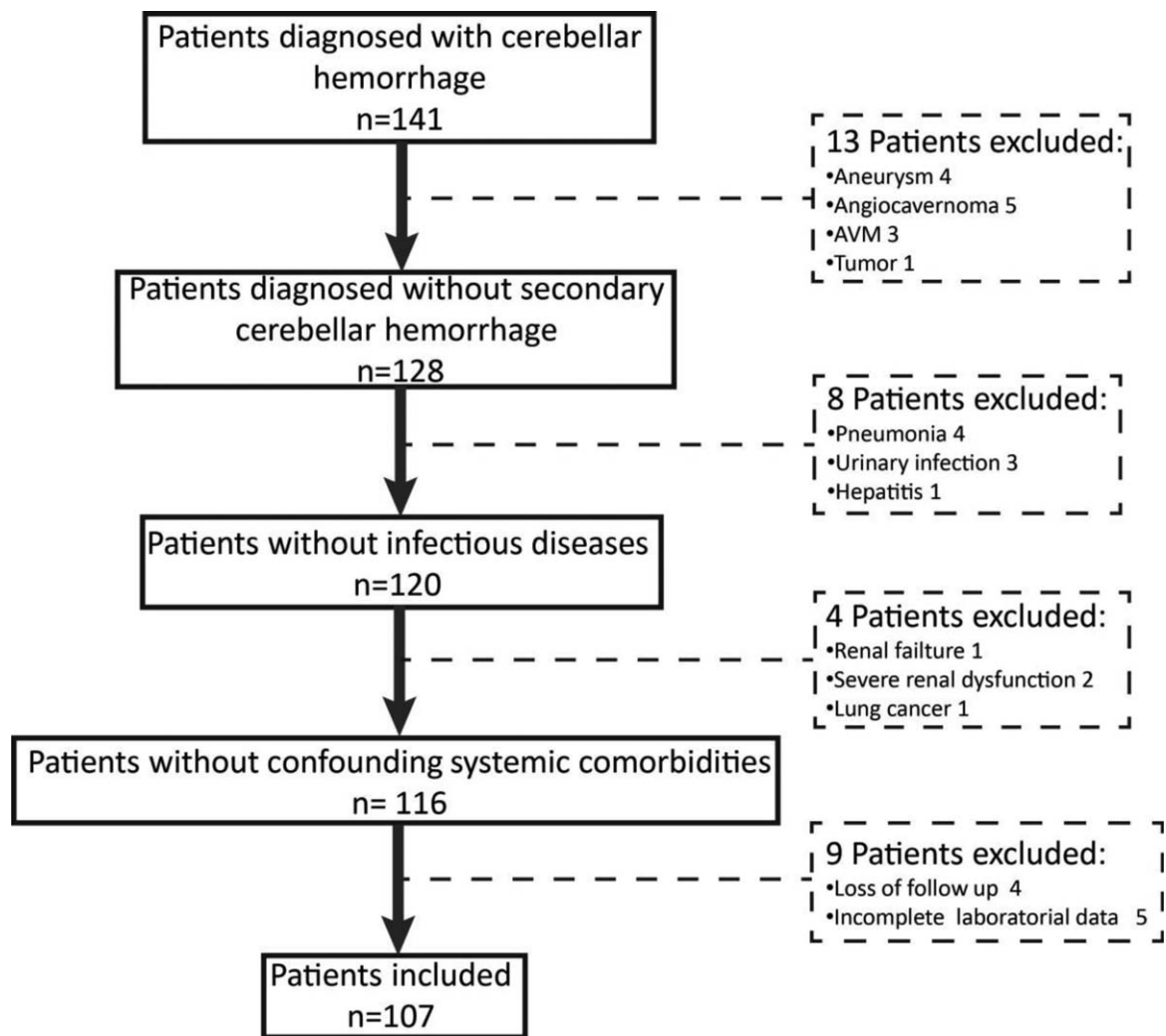


Figure 1. Flowchart of patient enrollment. AVM arteriovenous malformation.

