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Neutrophil–lymphocyte ratio predicts the outcome of intracerebral hemorrhage

A meta-analysis

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Abstract

Background: The neutrophil–lymphocyte ratio (NLR) is increasingly recognized as a systemic inflammation factor. It has been used as a predictor for clinical outcomes in cancers. However, its relationship with intracerebral hemorrhage (ICH) is still disputed. We sought to evaluate the prognostic role of NLR in ICH.

Methods: We searched PubMed, Cochrane Library, Medline, and EMBASE for potentially relevant articles from inception to April 8, 2018. Efficacy outcomes included major disability at 90 days, short-term mortality or in-hospital mortality. Odds ratio (OR) with 95% confidence interval (95% CI) were pooled to assess the association between NLR and ICH.

Results: A total of 7 trials with 2176 patients were included in this meta-analysis. It revealed that higher NLR had a higher risk of major disability at 90 days (OR: 2.20; 95% CI: 1.27–3.81) and higher mortality at short-term (OR: 1.31; 95% CI: 1.02–1.68) in ICH; without statistically significant association with in-hospital mortality (OR: 1.02; 95% CI: 0.91–1.15).

Conclusions: Our meta-analysis proved that high NLR was a predictor of major disability and mortality at short term in ICH patients, but not a predictor of in-hospital mortality.

Abbreviations: AIS = acute ischemic stroke, CI = confidence interval, ICH = intracerebral hemorrhage, MRS = modified Rankin Scale, NLR = neutrophil–lymphocyte ratio, NOS = Newcastle-Ottawa scale, OR = odds ratio.

Keywords: functional outcome, intracerebral hemorrhage, modified Rankin Scale, mortality, neutrophil–lymphocyte ratio, prognosis

1. Introduction

Stroke is defined as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause.[1] It is the leading cause of disability and mortality in the worldwide.[2,3] Among all strokes, ICH comprises the second most common type, which accounts for about 10% to 20%.[4,5] Its fatality rate is approximately 40% at 1 month and 54% at 1 year. Only 12% to 39% of survivors can achieve functional independence at long-term.[6] It remains a critical disease with little effective treatment options available at present.

Although the pathology of ICH has not been investigated very well, inflammation is suggested as one of the major pathological pathways involved in the progression of ICH.[7] In animal models, strong inflammatory reaction occurs after ICH, including blood leukocyte infiltration, following release of various cytokines and microglia activating.[8] Proof from experimental studies indicates that leukocytes release cytokine after ICH and cause secondary brain injury.[9] Mounting evidence has shown that elevated leukocyte levels may associate with worse neurological function and higher mortality after ICH.[10,11] The NLR, which is calculated as the ratio of absolute neutrophil count to absolute lymphocyte count, is increasingly known as an indicator of systemic inflammation.[12] Neutrophils induce inflammatory responses while lymphocytes have anti-inflammatory and endothelial protective functions.[13] The increase of NLR indicates that the neutrophil-associated inflammatory reaction is increased and the lymphocyte-mediated anti-inflammatory reaction is reduced.[13] The higher the overall NLR, the more intense the inflammatory response.[13] Lately, NLR has been associated with in-hospital mortality, early neurological deterioration, and 3-month prognosis in patients with ICH. Lattanzi et al[14] reported that higher neutrophils, lower lymphocytes, and higher NLR predicted worse prognosis at 3 months in ICH patients. Giede-Jeppe et al[15] found that NLR was associated with mortality in ICH patients. Tao et al[16] also proved that elevated NLR level predicted poor outcome at 90-day after ICH independently. However, Sun et al[17] came to an inverse opinion that high NLR level was not associated with poor outcome in ICH patients.

