The prediction of neutrophil to lymphocyte ratio for outcomes in ischemic stroke

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ABSTRACT

Objective: Neutrophil to lymphocyte ratio (NLR) is a prognostic inflammatory biomarker in patients with cardiovascular disease and hemorrhagic stroke. This metaanalysis aims to evaluate the prognostic values of NLR in predicting clinical outcomes in patients with ischemic stroke.

Methods: A literature search was performed using the databases PubMed, EMBASE, Cochrane Central Register of Controlled Trials and China National Knowledge Infrastructure. Two reviewers independently retrieved papers that met the inclusion criteria. Subgroup analyses were performed using in-hospital mortality, 90-day mortality and 90-day poor outcomes (mRS>2) as the outcome measures.

Results: Eight studies with 3855 patients were included in the analysis. An elevated NLR was a strong predictor for in-hospital mortality (OR: 1.05; 95% CI: 1.03-1.07, p<0.001) and for 90-day poor outcomes (OR: 2.28; 95% CI: 1.39-3.73, p<0.001), but not for 90-day mortality (OR: 3.04; 95% CI: 0.74-12.55, p=0.12). After performing subgroup analysis, the NLR was found to predict 90-day mortality with a high (>5) cut-off values (OR: 6.69; 95% CI: 1.70-26.33, p=0.007). The lower cut-off values had no significance (OR: 2.17; 95% CI: 0.43-10.86, p=0.35).

Conclusions: A high NLR was significantly associated with higher rates of inhospital mortality and 90-day poor outcome in patients with ischemic stroke, especially with a high mean NLR or high cut-off values. With a high cut-off value (>5), NLR could predict the 90-day mortality after ischemic stroke.

INTRODUCTION

Ischemic stroke is the major cause of stroke and accounts for 80-85% of all cases [1-3]. Ischemic stroke is associated with high rates of mortality and morbidity [4]. The subsequent inflammatory reaction involves cytokine release and recruitment of inflammatory cells. This inflammatory reaction is responsible for the secondary brain injury, and is a major prognostic factor after ischemic stroke [5, 6].

Many inflammatory biomarkers have been identified as possible prognostic predictors in ischemic stroke. A review [7] of five studies demonstrated that the C reactive protein is significantly associated with poor longterm clinical outcomes in patients with ischemic stroke. Elevated white blood cell (WBC) counts after stroke onset could also predict the severity of stroke, the incidence of disability, and short-term mortality [8]. High neutrophil counts were correlated with the larger infarct volumes [9]. NLR is the ratio of neutrophil and lymphocyte and reflects the balance of the immune response. An imbalance of the immune system involving the NLR can be used as a biomarker for a systematic inflammatory response. In addition, it is used to predict the prognosis of patients with various cancers [10, 11], cardiovascular diseases [12, 13] and hemorrhagic stroke [14-16]. Recently, NLR was used to predict in-hospital mortality [17, 18], 90-day mortality [19-21] and 90-day poor outcomes (mRS≥3) [4, 21-23] in patients with ischemic stroke.

No systemic analysis looking at the predictive ability of NLR in patients with ischemic stroke. Thus, we performed a meta-analysis to determine the use of NLR in predicting clinical outcomes in patients with ischemic stroke.

MATERIALS AND METHODS

Search strategy

Following the PRISMA flow diagram [24] (Figure 1), A literature search was conducted using the databases PubMed, EMBASE, Cochrane Central Register of Controlled Trials and China National Knowledge Infrastructure (CNKI) using the key words 'ischemic stroke' OR 'brain infarction' AND 'lymphocyte' AND 'neutrophil'. The search looked at articles published from the time of creation of the database up until August 1st 2017. Additional studies were collected by reviewing the references listed in related articles.

Study selection

The full-text of the selected studies were independently evaluated by two reviewers. Inclusion criteria consisted of: 1- patients diagnosed with ischemic stroke on NCCT or MRI; 2- articles reporting the OR and 95% CI of NLR on mortality or poor outcomes, or the available data allows for the calculation of the OR and 95% CI; 3- Case-control studies, cohort studies or randomized controlled studies (RCTs). Review articles, case reports, and reports using animal models, were excluded.

Data extraction

The data were extracted according to a standard data form. Extracted data included author titles, publication year, country, study design, number of patients, mean age, gender, mean NLR, National Institutes of Health Stroke Scale (NIHSS) or Glasgow coma scale (GCS), study period, NOS score, hematoma/ischemic volume, time of performance of laboratory test, cut-off value of NLR, odds ratio (OR) and 95%CI of NLR on mortality and poor outcomes. If the ORs of multivariate regression analysis were unavailable, the ORs of univariate regression were used. The end points included in-hospital mortality, 90-days mortality, and the 90-day poor outcomes (mRS from 3 to 6).

