

# Prognostic role of neutrophil–lymphocyte ratio in patients with acute ischemic stroke

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## Abstract

**Background:** The aim of this study was to evaluate the prognostic role of neutrophil–lymphocyte ratio (NLR) in patients with acute ischemic stroke (AIS).

**Methods:** PubMed, Embase, Web of Science, Cochrane Library, and China National Knowledge Infrastructure were searched for potential eligible literature. The study characteristics and relevant data were extracted. Odds ratios (ORs) with 95% confidence intervals (CIs) were pooled to estimate the prognostic role of NLR in patients with AIS. Poor functional outcome was defined as modified Rankin Scale  $\geq 3$ .

**Results:** Nine studies with 2947 patients were included. The pooled OR of higher NLR for poor functional outcome at 3 months was 1.55 (95% CI, 1.21–2.00). The pooled ORs for death at 3 months, poor functional outcome at discharge, and symptomatic intracranial hemorrhage (sICH) were 2.35 (95% CI, 0.40–13.78), 2.38 (95% CI, 0.49–11.69), and 4.32 (95% CI, 2.46–7.61), respectively.

**Conclusion:** For patients with AIS, higher NLR was associated with poorer functional outcome at 3 months and may be associated with a higher risk of developing sICH. This readily available and inexpensive marker may be helpful in future clinical and research work. However, due to the limited number of included studies, more well-designed studies are warranted to further clarify this issue.

**Abbreviations:** AIS = acute ischemic stroke, CI = confidence interval, mRS = modified Rankin Scale, NLR = neutrophil–lymphocyte ratio, OR = odds ratio, rt-PA = recombinant tissue plasminogen activator, sICH = symptomatic intracranial hemorrhage.

**Keywords:** acute ischemic stroke, neutrophil–lymphocyte ratio, prognosis, survival

## 1. Introduction

Stroke is the second-leading cause of death and the third-leading cause of morbidity worldwide.<sup>[1,2]</sup> In China, the annual stroke mortality rate is approximately 157 per 100,000 people, making it the leading cause of mortality and adult disability.<sup>[3]</sup> Stroke also has a considerable impact on healthcare expenditures.<sup>[3,4]</sup> Among all strokes, ischemic stroke accounts for approximately 80% to 85%, and is characterized by the disruption of cerebral blood

flow.<sup>[5]</sup> Current treatment strategies for acute ischemic stroke (AIS) include intravenous or intraarterial recombinant tissue plasminogen activator (rt-PA) and mechanical endovascular therapies.<sup>[6]</sup> Besides the already known unfavorable prognostic factors in AIS, it is worthwhile to detect new ones and control them at an early stage.<sup>[7–9]</sup>

It has been suggested that inflammatory response is implicated in all stages of AIS.<sup>[10]</sup> Ischemic tissues release chemokines and cytokines, and recruit peripheral circulating leukocytes.<sup>[11]</sup> Among the leukocytes, neutrophils were found to be an important mediator and exacerbate ischemic brain injury.<sup>[12]</sup> And early neutrophilia has been identified to be associated with larger infarct volumes and increased stroke severity.<sup>[13]</sup> Lymphocytes also infiltrate the ischemic tissues and mediate inflammatory responses.<sup>[11]</sup> Some researchers have demonstrated that lower lymphocyte counts were associated with poor functional outcome at 3 months.<sup>[14]</sup> Neutrophil–lymphocyte ratio (NLR), as a systemic inflammation marker, has been reported to be correlated with poor prognosis in patients with various cancers and acute coronary syndrome.<sup>[15,16]</sup> Recently, NLR was shown to predict short-term outcome in patients with AIS.<sup>[17,18]</sup>

The aim of this study was to systematically summarize the existing evidence on the prognostic role of NLR in patients with AIS through performing a meta-analysis.

## 2. Methods

### 2.1. Search strategy

Since this is a meta-analysis, ethical approval was not necessary. We followed the developed guidelines for systematic reviews and meta-analyses in performing our study.<sup>[19]</sup> Databases, including

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JZ, QR, and YS have contributed equally to this work.

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PubMed, Embase, Web of Science, Cochrane Library, and China National Knowledge Infrastructure, were searched for relevant literature (last search ran on May 5, 2017). The following search terms were used: “neutrophil lymphocyte ratio” AND (“Stroke” OR “Brain Ischemia” OR “Brain Infarction” OR “Cerebral Infarction”). Reference lists of relevant articles were also screened for additional studies. Languages were restricted to English and Chinese.