The SCH patients with poor outcome exhibited larger hematoma, higher WBC, ANC and NLR, lower ALC, and Glasgow coma scale (GCS) scores, they were also more likely to present with IVH, hydrocephalus, brainstem and fourth ventricle compression (Table 1). In contrast to ICH patients, elderly patients with SCH seemed to have better short-term prognosis, although this trend did not reach a statistically significance ($P = .106$). We speculate that cerebellar atrophy in elderly patients might partially compensate the compression of adjacent vital tissue. Results from univariate analysis revealed that WBC, ANC, ALC, and NLR were associated with functional outcome, respectively (Table 2). After adjustment for potential confounding clinical variables, results from multivariable analysis demonstrated that only ANC, ALC, and NLR were durable predictive parameters for unfavorable outcome of SCH patients (Table 2).

The receiver operating curve (ROC) analysis was performed to compare the predictive abilities of relevant inflammatory predictors for poor outcome. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the area under the curve (AUC) of NLR for independently predicting poor outcome were 87.10%, 68.89%, 79.40%, 79.50%, and

0.751 respectively, whereas the best predictive cut-off value was 7.04. Fig. 2 shows the ROC curves and the AUC of laboratory parameters for predicting short-term prognosis of SCH patients. The NLR harbored the best predictive ability for 30 days poor outcome compared with other laboratory values. Spearman analysis revealed that GCS, IVH, WBC, ANC, ALC, AMC, systolic, and mean blood pressure were all correlated with NLR (Table 3). Furthermore, multiple linear regression analysis demonstrated that only admission GCS score, presence of IVH, ANC, and ALC independently predicted NLR (Table 4).

4. Discussion

We systematically investigated the impact of inflammatory response, as well as predictive ability of NLR for 30-day poor outcome of SCH patients. The major findings in the patients with SCH included:

- (1) admission GCS scores, presence of IVH, ANC, and ALC independently predicted NLR;
- (2) elevated NLR was independently and negatively associated with 30-day functional outcome of SCH patients;

Table 1
Baseline characteristics related to 30-day poor outcome in patients with cerebellum hemorrhage.

Characteristic	Baseline n=107	patients with favorable outcome (n=45)	patients with poor outcome (n=62)	P
Male	72 (67.3)	32 (71.1)	40 (64.5)	.473
Age, yr	54.74±12.04	56.96±11.70	53.13±12.12	.106
<50		42.92±3.84	43.73±4.44	.571
50 ≤ and ≤70		58.68±3.63	58.56±6.71	.933
>70		76.82±4.67	80.20±5.26	.272
Systolic blood pressure, mmHg	174.39±27.80	179.11±29.96	170.96±25.84	.136
Diastolic blood pressure, mmHg	100.36±19.16	100.28±17.01	100.41±20.71	.972
Mean arterial pressure, mmHg	125.02±20.25	126.54±20.54	123.92±20.50	.511
Medical history	–	–	–	–
Hypertension	75 (70.1)	35 (77.8)	40 (64.5)	.139
Diabetes mellitus	6 (5.6)	4 (8.9)	2 (3.2)	.209
Ischemic stroke	13 (12.1)	6 (13.3)	7 (11.3)	.749
Smoker	35 (32.7)	14 (31.1)	21 (33.9)	.764
Alcohol (>3 drinks per 24 hours)	33 (30.8)	13 (28.9)	20 (32.3)	.711
GCS score on admission	11 (8, 14)	14 (13, 15)	9 (7, 11)	<.001*
Hematoma size, mL	3.12±2.26	2.30±1.23	3.72±2.62	<.001*
Presence of SAH	33 (30.8)	14 (31.1)	19 (30.6)	.959
Presence of IVH	28 (26.2)	4 (8.9)	24 (38.7)	.001*
Hematoma site	–	–	–	.331
Cerebellar hemisphere	90 (84.2)	40 (88.9)	50 (80.6)	–
Vermis of Cerebellar	7 (6.5)	3 (6.7)	4 (6.5)	–
Hemisphere+Vermis	10 (9.3)	2 (4.4)	8 (12.9)	–
Horizontal hematoma extension	–	–	–	.263
Left	52 (48.6)	24 (53.3)	28 (45.2)	–
Right	43 (40.2)	18 (40.0)	25 (40.3)	–
Middle	7 (6.5)	3 (6.7)	4 (6.5)	–
Bilateral	5 (4.7)	0 (0)	5 (4.7)	–
Brainstem compression	26 (24.3)	5 (11.1)	21 (33.9)	.007*
Fourth ventricle compression	42 (39.3)	12 (26.7)	30 (48.4)	.028*
Hydrocephalus	29 (27.1)	5 (11.1)	24 (38.7)	.002*
WBC 10 ⁹ /L	13.25±4.52	11.58±5.21	14.46±3.53	.001*
ANC 10 ⁹ /L	11.05±4.48	9.54±5.12	12.14±3.62	.003*
ALC 10 ⁹ /L	1.21±0.53	1.37±0.52	1.10±0.53	.011*
AMC 10 ⁹ /L	0.62±0.24	0.62±0.25	0.63±0.24	.919
NLR	9.30 (5.69, 14.85)	5.87 (3.79, 9.92)	11.75 (8.70, 16.36)	<.001*

