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Neutrophil to lymphocyte ratio predicts poor outcomes after acute ischemic stroke: A cohort study and systematic review

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ABSTRACT

Background and purpose: The relationship between neutrophil to lymphocyte ratio (NLR) and prognosis after acute ischemic stroke (AIS) remains controversial. The aim of this cohort study and systematic review was to ascertain the association of admission NLR with major clinical poor outcomes after AIS.

Methods: We analyzed data from Chengdu stroke registry and performed a systematic review for previous literature. The outcomes were hemorrhagic transformation (HT), parenchymal hematoma (PH), symptomatic intracranial hemorrhage (sICH), 3-month death or disability (modified Rankin Scale ≥ 3), and 3-month death. Odds ratios (ORs) and 95% confidence intervals (CIs) of NLR as a continuous and categorical variable and poor outcomes were pooled separately. We also calculated the predictive accuracy of admission NLR in different outcomes.

Results: We included 808 patients from registry database and 9563 patients from previous studies. Our registry data showed that NLR ≥5 was associated with HT (OR 2.03, 95%CI 1.19–3.46), PH (OR 2.54, 95%CI 1.20–5.35) and 3-month death (OR 5.55, 95%CI 1.41–21.89); meta-analysis with our data and other observational studies indicated that higher NLR was associated with HT (OR 1.99, 95% CI 1.45–2.73), sICH (OR 2.22, 95% CI 1.60–3.09), 3-month death or disability (OR 1.68, 95% CI 1.18–2.38), and 3-month death (OR 2.79, 95% CI 1.57, 4.94). NLR had the highest predictive accuracy for 3-month death.

Conclusions: Higher NLR is positively associated with the risk of HT and 3-month death after stroke. Considering the limited predictive ability of a single biomarker, more studies should validate the role of NLR in prognostic models.

1. Introduction

Stroke is the second cause of deaths and the third cause of disability worldwide [1,2], with 6.5 million deaths and 1807 person-years of disability-adjusted life years in 2013 [3]. Ischemic stroke accounts for approximately 70% of new onset stroke and more than half of the survivors suffer from disability [2]. Exploring the key prognostic factors is crucial for clinicians to design the treatments accordingly and improve the clinical outcomes of stroke patients.

Post stroke inflammatory response has been found to play a key role in the secondary brain injury after acute ischemic stroke (AIS) [4]. Previous studies have shown the different roles of neutrophils and lymphocytes during this inflammatory process. Neutrophils are recruited to ischemic sites within the first few hours after stroke onset and then release chemical mediators, which are related to tissue damage exacerbation and poor neurologic improvement [5–8]. By contrast, stroke would trigger a special immunosuppression state, which may lead to lymphopenia [9]. Some types of lymphocytes seem to be the major cerebroprotective immunomodulators [10,11]; the decrease of these lymphocytes may contribute to the loss of neuroprotective function and cause neurological deterioration [8,12–14]. Thus, neutrophil to lymphocyte ratio (NLR) may associate with outcomes of patients with AIS.

Although many studies have investigated the association between NLR and outcomes after stroke, it is still controversial whether NLR is independently associated with Hemorrhagic Transformation (HT), as well as functional outcomes including death and disability. Maestrini indicated that NLR is associated with both symptomatic intracranial

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hemorrhage (sICH) and 3-month death in patients treated with reperfusion therapy [15], while other published data did not support their conclusions [16,17]. This may be due to the different definitions of outcomes, the impact of potential confounders, and the small numbers of individual studies. NLR was revealed to be associated with the risk of in-hospital pneumonia [18]. However, previous studies did not consider the potential confounding effect of pneumonia and no study adjusted it in their analyses. Thus, the association between NLR and functional outcomes may be overvalued. To figure out whether NLR predicts poor outcomes in patients with AIS, we analyzed the cohort in our stroke registry and systematically reviewed all the published data.

2. Materials and methods

2.1. Chengdu stroke registry

This study was one of the research projects of a registry-based observational study entitled "Clinical features, management and outcomes of severe ischemic stroke", which has been approved by the Scientific Research Department and Ethics Committee of West China Hospital [19]. The published protocol was available from https://bmjopen.bmj.com/content/8/10/e024900.long. We reported the study according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [20].

2.1.1. Study population

We identified patients from January 2014 to December 2015 at West China Hospital. The registry database has been previously described [21]. We included patients who were 1) admitted to the hospital within 7 days from stroke onset. 2) > 18 years old. Patients with a history of infection within 2 weeks before stroke onset, hematologic diseases, and malignant tumor were excluded. Informed consent was obtained from patients or their next of kin.

2.1.2. Data collection

Information on patients' characteristics, vascular risk factors, laboratory tests, in-hospital medications and complications, and clinical outcomes were recorded in the structured forms. All the patients had blood samples collected within 24 h after admission. Neutrophil to Lymphocyte Ratio (NLR) was calculated as the absolute neutrophil counts divided by the absolute lymphocyte counts. The first computed tomography (CT) was performed within 24 h after admission. Follow-up CT or Magnetic Resonance Imaging (MRI) was performed within 14 days after admission or when neurological deterioration occurred. Two neurologists blinded to clinical data evaluated HT and any disagreement was solved by discussion. We used the modified Rankin Scale (mRS) to assess the 3-month functional outcomes via telephone calls [22].