Quality assessment of the selected articles

The quality of cohort and case-control studies was evaluated by two reviewers independently utilizing the Newcastle-Ottawa scale criteria [25]. A Newcastle-Ottawa scale (NOS) score≥7 was set to define a report as a high quality report.

Data analysis

The OR and 95%CI of NLR on mortality and poor outcomes were pooled by Review Manager Version 5.3 (Cochrane collaboration, Oxford, UK) and the publication bias were assessed by STATA 13.0 (STATA Corporation, College Station, TX). When there was a significant heterogeneity with I² >50% or p<0.10, the random-effects model was used, otherwise, the fixed-effects model was adopted. The sensitivity analysis were used if the heterogeneity was quite high. The subgroup analyses were performed by countries, study design, mean NLR, cut-off values, time from onset to laboratory test, and the logistic regression models. The publication bias was assessed by Funnel plot with Begg rank correlation. If p value < 0.05 was set for significant statistical difference.

RESULTS

Literature research

The titles and abstracts of 168 articles were reviewed and 135 unrelated articles were excluded. After full review of the remaining 33 articles, 8 studies met the inclusion criteria and where used in the constriction of this meta-analysis. 25 articles were excluded, of which 19 articles failed to meet the inclusion criteria, and 6 articles did not report the required data.

Study characteristics

A total of 8 studies [4, 17-23] of 3855 patients were included and the study characteristics of were listed in Table 1. All studies (2 prospective and 6 retrospective) were published between 2013 and 2017 with mean age from 62 to 70 years. The mean NLR ranged from 2.1 to 4.0 with the cut-off values between 2.39 and 5.9. All of the ORs and 95% CI were calculated using multiple regression analysis other than two studies [19, 20]. All the included studies had a high quality with NOS score \geq 7.

In-hospital mortality

Two articles of 2093 patients were pooled for the association of NLR and the in-hospital mortality. The results showed that a high NLR increased the risk of

in-hospital mortality with OR of 1.05 (95%CI, 1.03-1.07, p<0.001, Figure 2) and no significant heterogeneity ($I^2=43\%$ and p=0.19).

90-day mortality

After pooling the results of three articles with 1032 patients, we found that a high NLR was not associated with the 90-day mortality with an OR of 3.04 (95%CI, 0.74-12.55, p=0.12, Figure 3). Using sensitivity analysis, we identified significant heterogeneity originating from the study of Maestrini [20]. After exclusion of the

aforementioned study, there was no heterogeneity ($I^2=0\%$ and p=0.87) between the remaining studies with OR of 6.18 (95%CI, 2.38-16.07, p<0.001).

Subgroup analysis

Subgroup analyses was performed according to study design, cut-off values of NLR, and the types of logistic regression (Table 2). The pooled ORs were 1.08 (95%CI, 1.03-1.13, p=0.001) in a retrospective article and 6.18 (95%CI, 2.38-16.07, p<0.001) in two perspective studies.

One article reported high cut-off values of NLR (>5), the OR was 6.69 (95%CI, 1.70-26.33, p=0.007).



Figure 1: The flow diagram of procedure to search the included studies.

Table 1: Characteristics of included studies

Author	Year	Country	Study design	Patients (n)	Sex (M/F)	Mean age (years)	Mean NLR	NIHSS	Treatments	Study period	NOS score
Xue, J. 2017	2017	China	retrospective	280	173/107	62	2.1	-	Multiplicate (endovascular)	2014-2015	8
Qun, S.	2016	China	retrospective	143	80/63	70	2.75	6	-	2015-2016	7
Celikbilek, A	. 2014	Turkey	prospective	70	33/37	69	3.3	-	-	2010-2011	7
Fang, Y. N.	2017	Taiwan	retrospective	1731	1092/639	68	3.99	-	Antiplatelet Drugs	2010-2017	8
Maestrini, I.	2015	Finland	prospective	846	430/416	71	3.40	10	rtPA	2010-2015	9
Fan, L.	2017	China	retrospective	362	216/146	63	4.0	9	-	2014-2015	7
Brooks, S. D.	2013	USA	retrospective	116	53/63	67	3.74	17	Endovascular	2008-2011	7
Zhai, M.M.	2017	China	retrospective	307	227/80	63	2.90	4	-	2014-2015	7

NIHSS: National Institutes of Health Stroke Scale, GCS: Glass coma scale, NOS: Newcastle-Ottawa scale score

