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Early increase of neutrophil-to-lymphocyte ratio predicts 30-day mortality in patients with spontaneous intracerebral hemorrhage

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Summary

Aims: To examine whether early rise of neutrophil-to-lymphocyte ratio (NLR) after patient hospitalization correlates with 30-day mortality in patients with spontaneous intracerebral hemorrhage (ICH).

Methods: This retrospective study included all patients receiving treatment for spontaneous ICH between January 2015 and September 2016 at the Jiading District Central Hospital Affiliated Shanghai University of Medicine & Health Sciences in Shanghai, China. NLR was determined at admission (T1), at 24-48 hours (T2) and 5-7 days (T3). NLR and clinicopathologic features were compared between those who survived for >30 days vs not. Multivariate regression was used to identify risk factors for 30-day mortality.

Results: A total of 275 subjects were included in the analysis: 235 survived for at least 30 days; the remaining 40 subjects died within 30 days. The patients who died within 30 days had higher ICH score, larger ICH volume, and lower GCS score (all $P < 0.05$). In comparison with the baseline (NLR_{T1}), NLR at 24-48 hours (NLR_{T2}) and 5-7 days (NLR_{T3}) was significantly higher in patients who died within 30 days ($P < 0.05$), but not in patients surviving for >30 days. In the multivariate analysis, the 30-day mortality was associated with both NLR_{T2} (OR 1.112, 95%CI 1.032-1.199, $P = 0.006$) and NLR_{T3} (OR 1.163, 95%CI 1.067-1.268, $P = 0.001$). Spearman correlation analysis showed that both NLR_{T2} and NLR_{T3} correlated inversely with GCS score and positively with ICH score and ICH volume at the baseline.

Conclusions: Early rise of NLR predicts 30-day mortality in patients with spontaneous ICH.

KEYWORDS

inflammation, mortality, neutrophil-to-lymphocyte ratio, spontaneous intracerebral hemorrhage

The first two authors contributed equally to this study.

1 | INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) refers to nontraumatic rupture of primary intracranial blood vessels, allowing blood to flow into the brain parenchyma or cerebral ventricles, resulting in the formation of hematoma that causes neuronal and glial injury and subsequent inflammatory response.[1] ICH carries high risk of morbidity and mortality.[2]

Inflammatory response in ICH is intimately associated with hematoma expansion.[3] Neutrophil-to-lymphocyte ratio (NLR) is an important determinant of inflammatory response[4] and has been proposed as a prognostic indicator in many clinical contexts, including short-term morbidity and mortality after acute ischemic stroke, ST segment-elevated myocardial infarction, and acute cardiac insufficiency.[5-7] NLR has also been used as a predictor of long-term morbidity and mortality in malignancy, autoimmune diseases, and metabolic syndrome.[8-11] In patients with ICH, NLR has been closely associated with 30-day mortality and 90-day disability as well as risk of cerebral hematoma enlargement.[3,12-14]

NLR varies with severity of bleeding during hemorrhagic transformation after cerebral thrombolysis[15] and with the duration between ICH onset and blood sampling.[12,16,17] The fact that NLR changes with ICH progression raises the question of under what conditions.[13] NLR is a useful prognostic indicator in ICH. In this study, we examined the relationship between NLR at different time points and 30-day mortality in patients with spontaneous ICH.

2 | METHODS

2.1 | Study subjects

The initial screen included 307 patients receiving treating for spontaneous ICH at the Jiading District Central Hospital Affiliated Shanghai University of Medicine & Health Sciences between January 2015 and September 2016. For inclusion in data analysis, subjects must meet the following criteria: (i) first attack of spontaneous ICH, verified by CT scans; 2) age ≥18 years. Subjects were excluded from analysis if (i) hospital admission was >24 hours after disease onset; (ii) comorbidity with hematologic disorders or a history of malignancy; (iii) use of immunosuppressants of anticoagulants; (iv) a history of infection within the past 2 weeks; (v) stroke within the past 6 months. The final analysis included 275 patients (75.7% men; age range, 27-94 years). The diagnosis was established by computed tomography (CT) and conforms to the criteria of the American Heart Association and American Stroke Association[18] in all 275 cases.

2.2 | Study methods

Demographic information, medical history (eg, hypertension and diabetes), Glasgow coma scale (GCS) score, and head CT scan results were retrieved from medical records. Hemorrhage location was recorded as supra- vs infratentorial based on head CT. Hematoma volume was calculated using the ABC/2 software[19] and the formula $a \times b \times c \times 1/2$, where a refers to hematoma thickness, and b and c refer to the largest vertical diameters of the high-intensity region on CT scan. ICH score was calculated based on clinical data and CT results.[20]

Venous blood was obtained at admission (T1; n = 275), at 24-48 hours after admission (T2; n = 268), and at 5-7 days after admission (T3; n = 256). For comparison, study subjects were divided artificially into a subgroup surviving for > 30 days (n = 235) vs a subgroup who died within 30 days (n = 40).