2.1.3. Outcome definitions

Our outcomes were HT and its subtypes, as well as 3-month functional outcomes. HT was defined as hemorrhage detected on follow-up neuroimaging examination after ischemic stroke [23], and then classified by European Cooperative Acute Stroke Study (ECASS) criteria into 2 types: hemorrhagic infarct (HI) and parenchymal hematoma (PH). Based on the severity of hemorrhage, it could be further divided into HI-1, HI-2, PH-1, and PH-2. Meanwhile, sICH was defined as intracranial hemorrhage with any neurological deterioration according to National Institute of Neurological Diseases and Stroke (NINDS) criteria [24]. Therefore, HT was also subcategorized into 2 types according to NINDS criteria: sICH and asymptomatic intracranial hemorrhage. Three-month functional outcomes included 3-month death or disability (mRS scores being 3 to 6) and 3-month death (mRS score of 6).

2.1.4. Statistical analysis

Data were analyzed by SPSS version 21.0 (IBM, USA). A two-sided $P < .05$ was considered significant. For baseline characteristics between patients with high and low NLR levels, we conducted Student *t*-test or Mann–Whitney *U* test for continuous variables, and chi-squared test or Fisher's exact test for categorical variables if appropriate. We used binary logistic regression model to investigate the independent association between NLR and outcomes. We conducted three models. In model 1, we adjusted for age, sex, and NIHSS score. In model 2 and 3, we additionally adjusted for confounding variables. The potential confounding factors were selected when the factor had $p < .1$ in univariate analysis or changed the Odds Ratios (ORs) by at least 10% when adding or removing the factor from the model [20,25]. Two separate analyses were carried out for NLR as a continuous variable and a categorical variable. ORs and its 95% Confidence Intervals (CIs) were reported.

We also calculated the area under the curve (AUC) of Receiver Operating Characteristic (ROC) to determine the predictive accuracy for all the outcomes. The average NLR cut-off value reported in the previous studies was used to categorize our cohort data and calculate the sensitivity and specificity to compare the discriminative ability of our cohort data and previously published data.

2.2. Systematic review

We performed the systematic review based on Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [26]. This protocol was registered in the International Prospective Register of Ongoing Systematic Reviews website and the registration number was CRD42019123855 (available from https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID = 123,855).

2.2.1. Literature search

Two reviewers (L. W. and Q. S.) performed a comprehensive literature search independently without any language restriction. We searched the published literature that investigated the role of NLR as a risk factor of poor outcomes in patients with AIS up to Jan 2019 in electronic databases, including PubMed and China National Knowledge Infrastructure. We used the following keywords: 'neutrophil lymphocyte ratio' and 'stroke or cerebral infarction' combined their synonyms to search (The full search strategies were displayed in the Supplementary material). We also reviewed the reference lists of all identified relevant articles to supplement the search.

2.2.2. Inclusion and exclusion criteria

Studies were eligible if they met the following criteria: (1) Patients were 18 years or above and were diagnosed with AIS; (2) Blood samples were taken shortly after the symptom onset to measure admission NLR; (3) At least one of the outcomes was evaluated: HT, HT subtypes (sICH and PH), death or disability (mRS ≥ 3), and death; and (4) studies were designed as cohort or case-control. The exclusion criteria were as follows: (1) Studies included patients with hemorrhagic stroke or transient ischemic attack (TIA); (2) Duplicated publications; (3) Abstracts, reviews, case reports, letters, or meta-analysis.

2.2.3. Data collection and quality assessment

L. W. and Q. S. extracted the data independently and the disagreements were solved by the discussion with the third reviewer (C. W.). The following information was collected: study characteristics, patients' information, statistical data. Since the data for meta-analysis were obtained from the previously published literature, no ethical approval and patient consent were required.

Given all the studies were observational studies, we modified the Newcastle-Ottawa Scale (NOS) to evaluate the quality of studies [27,28]. CT/MRI performed at the day 7 after stroke onset was defined as the adequate duration for detecting HT; 3-month was considered as adequate follow-up duration. The maximum point was 9 and studies with 7 to 9 points were considered adequate quality.

2.2.4. Statistical analysis

Statistical analyses were conducted by the software Stata version 12.0 (STATA Corporation, College Station, TX). A two side *P* value < .05 was considered statistically significant.

Firstly, we investigated the associations between admission NLR and HT, HT subtypes, 3-month death or disability, and 3-month death. Separate meta-analyses were carried out to evaluate the continuous and categorical association between NLR and different clinical outcomes. We pooled ORs and 95% CIs from our registry data and previously published data.

Then, we pooled the AUC by drawing the hierarchical summary receiver operating characteristic (HSROC) curve. We also performed bivariate mixed-effects model to calculate the pooled sensitivity and specificity.

We adopted a random-effects model for all the analyses because of the presumed heterogeneity among studies. I^2 index was used to measure the inconsistency among studies and was divided into different levels according to the value of I^2 index: no heterogeneity (0%), low heterogeneity (0%–25%), moderate heterogeneity (25%–50%), and high heterogeneity (50%–100%) [29].

Sensitivity analysis was carried out for patients receiving reperfusion therapy. For the individual study, the study was included if more than 70% of the patients in this study treated with either intravenous thrombolysis or endovascular treatment.