## 2.2. Study selection

The study selection process was performed independently by 2 reviewers (JZ and YS), with any disagreements being discussed. Studies were considered eligible according to the following inclusion criteria: the patients were diagnosed with AIS; white blood cell counts were assessed after admission, and NLR was calculated; patients were followed up for survival outcomes or functional outcomes; and enough data were reported to estimate the prognostic role of NLR in patients with AIS. Conference abstracts, letters, case reports, reviews, unrelated articles, and studies without enough data were excluded.

## 2.3. Data extraction

Two researchers (JZ and QR) independently extracted relevant data from the eligible studies and disagreements were resolved by consensus. The primary data were odds ratio (OR) for poorer outcomes with 95% confidence interval (CI), or the data that could be used to calculate the OR and 95% CI. OR calculated from multivariate analysis was extracted if both univariate and multivariate analyses were provided. The study and patients' characteristics included first author, publication year, patient source, number of patients, median or mean age of patients, interval between stroke onset and admission, sampling time of the blood, and the cut-off value of NLR.

## 2.4. Statistical analysis

We define poor functional outcome as modified Rankin Scale (mRS)  $\geq 3$ . The logOR and variance were calculated from the OR and 95% CI, and were used for aggregation. Forest plots were used to estimate the pooled prognostic role of NLR in patients with AIS. The pooled OR was considered significant if the *P* value was  $<.05$  and the 95% CI did not overlap 1. Subgroup analyses were performed based on patient source, and sampling time of the blood. The between-study heterogeneity was also assessed, with  $P < .10$  or  $I^2 > 50\%$  implying significant heterogeneity.<sup>[20]</sup> A random-effects model was used if heterogeneity was present. Furthermore, sensitivity analysis was performed to test the contribution of each study to heterogeneity by excluding individual studies one at a time. Publication bias was assessed by Begg test with  $P > .05$  indicating no significant publication bias. All the statistical analyses above were performed by STATA 11.0 (STATA Corporation, College Station, TX).

## 3. Results

### 3.1. Literature research

The initial literature search retrieved 412 studies. After removing duplicates, 289 studies were screened by titles and abstracts. Then, 262 studies were excluded according to the predefined criteria. The rest 27 studies were assessed in full text and 18 were

further excluded due to unrelated or lack of enough data. Eventually, 9 articles<sup>[7–9,21–26]</sup> met the inclusion criteria and were included. The study selection process was shown in Fig. 1.

### 3.2. Study characteristics

The basic characteristics of the 9 included studies were shown in Table 1. Among them, 6 were from China, 1 was from Korea, 1 was from the United States, and 1 was from France and Finland. A total of 2947 patients were included (mean 327). Blood samples were drawn on admission or in the first 24h after admission. The cut-off values of NLR varied between studies. The outcome measures included poor functional outcome at discharge, poor functional outcome at 3 months, death at 3 months, and symptomatic intracranial hemorrhage (sICH). All the ORs were adjusted except one (not reported).

### 3.3. Overall analysis

Six studies used the outcome measure of poor functional outcome at 3 months. The pooled OR of the 6 studies was 1.55 (95% CI, 1.21–2.00) (Fig. 2), indicating that higher NLR was associated with higher risk of poor functional outcome at 3 months in patients with AIS. Significant between-study heterogeneity was observed ( $I^2 = 85.1\%$ ,  $P < .001$ ). Sensitivity analysis identified that the study by Maestrini et al<sup>[8]</sup> was a significant contributor to the heterogeneity. After excluding this study, the heterogeneity shrank to 58.3% and the pooled OR remained statistically significant (OR 1.76; 95% CI, 1.33–2.33).

Two studies used the outcome measure of death at 3 months, and the pooled OR of higher NLR was 2.35 (95% CI, 0.40–13.78). Another 2 studies used the outcome measure of poor functional outcome at discharge, and the pooled OR of higher NLR was 2.38 (95% CI, 0.49–11.69). Two studies examined the risk of sICH in patients with AIS, and the pooled OR of higher NLR was 4.32 (95% CI, 2.46–7.61).