2.3 | Statistical methods

Data were analyzed using SPSS 19.0 (IBM, Chicago, IL, USA). All continuous variables are expressed as median (interquartile range, IQR) and were analyzed using the nonparametric Mann-Whitney test. Categorical data are expressed as frequencies and were analyzed using the chi-squared test. Changes of NLR over time were examined using repeated-measurements test. Spearman correlation was used to analyze factors associated with NLR. Multivariate logistic regression was used to identify risk factors for 30-day mortality. $P < 0.05$ was considered statistically significant.

2.4 | Ethical approval

The study protocol was approved by the Ethics Review Board of Jiading District Central Hospital (2017-ZD-03). All subjects were de-anonymized. Written informed consent was waived by the Ethics Review Board.

3 | RESULTS

A total of 275 subjects were included in the analysis: 235 survived for at least 30 days; the remaining 40 subjects died within 30 days. In comparison with those who survived for at least 30 days, subjects who died within 30 days had significantly lower GCS score, higher score, and hemorrhage volume ($P < 0.05$ for all; Table 1).

The two groups had comparable NLR at admission (Figure 1). In subjects who died within 30 days, early increase in NLR was apparent: NLR was 2.4 (1.4-6.9) upon admission (T1), 11.3 (8.0-19.4) at 24-48 hours (T2), and 12.9 (3.2-20.1) at 5-7 days (T3; $P = 0.037$). In the subjects who survived for at least 30 days, NLR remained relatively stable: 3.3 (1.9-6.1) at T1, 4.9 (2.8-7.9) at T2, and 4.2 (2.5-6.3) at T3 ($P = 0.122$). At both T2 and T3, NLR was significantly higher in those who died within 30 days ($P < 0.05$).

In multivariate regression, ICH volume, NLR_{T2}, and NLR_{T3} were independent risk factors for 30-day mortality, even after adjustment for other variables (Table 2). NLR_{T1} was not associated with 30-day mortality.

TABLE 1 Clinicopathologic features in patients who survived or died within 30 d

	Survived (n = 235)	Died (n = 40)	P
Demographics			
Male, n (%)	178 (75.7)	29 (72.5)	0.660
Age in yr, median (P_{25},P_{75})	69 (53, 79)	71 (52, 82)	0.889
Age ≥80 yr, n (%)	57 (24.3)	12 (30.0)	0.439
Comorbidities, n (%)			
Hypertension	171 (72.8)	27 (67.5)	0.493
Diabetes	29 (12.3)	5 (12.5)	0.977
Smoking	126 (53.6)	25 (62.5)	0.297
Alcohol drinking	97 (41.3)	14 (35.0)	0.454
Atrial fibrillation	49 (20.9)	13 (32.5)	0.103
Cerebrovascular disease family history	1 (0.4)	0 (0.0)	1.000
Dyslipidemia	62 (26.4)	13 (32.5)	0.422
Duration from onset to hospitalization, h	5.0 (2.0, 15.1)	6.3 (2.7, 11.6)	0.936
Site of bleeding, n (%)			
Supratentorial	207 (88.1)	33 (82.5)	0.327
Infratentorial	28 (11.9)	7 (17.5)	
ICH volume in mL, median (P_{25},P_{75})	8.9 (3.3, 22.4)	45.6 (20.1, 80.0)	**<0.001**
ICH volume ≥30 mL, n (%)	42 (17.9)	27 (67.5)	**<0.001**
Concurrent ventricular hemorrhage, n (%)	58 (24.7)	13 (32.5)	0.296
GCS score, median (P_{25},P_{75})	14.0 (12.0, 15.0)	8.0 (5.0, 11.0)	**<0.001**
ICH score, median (P_{25},P_{75})	1.0 (0.0, 2.0)	3.0 (2.0, 3.0)	**<0.001**
Blood pressure in mm Hg, median (P_{25},P_{75})			
Systolic at admission	163 (144, 184)	170 (141, 190)	0.492
Diastolic at admission	90 (78, 103)	88 (74, 102)	0.633
Systolic at 24 h after admission	148 (132, 160)	147 (131, 158)	0.571
Diastolic at 24 h after admission	82 (75, 91)	87 (73, 92)	0.990
Drug use within first week			
Mannitol	168 (71.5)	33 (82.5)	0.147
Hyperosmolar saline	17 (7.2)	3 (7.5)	0.952
Corticosteroids	22 (9.4)	7 (17.5)	0.121
Anti-epileptic drugs	7 (3.0)	3 (7.5)	0.165
Subject number at various times			
T1	275	0	
T2	268	7	
T3	256	19	