Data are expressed as n (%), mean ± standard deviation, median (interquartile range), as appropriate.

SAH=subarachnoid hemorrhage; IVH=intraventricular hemorrhage; GCS=Glasgow coma scale; WBC=white blood cells; ANC=admission neutrophil count; ALC=admission lymphocyte count; AMC=admission monocyte count; NLR=neutrophil to lymphocyte ratio.

(3) the critical threshold of NLR is 7.04, which was identified for predicting 30-day outcome of ICH.

Moreover, ANC and ALC were also identified as independent prognostic factors for 30-day poor outcome in SCH patients. Up to date, this is the first research in estimating the predictive ability of NLR for the prognosis in SCH patients.

It is well documented that cerebrovascular diseases, including ischemia stroke, subarachnoid hemorrhage, and ICH were

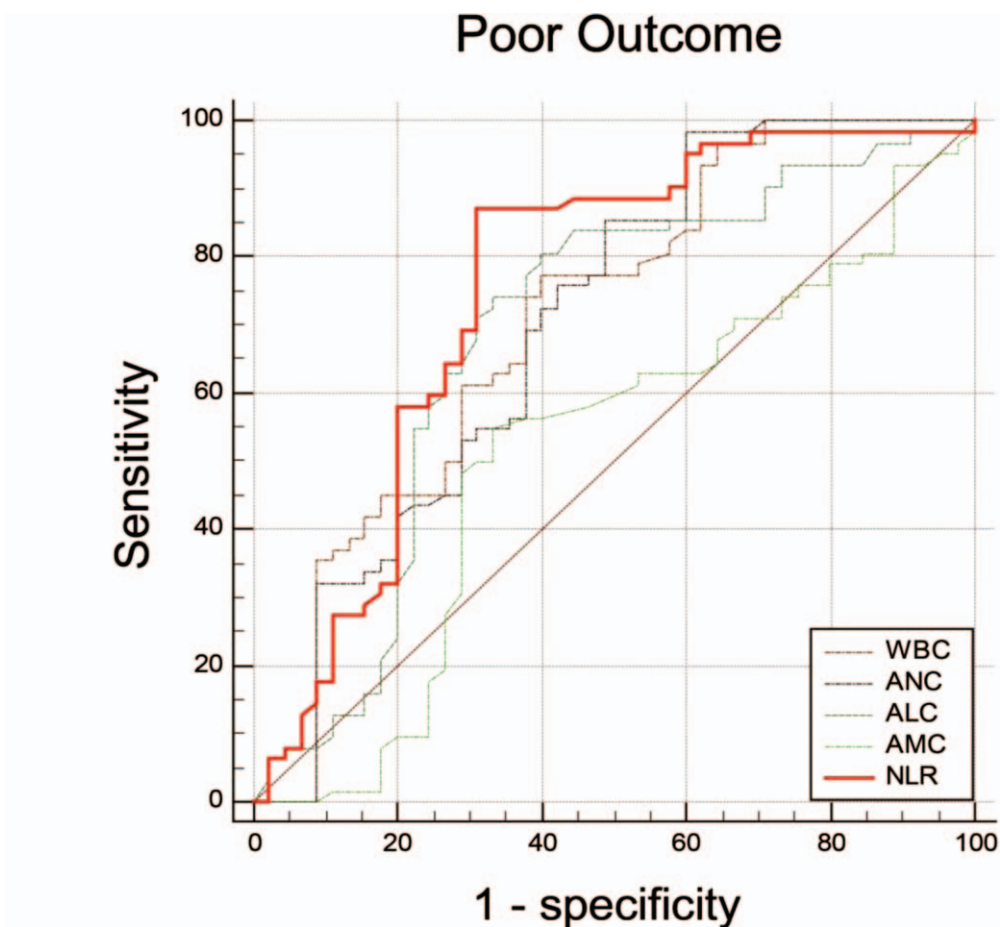
associated with local and/or systemic inflammation.^[5] As one of the most important clinical parameters for inflammation, absolute leukocyte counts are usually used to evaluate immune status in patients with different diseases. Previous studies indicated that neutrophils mediated blood-brain barrier injury and white matter damage resulted in neurotoxicity after ICH by releasing matrix metalloproteinase, TNF- α , elastase, and reactive oxygen species,^[19–21] whereas lymphocytes played a critical role