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Due to the disputation, 2 meta-analyses assessing the association between NLR and ICH were conducted.[18,19] Zhang et al[18] reported that high NLR predicted poor neurological functional outcome but not mortality at 90 days. In sharp contrast, Ye et al[19] declared that higher NLR was correlated with mortality but not the poor outcome at 90-day. The authors of both meta-analyses showed that their results should be taken with caution due to the small amount of trials and patients. They called for more studies to be conducted. Lately, new studies assessing the association between NLR and ICH have been reported. Thus, we carried on this meta-analysis to further measure the prognostic role of NLR in ICH.

2. Materials and methods

2.1. Search strategy and selection criteria

S1 Checklist, http://links.lww.com/MD/D66 showed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) checklist. We conducted a detailed protocol according to PRISMA (dx.doi.org/10.17504/protocols.io.qzwdx7e [PROTOCOL DOI]). PubMed, Cochrane Library, EMBASE and Medline from inception to April 8, 2018 were searched by 2 researchers separately. Keywords including intracranial hemorrhage, intracerebral hemorrhage, neutrophil–lymphocyte ratio, neutrophil to lymphocyte ratio were used. Languages were restricted to English. The study selection process was performed independently by 2 reviewers. They looked through titles and abstracts to exclude unrelated articles. Potential articles were further reviewed by evaluating the full text. Any discrepancy was discussed and resolved. Our inclusion criteria were as follows: Patients with spontaneous intracerebral hemorrhage. Studies evaluated the relationship between NLR level and ICH. One or more efficacy outcome including major disability at 90 days, short-term mortality and in-hospital mortality was evaluated. The OR and 95% CI of efficacy outcome were provided or can be calculated. The study must be a case-control study, cohort study, or randomized controlled study. Exclusion criteria included: The article is not in English; Related data was deficient. We obtained ethical approval for this meta-analysis from the ethics committee of the first affiliated hospital of Shantou University Medical College.

2.2. Data extract and quality assessment

Data from included studies were extracted by 2 reviewers independently. Any disparity was settled by consultation. Variables including year of publication, author information, baseline characteristics of participants (number of patients, age, and sex), sample time of blood, optimal cut-off value of NLR, study design, OR, and 95% CI on efficacy outcome were extracted. Newcastle-Ottawa scale (NOS) was utilized to evaluate the quality of nonrandomized researches in this meta-analysis by 2 reviewers independently. Studies with NOS score $>$ 6 were considered high-quality studies.[20]

2.3. Definition of efficacy outcomes

The efficacy outcomes included major disability at 90 days, short-term mortality or in-hospital mortality. Major disability was defined as a modified Rankin Scale (MRS) from 3 to 5. Short-term mortality was determined as mortality at 30 days or 90 days.

2.4. Data synthesis and analysis

We calculated the logOR and used the forest plots to assess the association between NLR and ICH. Heterogeneity among studies was evaluated and I^2 $>50\%$ indicated significant heterogeneity.[21] When no heterogeneity existed, a fixed effect model was chosen to pool OR. Otherwise, a random effect model was used. We also performed a sensitivity analysis to evaluate the donation of each study to heterogeneity. Publication bias was measured by utilizing the funnel plot with Egger test.[22] P value $<.05$ and the 95% CI not overlapping 1 was defined as statistically significant. STATA 12.0 was used to perform analyses.

3. Results

3.1. Search result

We found 80 articles in total; 34 of them were excluded because of duplication. By browsing titles and abstracts, we further eliminated 36 articles on account of the inclusion criteria. Eventually, 10 remaining articles were potentially eligible. After reading the complete text, we discovered that 2 of them were based on the same trial. Accordingly, we included the article with more detailed data[15] and excluded the other one.[23]. The study endpoints of another 2 articles were not the same efficacy outcome with our meta-analysis. Therefore, we discarded these 2 studies as well.[24,25] Eventually, 7 articles were included in the analysis.[14,17,23,16,26–28]Figure 1 shows the flow diagram.