3. Results

3.1. Chengdu stroke registry

3.1.1. Baseline characteristics

The patients included at each stage of analysis was summarized in the flow diagram (Fig. 1). Briefly, 1135 consecutive patients with AIS were enrolled in the registry. After excluding patients with onset to admission time > 7 days (n = 266); patients younger than 18 years (n = 1); patients with malignant tumor (n = 17); patients without information on NLR results (n = 23); patients treated with thrombolysis (n = 20); 808 patients were included in the analysis of hemorrhagic transformation. Besides, 126 patients lost to follow up at 3 months were excluded in the analysis of 3-month functional outcome. Among 808 patients, the average age was 63.9 ± 13.7 years; 479 (59.3%) were males. The median onset to admission time was 48 h (interquartile range, 24–96 h). The median and interquartile range of NLR was 3.38 [2.36–5.47]. We used 5 as the cut-off value for NLR, based on the average cut-off value of previous studies, to divide all the patients into 2 groups.

Table 1 shows the baseline characteristics of patients with low and high levels of NLR. Patients with higher NLR were older, had higher NIHSS scores, a lower rate of hyperlipidemia, and a higher rate of atrial fibrillation.

The median and interquartile range of HT occurrence was 5 [2,9] days after stroke onset. HT occurred in 10.15% patients (82/808), with 13 HI-1, 27 HI-2, 23 PH-1, and19 PH-2. Meanwhile, 19 patients had sICH (2.35%). Forty-four percent of HT was detected by follow up CT and 56% by MRI. Additionally, 682 patients had follow-up data of 3-month functional outcome. Among them, 195 patients experienced 3-

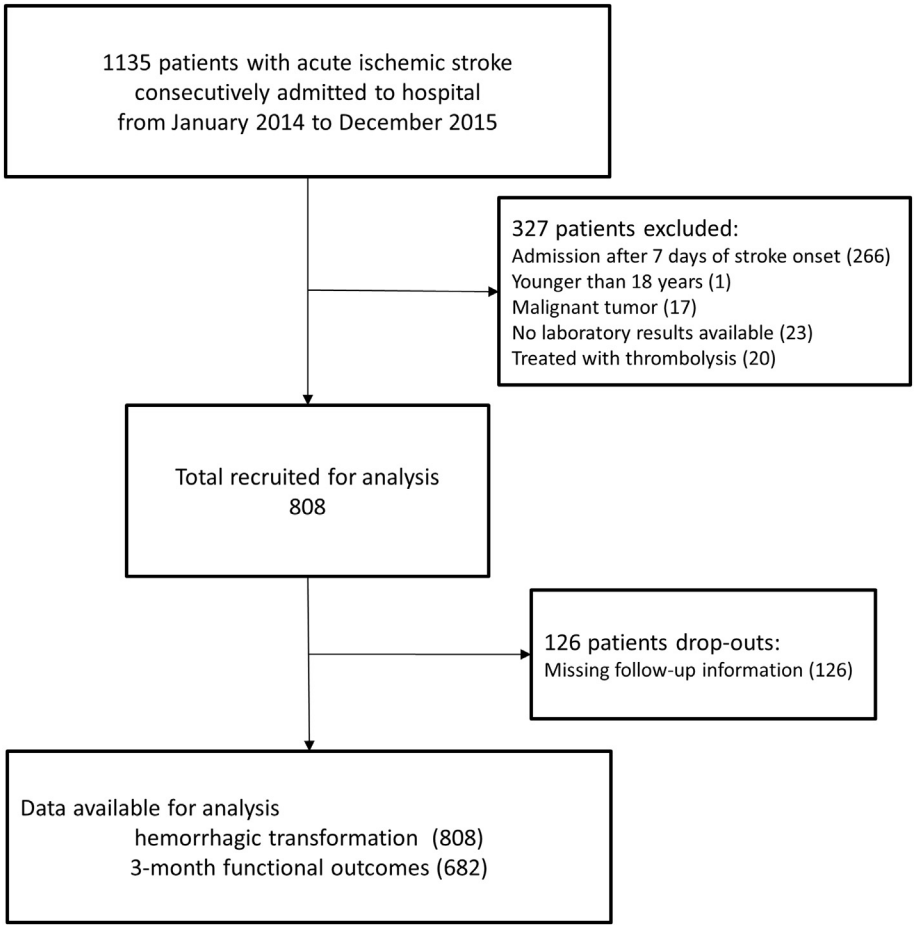

Fig. 1. The flow diagram of the selection process of eligible patients in cohort.

Table 1
Patient characteristics, stratified by neutrophil to lymphocyte ratio level < 5 and ≥ 5.