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Author	Hematoma/ ischemic volume (ml)	Time from onset to laboratory test (hours)	Cut-off value	poor outcome (OR) [#]	mortality (OR) [#]	Follow up
Xue, J. 2017	1.9	24	2.39	1.455(1.083-1.956)	-	90-day
Qun, S.	1.57	12	2.99	2.547(1.567-4.137)	-	90-day
Celikbilek, A.	-	<24	4.1	-	5.73(1.51-21.82)*	90-day
Fang, Y. N.	-	48	3.2	-	1.04(1.01-1.06)	In-hospital
Maestrini, I.	-	2.4	4.8	3.97(2.94-5.35)*	1.08 (1.03-1.13)	90-day
Fan, L.	-	<48	Per 1	-	1.07(1.03-1.11)	In-hospital
Brooks, S. D.	-	-	5.9	6.73(1.27-35.73)	6.69(1.7-26.3)	90-day
Zhai, M.M.		4h	2.84	1.427(1.247-1.634)	-	90-day

#: multivariate regression analysis, *: univariate regression analysis, OR: odds ratio.

The low cut-off values of NLR (<5), the OR for 90day mortality was 2.17(95%CI, 0.43-10.86, p=0.35). The pooled ORs of the study were 5.73 (95%CI, 1.51-21.74, p=0.01) and 2.35 (95%CI, 0.40-13.77, p=0.34) by univariate regression analysis and multivariate regression analysis, respectively.

90-day poor outcomes

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Five articles reporting data from 1692 subjects were pooled to evaluate the relationship between NLR and 90-day poor outcomes. The results of the five articles suggest that a higher NLR is associated with higher poor outcome rates in patients with ischemic stroke with OR of 2.28 (95%CI, 1.39-3.73, p<0.001, Figure 4). Significant heterogeneity was detected (I²=91%, p<0.001) between these studies. Using sensitivity analysis we attributed the

origin of heterogeneity to the study of Maestrini [20]. After excluding this study, the heterogeneity decreased with $I^2=64\%$ and OR of 1.71(95%CI, 1.26-2.31, p<0.001).

Subgroup analysis

In the China and non-China groups, the pooled ORs were 1.60 (95%CI, 1.24-2.08, p<0.001) and 4.04 (95%CI, 3.00-5.42, p<0.001) respectively. The pooled ORs of four retrospective studies was 1.71 (95%CI, 1.26-2.31, p<0.001) and one prospective study reported the OR of 3.97 (95%CI, 2.94-5.36, p<0.001) for 90-day poor outcome. In low and high mean NLR group, the pooled OR were 4.04(95%CI, 3.00-5.42, p<0.001) and 1.60(95%CI, 1.24-2.08, p<0.001) respectively. The pooled ORs were 6.73 (95%CI, 1.27-35.66, p=0.03) in high cutoff group (>5) and 2.11(95%CI, 1.28-3.49, p=0.004) in low cut-off group (<5). Four studies reported the time from

onset to laboratory test and the time ranged from 2.4 to 48 hours. The pooled ORs of study were 3.97 (95%CI, 2.94-5.36, p<0.001) and 1.71 (95%CI, 1.26-2.31, p=0.0006) by univariate regression analysis and multivariate regression analysis respectively.

publication bias

The funnel plots showed no publication bias for 90-day mortality and 90-day poor outcomes (Figure 5). Begg's test performed using STATA 13.0 also showed no evidence of publication bias (p=0.296 and p=0.462).

DISCUSSION

Inflammation plays an important role in the development of ischemic stroke [3]. NLR reflects the immune status (lymphocytes) [26] and the degree of inflammatory infiltration (neutrophil) [26-28]. Recently,

NLR was considered as a predictor for clinical outcomes in hemorrhagic [14, 15, 29] and ischemic stroke [17, 20, 30]. To our best knowledge, the present study is the first meta-analysis to evaluate the predictive value of NLR for the clinical outcomes in patients with ischemic stroke. We found that a high NLR was associated with higher rates of in-hospital mortality and 90-day poor outcomes, but not for the 90-day mortality in patients with ischemic stroke.

The inflammatory response increases the risk of hemorrhagic transformation [31], damage to the BBB and development of cerebral edema [32]. NLR reflects the ensuing inflammatory reaction after ischemic stroke, which could explain the fact that NLR could predict the clinical outcome.

The higher NLR was associated with 90-day mortality in prospective groups and retrospective groups, which was not consistent with the pooled results of all included studies. In addition, we found the OR of prospective studies (6.18) was higher than the OR of



Figure 2: Forest plots for association of NLR and in-hospital mortality.