### 3.4. Subgroup analysis

We subdivided the 6 studies using the outcome measure of poor functional outcome at 3 months. The pooled OR was 1.66 (95% CI, 1.30–2.12) for the 4 studies from Asia, and 2.23 (95% CI, 0.39–12.58) for the 2 non-Asian studies. Besides, 4 studies used blood samples on admission, and the pooled OR was 2.06 (95% CI, 1.06–4.02). The rest 2 studies using blood samples in 24h after admission had a pooled OR of 1.43 (95% CI, 1.27–1.62).

All the pooled results above were shown in Table 2.

### 3.5. Publication bias

No significant publication bias was found in the meta-analysis (Table 2). The Begg plot of publication bias of the 6 studies (using the outcome measure of poor functional outcome at 3 months) was shown in Fig. 3 ( $P = .707$ ).

## 4. Discussion

This study aimed to evaluate the prognostic role of NLR in patients with AIS. We performed a meta-analysis of the relevant literature. To our best knowledge, this is the first meta-analysis on this topic. Our results showed that higher NLR was associated with poorer functional outcome at 3 months and may be associated with a higher risk of developing sICH.

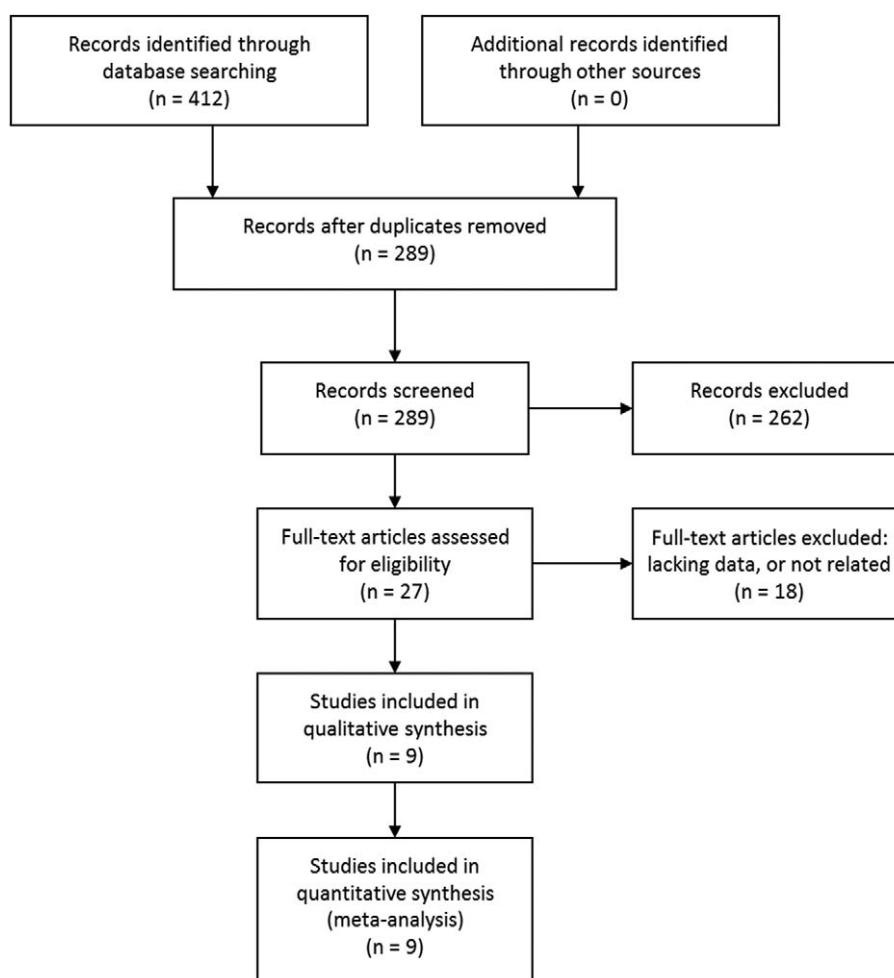


Figure 1. Selection process of studies.