Variable	Reference group	Elevated group	*p*-Value
NLR	< 5	≥5	
	n = 568	*n* = 240	
Age, years, mean (SD)	62.9 (13.6)	66.6 (13.6)	< 0.001
Male, n (%)	331 (58.3)	148 (61.7)	0.370
NLR, median (Q1-Q3)	2.7 (2.1–3.6)	7.1 (5.8–10.3)	< 0.001
Onset to admission time, h, median (Q1-Q3)	48 (24–96)	48 (24–96)	0.141
Baseline NIHSS score, median (Q1-Q3)	3 (2–7)	9(3–14)	< 0.001
Hypertension, n (%)	362 (63.7)	140 (58.3)	0.148
Diabetes, n (%)	154 (27.1)	48 (20.0)	0.033
Hyperlipidemia, n (%)	99 (17.4)	22 (9.2)	0.003
Atrial fibrillation, n (%)	61 (10.7)	44 (18.3)	0.003
Rheumatic heart disease, n (%)	23 (4.1)	13 (5.5)	0.388
Coronary heart disease, n (%)	30 (5.4)	15 (6.4)	0.581
History of stroke, n (%)	70 (12.3)	37 (15.4)	0.240
Smoking, n (%)	177 (31.2)	68 (28.3)	0.424
Alcohol consumption, n (%)	135 (23.8)	58 (24.2)	0.903
Hemoglobin, g/L, mean (SD)	136.6 (19.4)	133.1 (20.5)	0.019
Blood platelet count, $^{\wedge}10^9$/L, mean (SD)	172.7 (60.9)	164.2 (71.8)	0.089
HT, n (%)	38 (6.7)	44 (18.3)	< 0.001
PH, n (%)	17 (3.0)	25 (10.4)	< 0.001
sICH, n (%)	9 (1.6)	10 (4.2)	< 0.001
3-m death or disability, n (%)	120 (25.3)	75 (36.2)	0.004
3-m death, n (%)	3 (0.6)	18 (8.6)	< 0.001
Therapy after admission			
Antiplatelet, n (%)	540 (95.1)	229 (95.4)	0.834
Anticoagulation, n (%)	32 (5.6)	17 (7.1)	0.430
TOAST			0.189
Large-artery atherosclerosis, n (%)	203 (36.6)	83 (35.8)	
Small-artery occlusion, n (%)	110 (19.9)	33 (14.2)	
Cardio-embolism, n (%)	86 (15.5)	51 (22.0)	
Undetermined etiology, n (%)	15 (2.7)	5 (2.2)	
Other etiology, n (%)	140 (25.1)	60 (25.9)	
In-hospital complications			
Pneumonia, n (%)	119 (21.0)	96 (40.0)	< 0.001
Urinary tract infection, n (%)	19 (3.3)	13 (5.4)	0.168
Gastrointestinal bleeding, n (%)	10 (1.8)	19 (7.9)	< 0.001
Length of stay, d, median (Q1-Q3)	10 (8–13)	12 (8–18)	< 0.001

NLR, neutrophil to lymphocyte ratio, NIHSS, National Institutes of Health Stroke Scale, n, number, SD, standard deviation, HT, hemorrhagic transformation, PH, parenchymal hematoma, sICH, symptomatic intracranial hemorrhage, 3-m, 3-month, d, day. TOAST, Trial of Org 10,172 in Acute Stroke Treatment classification.

month death or disability (29%); 21 died within 3 months (3.1%).

3.1.2. The admission NLR and HT

Supplementary Fig. 1 shows the NLR levels in different ECASS subtypes. PH-2 group had the highest NLR levels compared with other groups. As shown in Table 2, univariate analysis found that NLR level was associated with HT and PH. After adjusting for age, sex, baseline NIHSS, hyperlipidemia, atrial fibrillation, smoking, antiplatelet, no significant association was discovered when NLR was treated as a continuous variable; however, when regarding NLR as a categorical variable with the cut-off value, it was independently associated with HT (OR 2.10, 95%CI 1.25–3.51) and PH (OR 2.54, 95%CI 1.25–5.18), rather than sICH (OR 1.90, 95%CI 0.68–5.30) after adjustment for age, sex, and NIHSS scores (model 1). Additionally, NLR ≥5 remained significantly associated with HT and PH when further adjustment for hyperlipidemia, atrial fibrillation, smoking, antiplatelet therapy (OR 2.03, 95%CI 1.19–3.46) and (OR 2.54, 95%CI 1.20–5.35), respectively (model 2).

The AUC for the ability of NLR to predict HT was (0.67, 95% CI [0.61, 0.73]), which was lower than that to predict PH (0.70, 95% CI [0.62, 0.78]), but higher than that to predict sICH (0.61, 95% CI [0.46, 0.76]). However, the specificity of NLR predicting HT was higher than that of PH and sICH (73% versus 72% and 71%, Supplementary Table 1).

3.1.3. The admission NLR and 3-month outcomes

Supplementary Fig. 2 shows the NLR levels in different 3-month mRS subgroups. Three-month death group had the highest NLR levels compared with other groups. NLR levels in patients grouped by onset to admission time are displayed in Supplementary Fig. 3. The medians and interquartile ranges of NLR for patients admitted at day 1, day 1–3, day 3–5, day 5–7 after onset were 3.5 [2.4–6.0], 3.3 [2.5–5.7], 3.0 [2.2–5.0], and 3.6 (2.4–5.3), respectively (p = .057). In univariable analysis, NLR was associated with 3-month death or disability no matter what form it was; however, multivariable regression analysis did not identify significant association after adjusting for age, sex, and NIHSS scores in model 1 or further adjusting other factors in model 3 (Table 2). On the contrary, both NLR increase in 1-unit and NLR ≥5 were associated with 3-month death in model 1 (OR 1.13, 95%CI 1.05–1.23; OR 6.66, 95%CI 1.75–25.36, respectively). In model 3, further adjusting for in-hospital pneumonia, urinary tract infection, and other potential factors did not change the results substantially (OR 1.13, 95%CI 1.03–1.23; OR 5.55, 95%CI 1.41–21.89, respectively). Table 2 summarizes the results of univariable and multivariable analyses.

The accuracy for NLR predicting 3-month death or disability was low: AUC being 0.58 with sensitivity of 38% and specificity of 73%; but for predicting 3-month death, the discriminative ability was relatively better: AUC being 0.81 with sensitivity of 86% and specificity of 71%. (Supplementary Table 1).