Table 2
Associations of laboratory values on admission with poor outcome in patients with SCH.

Characteristic	Crude		Adjusted	
	OR (CI)	P	OR (CI)	P
WBC	1.171 (1.060–1.293)	<.01	1.014 (0.889–1.155)	.839
ANC	1.155 (1.046–1.274)	<.01	1.207 (1.082–1.450)	<.01
ALC	0.347 (0.145–0.827)	<.01	0.265 (0.095–0.744)	.01
NLR	1.129 (1.050–1.214)	<.01	1.785 (1.463–2.666)	<.01

Adjustment by brainstem compression, fourth ventricle compression, hydrocephalus, presence of IVH, GCS score, and hematoma volume.

SCH=spontaneous cerebellar hemorrhage; CI=confidence interval; OR=odds ratio; WBC=white blood cells; ANC=absolute neutrophil count; ALC=admission lymphocyte count; NLR=neutrophil to lymphocyte ratio.



	Sensitivity	Specificity	PPV	NPV	Cut-off point	AUC	p
WBC	77.42%	60.00%	72.70%	65.90%	11.17	0.707	<0.001
ANC	98.39%	40.00%	69.30%	94.70%	6.87	0.701	<0.001
ALC	74.19%	66.67%	75.40%	65.20%	1.23	0.687	<0.001
AMC	54.84%	66.67%	69.40%	51.70%	0.59	0.515	0.806
NLR	87.10%	68.89%	79.40%	79.50%	7.04	0.751	<0.001

Figure 2. Receiver operating characteristic curves of WBC, ALC, ANC, AMC, and NLR. WBC White blood cells; ANC=Admission neutrophil count; ALC= Admission lymphocyte count; AMC=Admission monocyte count; NLR=Neutrophil to lymphocyte ratio.

in host defense.^[22,23] Numbers of clinical and experimental studies^[5,7,11,21] demonstrated that elevated WBC and ANC and decreased ALC due to ICH-induced inflammatory contributed to the secondary brain injury and associated with poor neurological function outcomes. However, these studies mostly based on the cases of ICH patients with SH, which has different pathological processes and alternative treatment strategies by comparing with SCH. For instance, strong evidence from WHO guideline indicated that surgical evacuation should be performed when SCH patients present the symptoms or signs of brainstem compression/obstructive hydrocephalus, whereas the indications of surgery for SH patients are still controversial.^[24] Notably, due to the vital structures (i.e., brainstem or fourth ventricle), patients with SCH may arrive worse symptoms at nadir faster than other ICH patients, thus lead to higher percentiles for both morbidity and mortality. The limited space for the characterized anatomic

structure of posterior fossa could also make the SCH patients more sensitive to edema, which is often caused by inflammatory response.^[16] Lastly, activation of endothelial cells is markedly different in anterior and posterior circulation after stroke.^[25,26] Overall the evidences listed above, the differences between SCH and SH were not only the location of hematoma but also the pathological process after ictus. Furthermore, findings from clinical research indicated that the pathological progressions may vary between SCH and SH. Warfarin-treated patients could only prevent the hematoma formation in infratentorial area,^[27] but increased serum homocysteine on hematoma volume in thalamoganglionic ICH.^[28]