3.2. Characteristic of studies

The study characteristics were present in Table 1. A total of 2176 patients were included in this meta-analysis. One of the included studies[27] did not provide basic characteristics of the trial and its NOS score cannot be calculated. The other 6 contained 1225 men and 902 women. Mean age ranged from 58.5 to 72.5 years old. The optimal cut-off values of NLR ranged from 4.58 to 7.35. These 6 studies had high quality because of the NOS score $>$ 6.

3.3. Overall analysis

3.3.1. Association of NLR and 90-day major disability. There are 4 articles assessing the association of NLR and the major disability at 90-day. As shown in Fig. 2, the pooled OR was 2.20 (95% CI, 1.27–3.81). It meant that higher NLR predicted poor neurological outcome at 90-day. Significant heterogeneity among studies was found ($I^2=68.1\%$, $P=.025$). After performing a sensitivity analysis, we found that heterogeneity mainly came from the study by Lattanzi et al.[14] Subsequently, the heterogeneity fell to 26.8% and the pooled OR was still significant (OR 1.63; 95% CI, 1.275–2.087) after abolishing this study.

3.4. Publication bias

A funnel plot (Fig. 3) demonstrated an asymmetrical dispersion of the functional outcome at 90-day. However, the Egger test revealed that these 4 studies had no publication bias ($P=.274$, 95% CI -5.4–11.13). Even so, due to the limited amount of studies included, a type II error may exist. This result should be treated with caution.

3.5. Association of NLR and short-term mortality

Five studies evaluated the prognostic role of NLR on short-term mortality in ICH patients. As shown in Fig. 4, the pooled OR was