Study or Subgroup	log[Odds Ratio]	SE Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV. Random. 95% Cl
Brooks, S. D. 2013	1.9006 0.0	699 29.5%	6.69 [1.70, 26.33]	
Celikbilek, A. 2014	1.7457 0.66	804 29.9%	5.73 [1.51, 21.74]	_
Maestrini, I. 2015	0.077 0.02	242 40.6%	1.08 [1.03, 1.13]	•
Total (95% CI)		100.0%	3.04 [0.74, 12.55]	
Heterogeneity: Tau ² = Test for overall effect:	1.28; Chi² = 12.79, df = Z = 1.54 (P = 0.12)	Image: constraint of the second se		



Study or Subgroup	log[Odds Ratio] Sl	E Weight	Odds Ratio IV, Random, 95% C	Oo IV, Ra	dds Ratio ndom, 95% Cl	
Brooks, S. D. 2013	1.9066 0.8508	8 6.5%	6.73 [1.27, 35.66]			
Maestrini, I. 2015	1.3788 0.1532	2 23.6%	3.97 [2.94, 5.36]		-	
Qun, S. 2016 0.9349 0.2478		8 20.7%	2.55 [1.57, 4.14]			
Xue, J. 2017	0.375 0.150	7 23.7%	1.45 [1.08, 1.95]		-	
Zhai, M.M. 2017	0.3556 0.068	8 25.4%	1.43 [1.25, 1.63]		•	
Total (95% CI)		100.0%	2.28 [1.39, 3.73]		•	
Heterogeneity: Tau ² = Test for overall effect:	0.24; Chi² = 43.47, df = 4 (Z = 3.27 (P = 0.001)	0.001 0.1 Favours [experiment	1 10 al] Favours [control]	1000		

Figure 4: Forest plots for association of NLR and 90-day poor outcomes.

 Table 2: Subgroup analyses results of 90-day mortality

Groups	Ν	Model	Pooled OR (95% CI)	p value	Heterogeneity (I ² , P)
Total	3	random	3.04 (0.74-12.55)	0.12	0.002, 84%
Retrospective	1	-	1.08 (1.03-1.13)	0.001	-
Prospective	2	fixed	6.18 (2.38-16.07)	< 0.001	0.87,0%
Cut-off>5	1	-	6.69(1.70-26.33)	0.007	-
Cut-off <5	2	random	2.17(0.43-10.86)	0.35	0.01,83%
Univariate regression analysis	1	-	5.73 (1.51-21.74)	0.01	-
Multivariate regression analysis	2	random	2.35 (0.40-13.77)	0.34	0.009, 85%

N: number of included studies, OR: odds ratio, CI: confidence interval.

retrospective studies (1.08). This might attribute to the selection bias of incurred in retrospective studies. There was a statistically significant association between high NLR and 90-day mortality in the high cut-off group (>5), rather than in the low cut-off group (<5), suggesting that higher cut-off values could improve the accuracy of predicting 90-day mortality and that the cut-off values should be more than 5 in patients with ischemic stroke. The association of NLR and 90-day mortality in patients with ischemic stroke might be influenced by confounding factors. Previous studies [18, 33] reported some independent predictors for mortality, such as age, NIHSS and the volume of infarct. With multivariate regression analysis, Maestrini [20] and Brooks [21] adjusted the outcomes with onset-to-treatment, gender, atrial fibrillation, systolic BP, recanalization, application of tissue plasminogen activator (tPA), and they found that NLR was independently associated with 90-day mortality. The study [19] that used univariate regression analysis also suggested that NLR at admission is a

prognostic biomarker in acute ischemic stroke. However, after performing multivariate regression analysis, we found that the NLR was not an independent predictor for 90-day mortality with considering other factors. Compared with the 90-day poor outcomes, NLR was not an independent predictor for 90-day mortality and the risk of 90-day mortality was also influenced by other factors, such as age, history of myocardial infarction and National Institute of Health stroke scale (NIHSS) [20, 21]. One study [21] found the history of myocardial infarction and NIHSS had a higher OR (2.26 and 1.18) for 90-day mortality, and the NLR had a weaker predictive ability with OR of 1.08. However, compared with other independent factors, the NLR had the similar or higher OR for 90-day poor outcomes [21]. After pooling the data of included studies, the number of patients increased and the effects of other factors would be greater than NLR, which might explain the difference of NLR prediction between the 90-day mortality and 90day poor outcomes.