Our present study revealed that SCH patients with 30-day poor outcomes exhibited higher WBC and ANC, as well as lower ALC. The similar results were reported by Lattanzi et al^[12] increasing of neutrophils (odds ratio [OR]: 1.22 95% confidence

Table 3**Spearman correlation analysis with neutrophil to lymphocyte ratio in patients with SCH.**

Characteristic	NLR
Male	$r = -0.110$ ($P = .262$)
Age, yr	$r = -0.086$ ($P = .379$)
Systolic blood pressure, mmHg	$r = 0.352$ ($P < .001$)*
Diastolic blood pressure, mmHg	$r = 0.144$ ($P = .138$)
Mean arterial pressure, mmHg	$r = 0.211$ ($P = .029$)*
Hypertension	$r = 0.071$ ($P = .465$)
Diabetes mellitus	$r = -0.189$ ($P = .051$)
Ischemic stroke	$r = 0.076$ ($P = .437$)
Smoker	$r = -0.116$ ($P = .234$)
Drinking	$r = 0.052$ ($P = .596$)
GCS score on admission	$r = -0.365$ ($P < .001$)*
Hematoma size	$r = -0.033$ ($P = .765$)
Presence of SAH	$r = -0.105$ ($P = .281$)
Presence of IVH	$r = 0.276$ ($P = .004$)*
Hematoma site	$r = 0.002$ ($P = .984$)
Horizontal hematoma extension	$r = -0.089$ ($P = .363$)
Brainstem compression	$r = 0.035$ ($P = .724$)
Fourth ventricle compression	$r = 0.151$ ($P = .121$)
Hydrocephalus	$r = 0.015$ ($P = .881$)
WBC	$r = 0.713$ ($P < .001$)*
ANC	$r = 0.815$ ($P < .001$)*
ALC	$r = -0.693$ ($P < .001$)*
AMC	$r = 0.283$ ($P = .003$)*

Data are expressed as n (%), mean \pm standard deviation, median (interquartile range), as appropriate. SCH = spontaneous cerebellar hemorrhage; SAH = subarachnoid hemorrhage; IVH = intraventricular hemorrhage; GCS = Glasgow coma scale; WBC = white blood cells; ANC = admission neutrophil count; ALC = admission lymphocyte count; AMC = admission monocyte count; NLR = neutrophil to lymphocyte ratio.

interval [CI]: 1.03–1.44, $P = .023$) and decreasing of lymphocytes (OR: 0.57 95% CI: 0.33–0.99, $P = .046$) cooperated to predict the poor outcomes of SH patients at 3 months after ictus. Tao et al^[12] further confirmed this result with large sample studies by using more strictly exclusion criteria. In associating with our current data, these results revealed that inflammation plays a critical role for functional outcome in the patients with SCH. As the exact underlying mechanism remains unknown, we hypothesized that inflammation leads to a severe perihematomal edema^[29], and patients with SCH might be more sensitive to brain edema, which may result in compression of brainstem and fourth ventricle. Meanwhile, secondary brain injury resulting from the inflammatory cytokines or neutrophil-associated neurotoxicity could increase neuronal damage in the adjacent crucial brainstem region, which functionally triggers severe symptoms, such as coma and rapid neurological function deterioration. Moreover, low ALC impaired host defense and more easily to be infected in hospital.