Subgroup analyses were performed to examine the role of NLR in predicting functional outcome at 3 months in different settings. In Asian patients, higher NLR was found to be associated with worse functional outcome, but the association was not significant among non-Asian participants. However, the conclusion should be treated with caution, since the number of studies in each

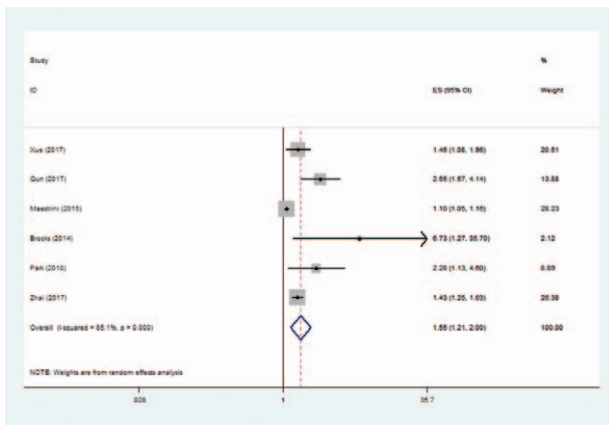
subgroup was limited, especially in the non-Asian group. We also divided the studies according to sampling time after admission. The pooled OR of the 4 studies using blood sample on admission was higher than that of the 2 studies using blood sample in 24 h after admission (2.06 vs 1.43). A possible explanation might be due to the dynamic change of leukocytes after stroke. So,

Table 1

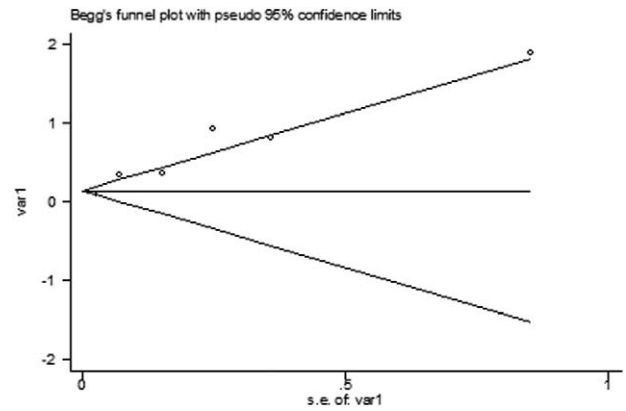
Characteristics of the included studies.

Author	Year	Country	N (F/M)	Age, y	Sample time	Optimal cut-off value	Outcome measure	Adjusted OR
Xue	2017	China	280 (107/173)	Mean 61.8	≤24 h	2.39	mRS at 3 mo	Yes
Qun	2017	China	143 (63/80)	Median 70	On admission	2.995	mRS at 3 mo	Yes
Zhai	2017	China	307 (80/227)	Mean 63	≤24 h	2.84	mRS at 3 mo	Yes
Maestrini	2015	France and Finland	846 (416/430)	Median 71	On admission	NR	mRS at 3 mo	Yes
						4.8	Death at 3 mo	Yes
						NR	sICH	Yes
Brooks	2014	The United States	116 (63/53)	Mean 67	On admission	5.9	mRS at 3 mo	Yes
						5.9	Death at 3 mo	Yes
Park	2010	Korea	371 (151/220)	Mean 68.2	On admission	NR	mRS at 3 mo	Yes
Zhao	2015	China	635 (185/450)	Mean 60.2	On admission	2.59	mRS at discharge	Yes
Gao	2014	China	60 (29/31)	Mean 54	On admission	NR	mRS at discharge	NR
Guo	2016	China	189 (66/123)	Mean 65.0	12–18 h	10.59	sICH	Yes

mRS=modified Rankin Scale, N (F/M)=number of patients (female/male), NR=not reported, OR=odds ratio, sICH=symptomatic intracranial hemorrhage.



**Figure 2.** Pooled odds ratio of higher neutrophil-lymphocyte ratio for poor functional outcome at 3 months in patients with acute ischemic stroke.



**Figure 3.** The Begg publication bias plot of the 6 studies using the outcome measure of poor functional outcome at 3 months.

exploring dynamic change of NLR in patients with AIS and the role of NLR at different time is a future direction, just like Guo et al<sup>[22]</sup> did.