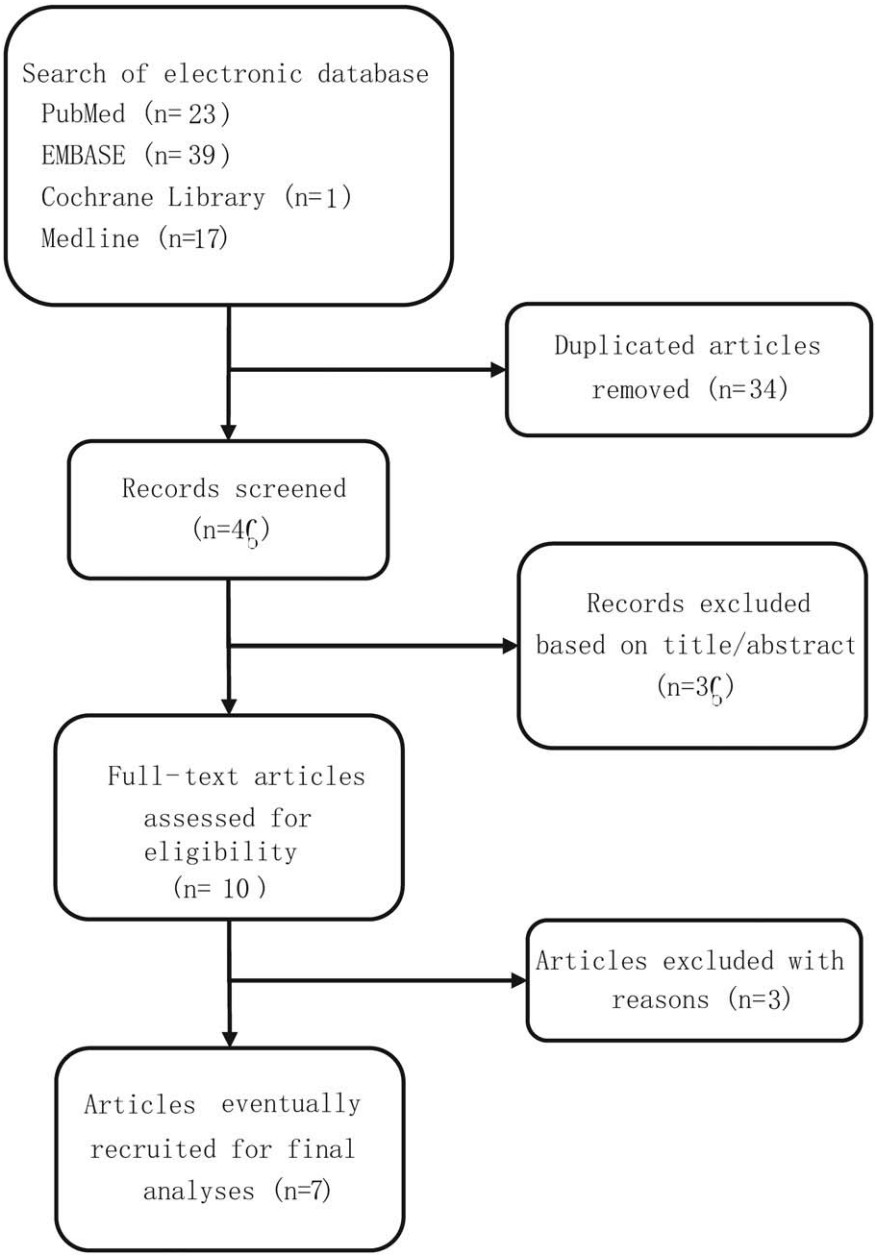

Figure 1. PRISMA flow diagram. The flow diagram of procedure to select studies.

1.31 (95% CI, 1.02–1.68, $I^2 = 90.3\%$, $P = .000$) by using a random-effect model. It revealed that higher NLR predicted higher mortality. After the sensitivity analysis, there was no significant change in heterogeneity by eliminating any single study.

3.6. Subgroup analysis

As to the 5 studies evaluating NLR on short-term mortality, 3 examined death at 90-day and 2 studies examined death at 30-day. Subgroup analysis showed that the pooled OR of the 3 studies examining death at 90 days was 1.58 (95% CI, 0.44–5.68, $I^2 = 93.3\%$, $P = 0.000$), and the pooled OR of the other two studies at 30 days was 1.80 (95% CI, 0.54–5.97, $I^2 = 80.1\%$, $P = .025$). The results demonstrated that NLR had no predictive effect on 90-day mortality or 30-day mortality separately. Heterogeneity in both subgroups was found.

3.7. Publication bias

The P value for the Egger test was .224 and the 95% CI was −29.44 to 45.50. It prompted that there was no significant publication bias among these 5 studies. A type II error may also exist due to the small numbers of studies.

3.8. Association of NLR and in-hospital mortality

Two studies assessed the association between NLR and in-hospital mortality. The result showed that the NLR had no

Table 1

Characteristics of studies.

Study	Study design	Number of patients	Mean age (SD)	Sex (M/F)	Sample time	Outcome measure	Optimal cut-off value	NOS score
Fei Wang 2015	Observational	224	67.97 (13.75)	141/83	On admission and next morning	Mortality at 30 d, in-hospital mortality	7.35	7
Fei Wang 2018	Retrospective	181	65.8 (14.3)	112/69	Next morning	Mortality at 30 d	7.35	7
Tao C 2017	Retrospective	336	58.5 (13.0)	216/120	On admission	Major disability (MRS 3–5), mortality and poor outcome at 90 d	6.28	7
Sun Y 2017	Prospective	352	64.2 (13.8)	234/118	Within 24 h of admission	Major disability (MRS 3–5), mortality at 90 days	7.85	8
Lattanzi 2016	Retrospective	177	67.1 (12.51)	63/114	On admission	Major disability (MRS 3–5) and poor outcome at 90 days	4.58	8
Seabra 2017	Retrospective	51	NR	NR	NR	Major disability (MRS 3–5) at 90 d and mortality at 30 days	NR	—
Giede-Jeppe 2017	Observational	855	Median 72.5 (NLR≥4.66) median 71 (NLR < 4.66)	457/398	On admission	Mortality and poor outcome at 90 d, in-hospital mortality	4.66	8

NOS score = Newcastle-Ottawa scale score, NR = not reported.

significant predictive value on in-hospital mortality by utilizing a random-effect model, with a pooled OR of 1.02 (95% CI, 0.91–1.15, $I^2 = 85.4\%$, $P = .009$, Fig. 5).