As a novel systemic inflammatory marker for central nervous diseases, NLR was studied in stroke for years.^[30,31] Despite of ischemic size, NLR has been demonstrated to associate with both short-term and long-term mortality in patients after ischemic stroke.^[32,33] In addition, NLR has also been identified as an independent predictor in ICH patients for 30-day mortality^[10] and 90-day mortality^[31], as well as the unfavorable outcomes.^[11] Previously studies elucidated the predictive ability of larger hematoma volumes in elevating NLR level and poor outcome in patients with SH (hematoma size usually >20 mL). However, it is unknown whether the relatively small hematoma size associated with NLR level is relating to the functional outcomes of SCH patients (hematoma size commonly <10 mL). Here, we revealed

Table 4**Multivariable linear regression with neutrophil to lymphocyte ratio.**

Characteristic	NLR	
	Standardized coefficient	P
Systolic blood pressure, mmHg	-0.047	.657
Diastolic blood pressure, mmHg	0.031	.776
GCS score on admission	-0.212	$<.001$
Presence of IVH	0.127	.011
WBC	-0.057	.828
ANC	0.731	.006
ALC	-0.489	$<.001$
AMC	-0.032	.573

NLR adjusted by systolic blood pressure, mean arterial pressure, GCS score on admission, presence of IVH, WBC, ANC, ALC, AMC.

IVH = intraventricular hemorrhage; GCS = Glasgow coma scale; WBC = white blood cells; ANC = admission neutrophil count; ALC = admission lymphocyte count; AMC = admission monocyte count; NLR = neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio.

that NLR showed excellent predictive ability of 1-month unfavorable outcome in SCH patients with a cut-off value of 7.04, which was consistent to the reported range of NLR (4.58–7.35) in the SH researches.^[10–12] As a systemic inflammatory parameter, elevating of NLR is also related to secondary brain injury and/or infection after ICH onset. It is well documented that systematic inflammatory reaction syndrome^[34] and/or post-stroke infectious complications^[35] could further aggravate the symptoms of ICH in patients, thus lead to an unfavorable outcome. In fact, NLR might be affected under several interference factors such as age, brain edema, and hematoma size. Li et al^[36] reported that elders exhibit higher NLR in health population, and Gusdon's study^[29] demonstrated that NLR is associated with brain edema growth in ICH patients. Accordingly, our univariate analyses results to identify the confounding factors in SCH patients. Brainstem compression, fourth ventricle compression, hydrocephalus, presence of IVH, GCS score and hematoma volume were associated with poor outcome. After adjustment for these factors, NLR still remains associated with the prognosis of SCH. Therefore, we found that NLR represented a steady prognostic predictor for ICH patients.

Our Spearman's analysis indicated that ANC, ALC, presence of IVH and GCS score on admission were all independently correlated with NLR. Other than that, NLR also exhibited the best predictive ability for the short-term outcome of SCH patients among all the inflammatory markers, such as WBC, ANC, ALC, and AMC, which could be altered by stress ulcer bleeding, dehydration, or overhydration. Actually, these results are not surprised since NLR not only provides more information on pro-inflammation and host defense activity^[11] but also brings us the dynamic balance of innate and adaptive immune responses during the disease onset. Therefore, we concluded that NLR presently exhibits better predictive ability than any other markers from blood tests from patients with SCH.

We admitted that several limitations still exist in our studies. First of all, the dynamic changes of NLR could not be investigated in this study due to the shortcoming of retrospective design. Following, although the multiple regression analysis was performed to minimize confounding effect, but we still could not exclude the possibility that the values of NLR were altered by lots of conditions, including hypertension, diabetes mellitus, and ischemic stroke. Thirdly, the calculation method of ABC/2 for hematoma volume is slightly less accurate than other methods. Moreover, since all individuals are from West China Hospital,

which is the largest hospital in middle-west and ranking number 2 in China. Due to the medical referral system, most of them might be in worse clinical condition, thus would lead to a potential bias of our studies. At last, the diagnosis of brainstem compression was only relying on radiological findings and clinical signs.

5. Conclusion

Increasing of admission NLR could independently predict the poor outcome of SCH patients at 1-months. And it also showed an excellent predictive ability for short-term prognosis of SCH. Our present study implies that inflammation may influence the functional outcomes of SCH by inducing brainstem compression and fourth ventricle compression. Further researches should be urgently conducted to concentrate on underlying pathological progression regarding with association between inflammatory states in setting of SCH.