Table 3: Subgroup analyses results of 90-day poor outcomes

Groups	Ν	Model	Pooled OR (95% CI)	p value	Heterogeneity (I ² , P)
Total	5	random	2.28 (1.39-3.73)	0.001	<0.001, 91%
China	3	random	1.60 (1.24-2.08)	< 0.001	0.08, 61%
Non-China	2	fixed	4.04 (3.00-5.42)	< 0.001	0.54, 0%
Retrospective	4	random	1.71 (1.26-2.31)	0.0006	0.04, 64%
Prospective	1	-	3.97 (2.94-5.36)	< 0.001	-
Mean NLR >3	2	fixed	4.04(3.00-5.42)	< 0.001	0.54,0%
<3	3	random	1.60(1.24-2.08)	< 0.001	0.08, 61%
Cut-off>5	1	-	6.73(1.27-35.66)	0.03	-
<5	4	random	2.11(1.28-3.49)	0.004	<0.001,93%
Univariate regression analysis	1	-	3.97 (2.94-5.36)	< 0.001	-
Multivariate regression analysis	4	random	1.71 (1.26-2.31)	0.0006	0.04, 64%

N: number of included studies, OR: odds ratio, CI: confidence interval.

The association of NLR and 90-day poor outcomes was evaluated in most of the included studies. After subgroup analysis, the pooled results of prospective studies and retrospective studies were consistent with the pooled results of five studies regarding the association of NLR and 90-day poor outcomes (Table 3). The pooled OR in non-China group was higher than OR in China group and there was no heterogeneity between the two studies, demonstrating that a higher NLR is associated with a higher predictive ability for 90-day poor outcomes in non-Chinese patients. In the analysis of 90-day poor outcomes (Table 3), the mean NLR of non-Chinese patients had a NLR (3.4-3.74) was higher than the NLR of Chinese patients (2.1-2.9), and the mean NLR could affect the prediction of 90-day poor outcomes in ischemic stroke. With a higher mean NLR, the predictive value for 90-day poor outcomes had a higher predictive ability with the increased pooled OR. Brooks [21] demonstrated an OR of 6.73 with a high mean NLR of 3.74, while Xue [4] report an OR for 90-day poor outcomes as 1.455 with a low NLR of 2.1. In addition, we found that the pooled OR in high mean NLR group (4.04) was higher than the OR in low mean NLR group (1.60). Although a higher NLR could predict the 90-day poor outcomes regardless of mean NLR and cut-off values, there were significant heterogeneity in low mean NLR group and low cut-off group. Thus, the NLR had a strong and reliable predictive ability for 90day poor outcomes with high mean NLR or high cut-off values.

NLR is a time dependent variable in patients with stroke. The NLR increases with time in the first few days. Many previous studies [26-28, 34] suggested that NLR increases within 12 h after onset and reaches the peak levels the second day. Accurately determining the optimal time to test requires additional research. Akil [35] found that the NLR of ischemic stroke patients was significantly higher than NLR of healthy patients and suggested the NLR could predict the risk of developing ischemic stroke. In addition, one study [4] also suggested that a high NLR is associated with a higher risk of recurrent ischemic stroke. Furthermore, Buck [9] demonstrated the higher NLR was associated with larger infarct volumes in patients with AIS, rather than lymphocyte counts. Recently, the platelet to lymphocyte ratio (PLR) was considered as a novel predictor for functional outcomes in patients with stroke [36, 37]. Until now, there was one study [36] regarding the influence of PLR to ischemic stroke, with a sensitivity of 73% and specificity of 69%, however, this study had the limited number of patients without multivariate regression analysis. Thus, the comparison of predictive ability between NLR and PLR needed more researches to assess.

Significant heterogeneity was presented in analysis of 90-day mortality and 90-day poor outcomes. We found that a major origin of the heterogeneity was the study by Maestrini [20]. The reason was that the OR of NLR for 90day poor outcomes was calculated by univariate regression analysis. In addition, the different treatments also could result in the heterogeneity. Maestrini [20] included patients who received IV recombinant tissue plasminogen activator, while Brooks [21] included patients who underwent endovascular stroke therapy.

Limitations

There were some limitations in this study. First, the heterogeneity was significant in the studies for 90-day mortality. Although the random-effect and the subgroup analysis were used to make the results more conservative, the association of NLR and 90-day mortality needs more evidence after adjusting the confounding factors. Second, treatment options varied between the studies. The therapeutic options utilized where not uniform in the same study, and in some instances they were not clearly reported. Future studies should display more treatment related information.

CONCLUSIONS

The synthesized evidence from the included studies showed that high NLR is associated with higher inhospital mortality and the 90-day poor outcomes rates in patients with ischemic stroke, especially with a high mean NLR or high cut-off value (>5). Nevertheless, the optimal time of laboratory test must be studied further.

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CONFLICTS OF INTEREST

No conflicts of interest.

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