3.2. Systematic review

3.2.1. Literature search

During the initial screening, we identified 191 records from English databases and 120 from Chinese databases. After screening the title and abstract, 236 irrelevant or duplicated articles were excluded and 75 potentially eligible articles were assessed by reviewing the full text. Then 52 studies were further excluded: (1) 10 studies included patients with hemorrhagic stroke or transient ischemic attack (TIA); (2) 25 studies focused on the association between NLR and other conditions including stroke severity evaluated by NIHSS scores (n = 4), stroke-associated complications (n = 11), or the risk of stroke (n = 10); (3) 5 studies did not have full-article published; (4) 12 studies were narrative review (n = 11) or meta-analysis (n = 1). Finally, 23 articles reporting 9563 patients were identified and therefore included in the current systematic review [15–17,30–46]. Supplementary Fig. 4 summarizes the study selection process and the screening steps.

3.2.2. Study characteristics

The full basic characteristics of the 23 included studies are presented in Table 3 and Supplementary Table 2. Eight studies excluded patients with hematologic disease, 15 excluded patients with cancer, and 14 excluded patients with premorbid infection.

For the 9563 patients, the median age was 66.5 years (interquartile range, 64–69) with 57.9% (5535) males, and 38.3% (3659) patients treated with reperfusion therapy. The median and interquartile range of onset to admission time was 12 [4.5–48] hours. All patients were taken blood samples on admission. The median NLR value was 3.7 (interquartile range, 3.02–4.41).

Moreover, 12.39% (176/1420) patients had HT and 8.1% (211/2601) patients experienced sICH; 45% (1652/3675) patients experienced death or disability at 3 months; 16% (413/2582) patients died

Table 2
Univariate and multivariate analyses of the neutrophil to lymphocyte ratio with different outcomes.

	Univariate analysis	Model 1	Model 2	Model 3
OR (95% CI) of NLR as a continuous variable				
HT	1.07 (1.03, 1.12)**	1.04 (0.94, 1.08)	1.02 (0.97, 1.07)	–
PH	1.07 (1.03, 1.12)**	1.04 (0.99, 1.09)	1.02 (0.97, 1.07)	–
sICH	1.04 (0.98, 1.11)	1.02 (0.94, 1.11)	1.00 (0.92, 1.09)	–
3-m death or disability	1.06 (1.02, 1.10)**	1.00 (0.96, 1.05)	–	0.98 (0.93, 1.03)
3-m death	1.16 (1.09, 1.24)*	1.13 (1.05, 1.23)**	–	1.13 (1.03, 1.23)*
OR (95% CI) of NLR as a categorical variable (≥5 vs < 5)				
HT	3.13 (1.97, 4.98)*	2.10 (1.25, 3.51)**	2.03 (1.19, 3.46)**	–
PH	3.77 (2.00, 7.12)*	2.54 (1.25, 5.18)**	2.54 (1.20, 5.35)**	–
sICH	2.70 (1.08, 6.73)**	1.90 (0.68, 5.30)	1.80 (0.63, 5.14)	–
3-m death or disability	1.68 (1.18, 2.39)**	0.98 (0.66, 1.47)	–	0.92 (0.60, 1.40)
3-m death	14.89 (4.34, 51.12)*	6.66 (1.75, 25.36)**	–	5.55 (1.41, 21.89)*

Model 1 bivariate logistic regression analyses with adjustment for age, sex, and baseline NIHSS.
Model 2 bivariate logistic regression analyses with adjustment for age, sex, baseline NIHSS, hyperlipidemia, atrial fibrillation, smoking, antiplatelet therapy.
Model 3 bivariate logistic regression analyses with adjustment for age, sex, baseline NIHSS, hyperlipidemia, atrial fibrillation, smoking, antiplatelet therapy, onset to admission, pneumonia, urinary tract infection, gastrointestinal bleeding, hemoglobin and length of stay.
HT, PH, and sICH were analyzed in Model 1 and 2.
Three-month death or disability and 3-month death were analyzed in Model 1 and 3.
OR odds ratio, CI, confidence interval, NLR, neutrophil to lymphocyte ratio, HT, hemorrhagic transformation, PH parenchymal hemorrhage, sICH symptomatic intracranial hemorrhage, 3-m, 3-month.
* $P < .001$.
** $P < .05$.

within 3 months; 27.8% (71/255) died within 2 months;14.3% (42/294) died within 1 month, and 6.2% (199/3201) died in hospital.

Eleven studies reported ORs of NLR as a continuous variable [30–37,39,41,47] and 8 studies reported ORs of NLR as a categorical variable [16,17,38,40,42–44,46], which had larger values of OR. One study reported both 2 kinds of ORs [15]. Three studies did not report ORs numerically [10,45,48]. All the quantitative analysis results were summarized in the Supplementary Table 3. Ten studies were ranked as adequate quality (7–9 points). The detailed quality assessment results of each study were displayed in the Supplementary Table 4.

3.2.3. The admission NLR and HT

Eight studies reported the association between NLR and hemorrhage after ischemic stroke [15,16,31–33,35,40,47]. Three studies reported NLR and HT [31,32,47]; 5 reported sICH [15,16,33,35,40]; One study reported OR of NLR obtained at 12–18 h after thrombolysis and PH, but did not provide OR of NLR on admission [40]. Supplementary Table 5 displays the different definition and classification of HT and sICH.