Author contributions

Conception and design: Zhang F, Yang M, Shi Y, and Tao C. Acquisition of data: Ren Y, Fu W, Shi Y, Tao C, Zhang F, and Li X.

Analysis and interpretation of data: Zhang F, Yang M, Xin T. Drafting the article: Zhang F, Yang M and Tao C, Li X, and You C.

Supervision: Yang M, Xin T, and You C.

Review & editing: All the authors.

Conceptualization: Fan Zhang, Chao You.

Data curation: Fan Zhang, Yanming Ren, Yan Shi, Wei Fu, Chuanyuan Tao, Xi Li, Mu Yang, Tao Xin.

Formal analysis: Fan Zhang, Yanming Ren, Yan Shi, Mu Yang, Tao Xin.

Funding acquisition: Fan Zhang, Mu Yang, Chao You.

Investigation: Fan Zhang, Yanming Ren, Wei Fu, Chuanyuan Tao, Xi Li, Mu Yang.

Methodology: Yanming Ren, Wei Fu, Chuanyuan Tao, Mu Yang.

Project administration: Yanming Ren, Mu Yang.

Resources: Yanming Ren, Xi Li, Mu Yang, Chao You.

Software: Fan Zhang, Chuanyuan Tao.

Supervision: Tao Xin, Chao You.

Validation: Fan Zhang, Mu Yang.

Visualization: Mu Yang, Chao You.

Writing – original draft: Fan Zhang, Chuanyuan Tao, Chao You.

Writing – review & editing: Wei Fu, Chuanyuan Tao, Mu Yang, Tao Xin, Chao You.