As we mentioned above, inflammatory response is important in ischemic stroke. And elevated white blood cell count is associated with worse outcome in patients with AIS.<sup>[27]</sup> Neutrophils are recruited rapidly in cerebral vessels within hours.<sup>[28]</sup> Higher neutrophil counts are shown to be related with more severe stroke at admission.<sup>[14]</sup> Neutrophils infiltrated in ischemic brain may lead to the release of inflammatory mediators, thus damaging the tissues.<sup>[29]</sup> Besides, some investigators suggested that the inverse effect of higher neutrophil counts may be due to the release of matrix metalloproteinase-9 by neutrophils.<sup>[8]</sup> Lymphocytes accumulate in the ischemic brain 3 to 6 days after stroke, which is later than neutrophils.<sup>[30]</sup> The role of lymphocytes in AIS is controversial. Some studies proved that lymphocytes could repair the injury by inflammation.<sup>[7,31]</sup> However, some studies demonstrated that lymphocytes could cause the release of proinflammatory cytokines and cytotoxic substances which damage the ischemic brain.<sup>[32]</sup> Kim et al<sup>[14]</sup> found that, in patients with AIS, lower lymphocyte counts were associated with poor functional outcome at 3 months.

NLR reflects the balance between neutrophils and lymphocytes.<sup>[8]</sup> Every included study reported a negative impact of higher NLR on patients' outcome. And our meta-analysis demonstrated that higher NLR was associated with poorer functional outcome at 3 months and higher risk of developing

sICH. More work is needed to explore the underlining molecular mechanism. Although we fail to prove the correlation between higher NLR and poorer functional outcome at discharge or higher risk of death at 3 months, the numbers of studies using these outcome measures were both only 2, thus more studies were needed to clarify this.

This readily available and inexpensive test could be used as a predictor of outcome in patients with AIS.<sup>[9]</sup> NLR could be used to predict outcomes with other markers, and even be used as a criterion for patients' enrollment in clinical trials.<sup>[9]</sup> Moreover, these findings also support the anti-inflammatory therapy as a potential treatment for AIS.<sup>[21]</sup>

Significant between-study heterogeneity was present in this meta-analysis, and sensitivity analysis revealed that the study by Maestrini et al<sup>[8]</sup> was a major contributor to the heterogeneity. After excluding this study, the heterogeneity shrank from 85.1% to 58.3% and the pooled OR remained statistically significant. The reason why this study contributed greatly to heterogeneity might be that it was the only study that included patients admitted within the time window of using rt-PA and collected blood samples before the bolus of rt-PA. Other potential sources of heterogeneity may be from different patient sources, different time of blood collection after admission, and different cut-off values NLR.

There were several limitations in our study. First, the meta-analysis was based on a limited number of studies, and the number of studies in each subgroup was even smaller. Therefore,

**Table 2**  
Summary of meta-analysis results.

	N	Model	Pooled OR (95% CI)	P	Heterogeneity (I <sup>2</sup> , P)	Conclusion	Publication bias
<b>Total</b>							
PFO at 3 mo	6	Random	1.55 (1.21–2.00)	.001	85.1%, <.001	Positive	0.707
Death at 3 mo	2	Random	2.35 (0.40–13.78)	.343	85.3%, .009	Negative	1.000
PFO at discharge	2	Random	2.38 (0.49–11.69)	.285	88.9%, .003	Negative	1.000
sICH	2	Fixed	4.32 (2.46–7.61)	<.001	10.3%, .291	Positive	1.000
<b>Subgroups</b>							
Asian	4	Random	1.66 (1.30–2.12)	<.001	53.9%, .090	Positive	
Non-Asian	2	Random	2.23 (0.39–12.58)	.364	77.9%, .033	Negative	
Sample time: on admission	4	Random	2.06 (1.06–4.02)	.034	84.9%, <.001	Positive	
Sample time: ≤24 h	2	Fixed	1.43 (1.27–1.62)	<.001	0.0%, .907	Positive	

CI=confidence interval, N=number of included studies, OR=odds ratio, PFO=poor functional outcome, sICH=symptomatic intracranial hemorrhage.

caution should be applied as to the subgroup results. Second, some characteristics differed between the studies, such as the blood sampling time and cut-off values of NLR. So, more studies are needed to validate the prognostic role of NLR in patients with AIS. In addition, most of the included studies were from Asia (and most from China), the overall conclusions may need to be treated with caution. Furthermore, significant between-study heterogeneity was present and random-effects model was used. Besides, publication bias was a major concern for all meta-analyses. Although no publication bias was found in our study, it should not be completely excluded.

In conclusion, our results suggested that, for patients with AIS, higher NLR was associated with poorer functional outcome at 3 months and may be associated with a higher risk of developing sICH. This readily available and inexpensive marker may be a helpful tool in clinical work. These findings also suggest further exploration on modulating immune response to treat AIS. However, due to the limited number of included studies, more well-designed studies are warranted to further clarify this issue.

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