GCS, Glasgow coma scale; ICH, intracerebral hemorrhage.
The bold values indicate P < 0.05.
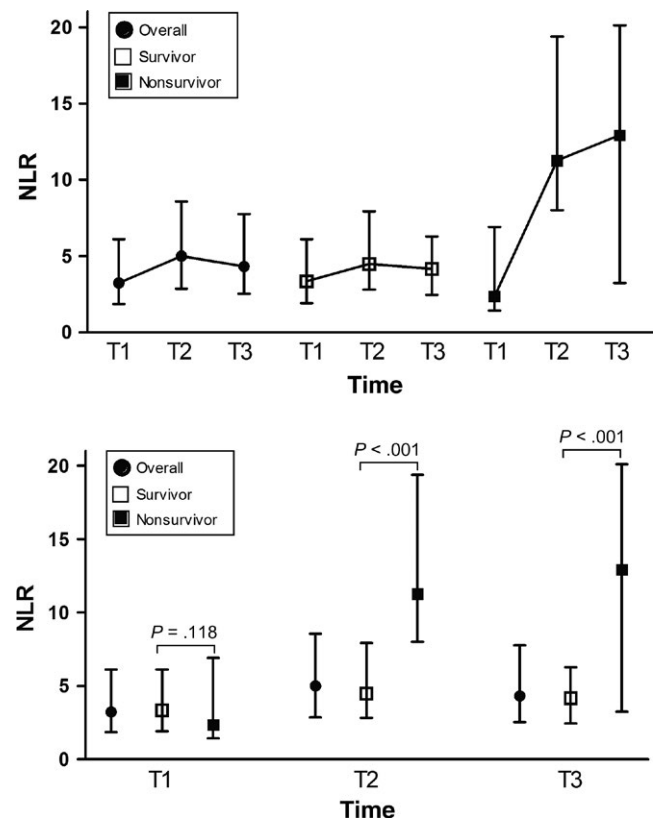
FIGURE 1 NLR over time in the subjects who died within 30 d versus in those surviving for >30 d. T1, at admission; T2, 24-48 h after admission; T3, 5-7 d after admission

Spearman correlation analysis showed that NLR_{T2} and NLR_{T3} correlated positively with hemorrhage volume, ICH scores, and mortality, and negatively with GCS score (all P < 0.05; Table 3). NLR_{T1} did not correlate with any variables.

4 | DISCUSSION

The present study found early increase in NLR after admission in subjects who died within 30 days. NLR within the first week after admission (both 24-48 hours and 5-7 days), but not upon admission, closely correlated with 30-day mortality.

Inflammatory response plays an important role in spontaneous ICH. Higher number of leukocytes, neutrophils, mononuclear cells, and other inflammatory cells correlates with poorer prognosis.[21-23] As a surrogate marker for inflammation, NLR is not influenced by exercise and dehydration.[24] In patients with spontaneous ICH, NLR is closely related to enlargement of hematoma[17] and predicts 30-day morbidity and mortality.[13] Increased NLR is also related to increased 90-day morbidity and mortality and decreased quality of life,[14] and has been shown to be an independent risk for ICH development in diabetic patients.[25] NLR increases with severity of hemorrhagic transformation and with time following cerebral thrombolysis.[15] Given that fact that inflammation occurs through all stages in patients with spontaneous ICH,[26] it is reasonable to

TABLE 2 Potential factors associated with 30-day mortality: results of multivariate regression

	OR	95% CI		P
Model 1				
Male	2.502	0.948	6.601	0.064
Age	1.005	0.978	1.033	0.718
NLR_{T1}	1.039	0.973	1.110	0.253
ICH volume	1.029	1.013	1.045	**<0.001**
GCS score	0.838	0.740	0.948	**0.005**
Infratentorial hemorrhage	3.213	1.028	10.041	**0.045**
Concurrent ventricular hemorrhage	1.387	0.558	3.446	0.482
Model 2				
Male	2.951	0.719	12.118	0.133
Age	1.013	0.970	1.058	0.546
NLR_{T2}	1.112	1.032	1.199	**0.006**
ICH volume	1.032	1.010	1.054	**0.004**
GCS score	0.892	0.747	1.066	0.209
Infratentorial hemorrhage	4.021	0.840	19.250	0.082
Concurrent ventricular hemorrhage	2.143	0.494	9.290	0.309
Model 3				
Male	2.587	0.507	13.199	0.253
Age	1.008	0.958	1.060	0.771
NLR_{T3}	1.163	1.067	1.268	**0.001**
ICH volume	1.033	1.008	1.058	**0.011**
GCS score	0.926	0.752	1.141	0.471
Infratentorial hemorrhage	4.767	0.776	29.289	0.092
Concurrent ventricular hemorrhage	1.831	0.317	10.572	0.499

GCS, Glasgow coma scale; ICH, intracerebral hemorrhage; NLR, neutrophil-to-lymphocyte ratio.
The bold values indicate $P < 0.05$.

speculate that NLR could reflect ICH progression. However, at what time point(s) NLR could serve as an ideal prognostic indicator remains unknown.