References

- Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. *Lancet* 2009;373:1632–44.
- 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.
- Zhang LF, Yang J, Hong Z, et al. Proportion of different subtypes of stroke in China. *Stroke* 2003;34:2091–6.
- Yang QD, Niu Q, Zhou YH, et al. Incidence of cerebral hemorrhage in the Changsha community. A prospective study from 1986 to 2000. *Cerebrovasc Dis* 2004;17:303–13.
- Wang J, Dore S. Inflammation after intracerebral hemorrhage. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab* 2007;27:894–908.
- Morotti A, Phuah CL, Anderson CD, et al. Leukocyte count and intracerebral hemorrhage expansion. *Stroke* 2016;47:1473–8.
- Mracsko E, Javidi E, Na SY, et al. Leukocyte invasion of the brain after experimental intracerebral hemorrhage in mice. *Stroke* 2014;45:2107–14.
- Aronowski J, Zhao X. Molecular pathophysiology of cerebral hemorrhage: secondary brain injury. *Stroke* 2011;42:1781–6.
- Silva Y, Leira R, Tejada J, et al. Molecular signatures of vascular injury are associated with early growth of intracerebral hemorrhage. *Stroke* 2005;36:86–91.
- 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;25:182–7.
- Lattanzi S, Cagnetti C, Provinciali L, et al. Neutrophil-to-lymphocyte ratio predicts the outcome of acute intracerebral hemorrhage. *Stroke* 2016;47:1654–7.
- Tao C, Hu X, Wang J, et al. Admission neutrophil count and neutrophil to lymphocyte ratio predict 90-day outcome in intracerebral hemorrhage. *Biomark Med* 2017;11:33–42.
- Sun Y, You S, Zhong C, et al. Neutrophil to lymphocyte ratio and the hematoma volume and stroke severity in acute intracerebral hemorrhage patients. *Am J Emerg Med* 2017;35:429–33.
- Giede-Jeppe A, Bobinger T, Gerner ST, et al. Neutrophil-to-lymphocyte ratio is an independent predictor for in-hospital mortality in spontaneous intracerebral hemorrhage. *Cerebrovasc Dis* 2017;44:26–34.
- Wu YT, Li TY, Chiang SL, et al. Predictors of first-week mortality in patients with acute spontaneous cerebellar hemorrhage. *Cerebellum* 2013;12:165–70.
- Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. *Lancet Neurol* 2015;14:914–25.
- Zheng H, Chen C, Zhang J, et al. Mechanism and therapy of brain edema after intracerebral hemorrhage. *Cerebrovasc Dis* 2016;42:155–69.
- Pong V, Chan KH, Chong BH, et al. Long-term outcome and prognostic factors after spontaneous cerebellar hemorrhage. *Cerebellum* 2012;11:939–45.
- Yamasaki Y, Matsuo Y, Zagorski J, et al. New therapeutic possibility of blocking cytokine-induced neutrophil chemoattractant on transient ischemic brain damage in rats. *Brain Res* 1997;759:103–11.
- Moxon-Emre I, Schlichter LC. Neutrophil depletion reduces blood-brain barrier breakdown, axon injury, and inflammation after intracerebral hemorrhage. *J Neuropathol Exp Neurol* 2011;70:218–35.
- Nguyen HX, O'Barr TJ, Anderson AJ. Polymorphonuclear leukocytes promote neurotoxicity through release of matrix metalloproteinases, reactive oxygen species, and TNF-alpha. *J Neurochem* 2007;102:900–12.
- Liesz A, Ruger H, Purrucker J, et al. Stress mediators and immune dysfunction in patients with acute cerebrovascular diseases. *PLoS One* 2013;8:e74839.
- Meisel C, Schwab JM, Prass K, et al. Central nervous system injury-induced immune deficiency syndrome. *Nat Rev Neurosci* 2005;6:775–86.
- Hemphill JC3rd, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2015;46:2032–60.
- Kim JS, Nah HW, Park SM, et al. Risk factors and stroke mechanisms in atherosclerotic stroke: intracranial compared with extracranial and anterior compared with posterior circulation disease. *Stroke* 2012;43:3313–8.
- Perko D, Pretnar-Oblak J, Sabovic M, et al. Differences between cerebrovascular reactivity to L-arginine in the anterior and posterior cerebral circulation. *Cerebrovasc Dis* 2011;31:358–64.
- Ma M, Meretoja A, Churilov L, et al. Warfarin-associated intracerebral hemorrhage: volume, anticoagulation intensity and location. *J Neurol Sci* 2013;332:75–9.
- Zhou F, Chen B, Chen C, et al. Elevated homocysteine levels contribute to larger hematoma volume in patients with intracerebral hemorrhage. *J Stroke Cerebrovasc Dis* 2015;24:784–8.
- Gusdon AM, Gialdini G, Kone G, et al. Neutrophil-lymphocyte ratio and perihematomal edema growth in intracerebral hemorrhage. *Stroke* 2017;48:2589–92.
- Tokgoz S, Kayrak M, Akpınar Z, et al. Neutrophil lymphocyte ratio as a predictor of stroke. *J Stroke Cerebrovasc Dis* 2013;22:1169–74.
- Tao C, Wang J, Hu X, et al. Clinical value of neutrophil to lymphocyte and platelet to lymphocyte ratio after aneurysmal subarachnoid hemorrhage. *Neurocrit Care* 2017;26:393–401.

- [32] Brooks SD, Spears C, Cummings C, et al. Admission neutrophil-lymphocyte ratio predicts 90 day outcome after endovascular stroke therapy. *J Neurointerv Surg* 2014;6:578–83.
- [33] Tokgoz S, Keskin S, Kayrak M, et al. Is neutrophil/lymphocyte ratio predict to short-term mortality in acute cerebral infarct independently from infarct volume. *J Stroke Cerebrovasc Dis* 2014;23:2163–8.
- [34] Boehme AK, et al. Systemic inflammatory response syndrome and outcomes in intracerebral hemorrhage. *Neurocrit Care* 2016;25:133–40.
- [35] Dirnagl U, Klehmet J, Braun JS, et al. Stroke-induced immunodepression: experimental evidence and clinical relevance. *Stroke* 2007;38:770–3.
- [36] Li J, Chen Q, Luo X, et al. Neutrophil-to-lymphocyte ratio positively correlates to age in healthy population. *J Clin Lab Anal* 2015;29:437–43.