In the meta-analysis which included our cohort and other observational studies, NLR increment by 1-unit was insignificantly associated with HT (OR 1.10, 95%CI 0.99–1.22) but significantly associated with sICH (OR 1.08, 95%CI 1.01–1.15), both with high heterogeneity. The forest plots show the ORs and 95%CIs of NLR as a continuous and categorical variable and different outcomes in each study (Figs. 2 and 3).

When compared high NLR with low NLR, elevated NLR was associated with a higher risk of HT and sICH. The pooled ORs were 1.99 (95% CI, 1.45–2.73) for HT (2 studies incorporating 2041 patients) and 2.22 (95% CI, 1.60–3.09) for sICH (5 studies with 3116 patients), with no heterogeneity.

The pooled analysis found similar predictive values for HT with our

Table 3
Baseline characteristic of included studies in systematic review.

NO	Author	Year	Sample size	Time of blood collection	Average age (y)	Male (%)	Average NLR	HT	3-m death or disability	3-m death	NOS
1	Gokhan	2013	654	NA	67.74	51.7	4.87	NA	NA	Yes	5
2	Tokgoz	2013	255	24	69.37	49	5	NA	NA	Yes	7
3	Tokgoz	2014	151	24	69.37	53.6	4.85	NA	NA	Yes	7
4	Celikbilek	2014	70	NA	69.53	47.1	3.3	NA	NA	Yes	5
5	Brooks	2014	116	6	68	46	3.74	NA	Yes	Yes	5
6	Maestrini	2015	846	4.5	71	50.8	3.72	Yes	Yes	Yes	5
7	Guo	2016	189	4.5	65	65.1	2.95	Yes	NA	NA	7
8	Xue	2017	280	144	61.8	61.8	2.1	NA	Yes	NA	6
9	Fang	2017	1731	48	68.02	63.1	3.99	NA	NA	Yes	7
10	Qun	2017	143	24	70	56	2.75	NA	Yes	NA	8
11	Fan	2017	362	48	63	59.7	4	NA	NA	Yes	5
12	Malhotra	2018	657	4.5	64.3	50	2.4	Yes	Yes	Yes	5
13	Duan	2018	616	6	66	59.7	7.08	Yes	Yes	Yes	8
14	Kocaturk	2018	107	12	67	53.3	3.68	NA	NA	Yes	8
15	Yu	2018	454	72	72.4	55.7	3.24	NA	NA	Yes	4
16	Goyal	2018	293	12	62	50	3.5	Yes	Yes	Yes	6
17	Wang	2018	199	6	65	64.3	6.51	NA	Yes	NA	8
18	Guo	2018	105	4.5	65.7	64.8	3.02	NA	Yes	NA	7
19	Pikija	2018	187	6	74	45.9	3.6	Yes	NA	NA	6
20	Song	2018	1233	168	64.1	63.5	3.89	Yes	NA	NA	6
21	Yilmaz	2018	143	NA	NA	53.1	4.41	NA	NA	Yes	4
22	Shi	2018	372	4.5, 24	64	65	NA	Yes	Yes	NA	8
23	Jin	2019	400	96	64	63.7	2.2	NA	Yes	NA	5

NO, number, y, year, HT, hemorrhagic transformation, 3-m, 3-month, NOS, Newcastle-Ottawa Scale, NA, Not Available.