Consistent with those of previous reports,[27-29] subjects who died within 30 days in our study had significantly higher ICH volume and ICH score and lower GCS score. Many factors may have contributed to the correlation between NLR and 30-day mortality. A previous study showed that leukocytes start to accumulate around and infiltrate the hematoma as early as 5 hours after ICH.[30] At 1-3 days after ICH, macrophages start to infiltrate the hematoma, with a plateau at 7-10 days after ICH.[31] In the current study, both NLR and ICH volume increased at 24 hours after ICH; such changes may reflect infiltration of inflammatory cells around the hematoma. We also found that NLR positively correlated with ICH volume, which is an important determinant of ICH mortality.

In contrast to the early NLR increase in subjects who died within 30 days, patients who survived had relatively stable NLR level within the first week after hospitalization, emphasizing the

need to monitor the dynamic changes in NLR within this period of time. Upon ICH, inflammatory cells that infiltrate the lesions and surrounding tissues activate glial cells, which in turn release pro-inflammatory cytokines, thus forming a vicious cycle.[32] Starting approximately 24 hours after ICH onset, the release of cytotoxic substances including hemoglobin, heme, and iron further aggravates the condition.[33] With the progression of ICH, apoptosis of cells become apparent, thus worsening the inflammatory response.[34] In the current study as well as an earlier report from this group of researchers, NLR at the time of admission (roughly 6 hours after disease onset) did not correlate with 30-day mortality. Such findings possibly reflect delayed inflammatory response in elderly patients.[35]

The current study has several limitations. First, its retrospective design and relatively small sample prevent conclusions about the potentially causal relationships. Second, the study was conducted based on patients hospitalized in a secondary hospital away from major metropolitan centers. As a result, subjects in the current

	NLR$_{T1}$		NLR$_{T2}$		NLR$_{T3}$	
	r	P	r	P	r	P
Male	0.112	0.064	0.086	0.205	0.070	0.377
Age	0.097	0.108	0.148	**0.028**	0.117	0.137
ICH volume	0.071	0.243	0.477	**<0.001**	0.261	**0.001**
Infratentorial hemorrhage	0.017	0.778	0.120	0.075	0.065	0.413
Concurrent ventricular hemorrhage	0.103	0.089	0.110	0.101	0.033	0.679
GCS score	−0.042	0.488	−0.436	**<0.001**	−0.373	**<0.001**
ICH score	0.032	0.593	0.339	**<0.001**	0.271	**<0.001**
Death	0.095	0.118	0.333	**<0.001**	0.284	**<0.001**

TABLE 3 Correlation of NLR with clinical features at various time points

GCS, Glasgow coma scale; ICH, intracerebral hemorrhage; NLR, neutrophil-to-lymphocyte ratio; T1, at admission; T2, at 24-48 h after admission; T3, at 5-7 d after admission. The bold values indicate $P < 0.05$.

study had generally less severe conditions. Such a notion is supported by the considerably lower mortality at 14.5% vs 40%-60% mortality in a previous report by Hemphill and colleagues.[20] This discrepancy may limit the extrapolation of our findings to severe ICH patients. Lack of influence of patient age on mortality reflects, in our opinion, mostly due to the generally less ill patients in the current study. This speculation is supported by much lower mortality in our study vs that reported previously for ICH patients. For example, the mortality was 45% in a previous study by Hemphill and colleagues[20] and only 14.5% in the current study despite of comparable age (66 ± 15 vs 66.4 ± 15.1 years of age; 21.7% vs 25.1% at >80 years). Intraventricular hemorrhage (IVH) is a proven risk factor of increased mortality and poor functional outcome.[36] Lack of difference in the presence of IVH between the 2 groups could be due to the relatively low rate of IVH in the current study (25.8%) vs 55% in the Hemphill study,[20] which in turn, could have attributed to the low mortality.

5 | CONCLUSION

In summary, the current study indicated substantial rise in NLR within the first week after hospitalization, but only in those died within 30 days and not in those surviving beyond 30 days. Future prospective studies are needed to validate this finding. Also, the mechanisms underlying such an association need further investigation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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