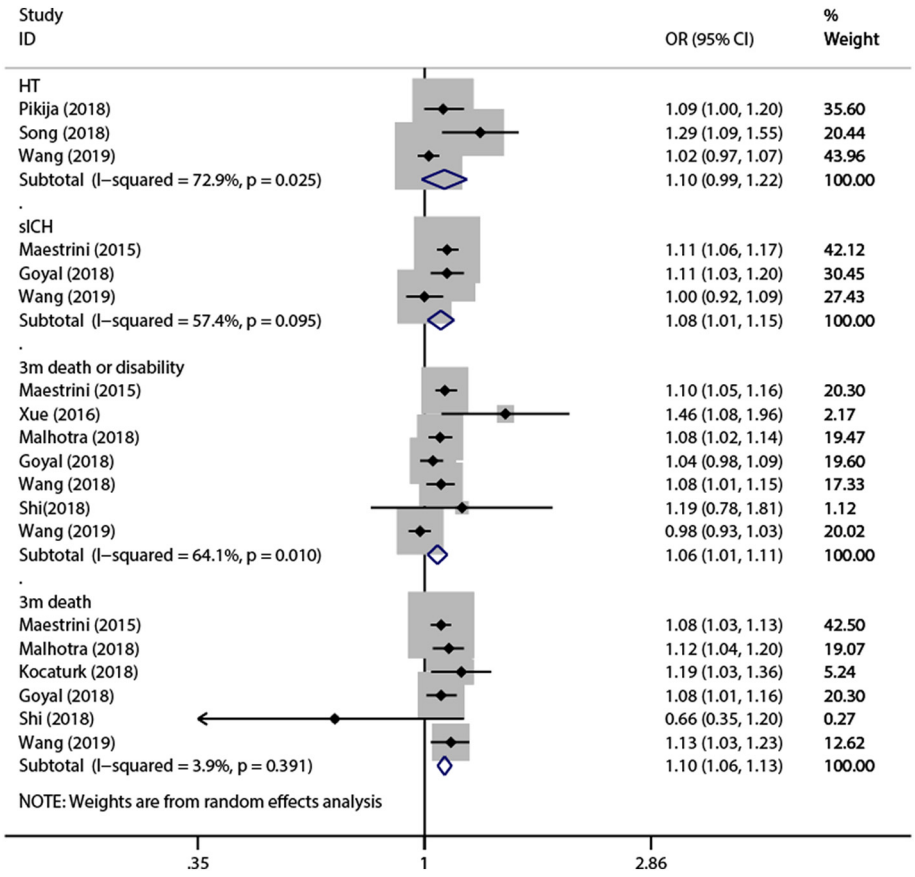

Fig. 2. The odds ratio and 95% confidence interval of neutrophil to lymphocyte ratio (NLR) predicting different outcomes, with NLR effect estimates expressed as a continuous variable (1-unit change).
HT, hemorrhagic transformation, sICH, symptomatic intracranial hemorrhage, 3 m, 3-month.

registry data, with AUC being 0.67; The AUC for NLR predicting sICH was 0.66 with sensitivity being 62% and specificity being 67%, Supplementary Table 1.

3.2.4. The admission NLR and 3-month outcomes

Ten studies with 3791 individuals reported the association between NLR and 3-month death or disability [15,16,30,33,35,37,38,43,46,47]. Fifteen studies reported information on death [10,15–17,33–36,39,41–45,47]. Among these studies, 8 on 3-month death [15,16,33–35,42,43,47]; 1 on death at 2-month [44]; 2 on 1-month death [10,41]; and 4 on death in-hospital [17,36,39,45].

Fig. 2 shows that the OR and 95% CI of NLR as a continuous variable for 3-month death or disability being 1.06 (1.01–1.11), comprising 3588 individuals; and for 3-month death, being 1.10 (1.06–1.13) with 3083 individuals.

Six studies with 2476 patients contributed data for NLR as a categorical variable to predict 3-month death or disability; 5 studies (2267 patients) contributed data for 3-month death. The pooled ORs were 1.68 (95% CI, 1.18–2.38) and 2.79 (95% CI, 1.57, 4.94), both with moderate to high heterogeneity (Fig. 3).

Compared with our registry data, meta-analysis of previous predictive accuracy data observed higher AUC, higher sensitivity, and lower specificity for 3-month death or disability, as well as lower AUC, lower sensitivity, and lower specificity for 3-month death, Supplementary Table 1.

3.2.5. Sensitivity analysis

Ten studies of patients treated with reperfusion therapy were included in the sensitivity analysis [15,16,30,32,33,35,40,43,46,47]. We found a higher risk of sICH, 3-month death or disability, and 3-month death in patients with higher NLR levels, with low to moderate heterogeneity among studies, Supplementary Table 3.

4. Discussion

In the present cohort study and meta-analysis, we evaluated the strength and consistency for the association, and predictive accuracy of admission NLR with HT and its subtypes, 3-month death or disability, and 3-month death with data from 10,388 patients. The NLR levels graded by the severity of HT and degree of unfavorable functional outcomes. Higher NLR was associated with a higher risk of HT and 3-month death in patients with AIS. When comparing the discriminative ability, the AUC for NLR predicting 3-month death was highest; the sensitivity was highest for predicting 3-month death and the specificity was highest for predicting HT, both in our registry data and meta-analysis. Consistent findings were observed when we synthesized patients treated with reperfusion therapy.

Mostly, biomarker levels are associated with outcome in continuous rather than categorical manner [49]. In our study, HT was associated with NLR as a categorical variable, not as a continuous variable. This may be the increase of HT risk per 1-unit NLR was too weak to be detected. Additionally, the association of NLR and PH was stronger than that of HT, which suggested that NLR may be associated with more severe hemorrhage rather than mild hemorrhage. Considering the potential confounding effect of infection in the association, we further adjusted pneumonia and urinary tract infection in model 3. We found no significant association between NLR and 3-month death or disability, while the association between NLR and 3-month death remained strong and stable.

The underlying mechanism why elevated NLR was associated with

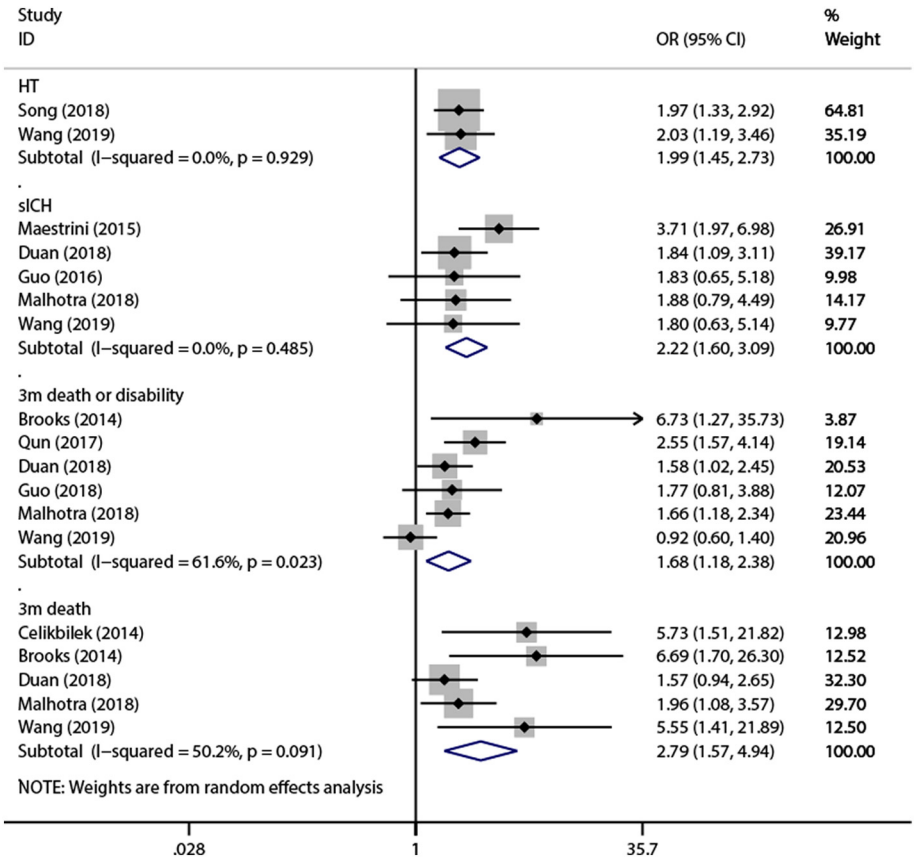

Fig. 3. The odds ratio and 95% confidence interval of neutrophil (NLR) to lymphocyte ratio predicting different outcome groups, with NLR effect estimates expressed as a categorical variable.
HT, hemorrhagic transformation, sICH, symptomatic intracranial hemorrhage, 3 m, 3-month.

poor outcomes may be related to the over-activation of inflammation and the state of immunosuppression. Firstly, after ischemic stroke, the damaged brain tissue would produce strong inflammatory response, along with the subsequent increase of inflammatory biomarkers such as NLR [50]. The normal value of NLR in healthy populations was 1.65 (mean), ranging from 0.78 to 3.53 [51], while average NLR values in our registry and meta-analysis were higher than that in healthy populations. Although inflammation is necessary to repair the cerebral injuries after stroke onset, overactivation of inflammation would cause harm to brain tissue, resulting in neurological deterioration, cerebral edema, and HT [4]. Secondly, a recent theory about post-immunosuppression has suggested that after stroke onset, the catecholamines are released into the blood by the over-activated sympathetic nervous system, which may reduce the circulating lymphocytes and increase the risk of following infection [9,13]. The finding of Kim verified the inverse association, stating that lower lymphocyte count was associated with 3-month poor functional outcome of stroke [8]. Thus, combing neutrophils and lymphocytes together, NLR may reflect the imbalance of overactive inflammation and the protective regulation, and have superiority over using neutrophils or lymphocytes alone [52].

Our main findings are in line with previous studies [31,53]. However, we further explored the association between NLR and PH as well as sICH. As far as we know, our study was the first to highlight the role of NLR predicting 3-month death independent of post-stroke pneumonia. We also analyzed our data and all the published data to compare the predictive values of NLR for different outcomes.

Several limitations of this study need to be acknowledged. Firstly, clinical heterogeneity or methodological heterogeneity might exist in the meta-analysis. However, the large sample size suggested the association was not due to a play of chance. Secondly, the time delay from blood sampling to stroke onset slightly differed among studies. It has been reported that neutrophils recruit as early as 5 h after stroke and peak at 24 h [4], so NLR values may demonstrate temporal variation [15]. However, we performed the same analysis for patients admitted within 24 h in our registry, and the results did not change materially (data not shown). Previously, most studies reported NLR measured within 24 h and before any treatment was associated with higher risk of hemorrhage and unfavorable outcome (14 studies involving 4236 patients). However, Guo reported that NLR obtained at 12–18 h after thrombolysis, not NLR on admission, was independently associated with hemorrhagic transformation [40]; Petrone indicated that the prognostic value of NLR was altered at different time points after stroke and NLR at 48–72 h post-stroke was a predictor of a unfavorable outcome [54]. Serial measurement might provide more information about the association. Further studies should focus on the relationship of prognoses and serially dynamically monitored NLR. It is worth investigating whether NLR detected at certain time points have better predictive value than NLR value on admission. Thirdly, although higher admission NLR was associated with more hemorrhage and less favorable outcomes, it is still unclear whether adding NLR to the prognostic model would improve the accuracy of reclassifying patient's prognoses, and whether using NLR could help clinicians to identify patients at a high risk of sICH following reperfusion therapy. Future studies are warranted to verify our results.

5. Conclusion

In conclusion, our cohort study and meta-analysis suggested that admission NLR was positively associated with the risk of HT and 3-

month death after AIS. However, considering the limited predictive ability of a single biomarker, more studies should be taken to validate whether the addition of NLR into conventional prognostic models would improve their performance of predicting unfavorable prognoses and optimizing individual risk stratification.

Author contributions

M. Liu are responsible for the conception and design of the study. S.M Wu, L.H. Deng, Y.X. Li and L.K. Zheng were responsible for the acquisition of the registry data. Q.H. Song and L.K. Zheng searched databases and extracted data for systematic review. L Wang and C.Y. Wang performed the data analysis. L Wang, Q.H. Song, C.Y. Wang wrote the first draft of the manuscript. L Wang and S.M Wu interpreted the data and wrote the final version. All authors critically revised the article for important intellectual content and approved the final version. M. Liu obtained public fundings.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.116445.

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