4. Discussion

This meta-analysis sought to evaluate the association between NLR and ICH. By April 8, 2018, a total of 7 published studies were included in our research. Of them, 4 studies reported major disability, 5 studies reported short-term mortality, and 2 articles assessed in-hospital mortality. Our results showed that high NLR had a predictive role for major disability at 90 days in ICH patients. Although significant heterogeneity among studied existed, it became very low after removing the study by Lattanzi et al, and the result was still valid. Higher NLR was also associated with higher mortality at short-term in our study. However, after performing the subgroup analyses, neither mortality at 90-day nor mortality at 30-day had significant association with NLR. Therefore, studies measuring the association between NLR and short-term mortality are needed. Our meta-analysis also demonstrated that NLR had no significant predictive value on in-hospital mortality.

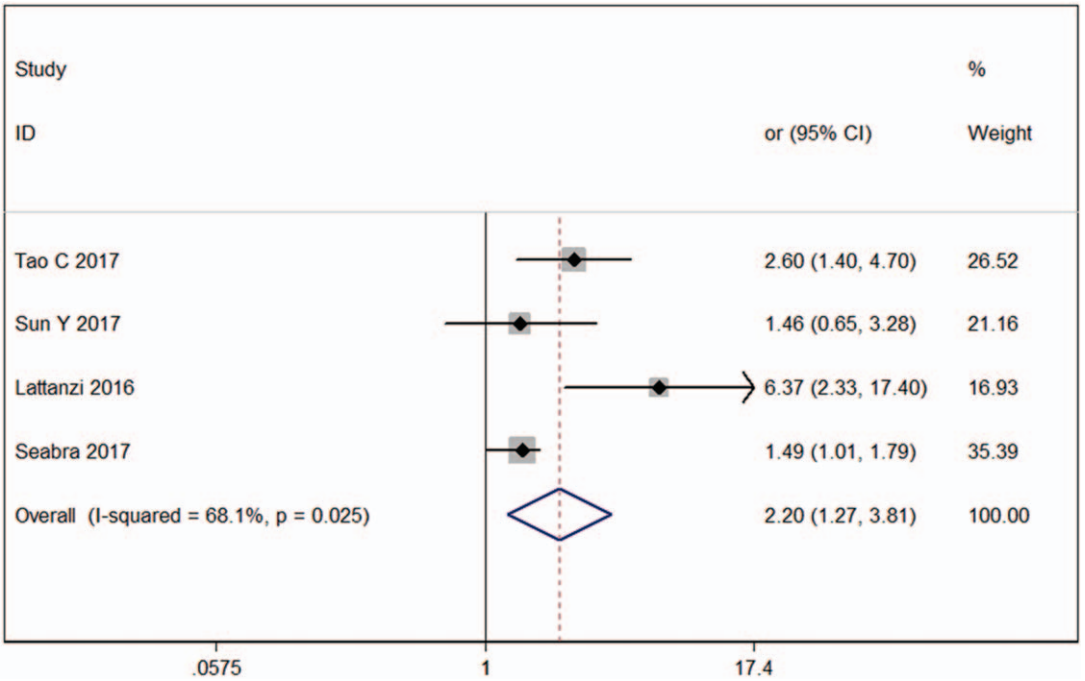

Figure 2. Forest plot for the association between NLR and major disability at 90-day. Pooled odds ratio of higher NLR for major disability at 90-day in patients with ICH. ICH = intracerebral hemorrhage, NLR = neutrophil–lymphocyte ratio.

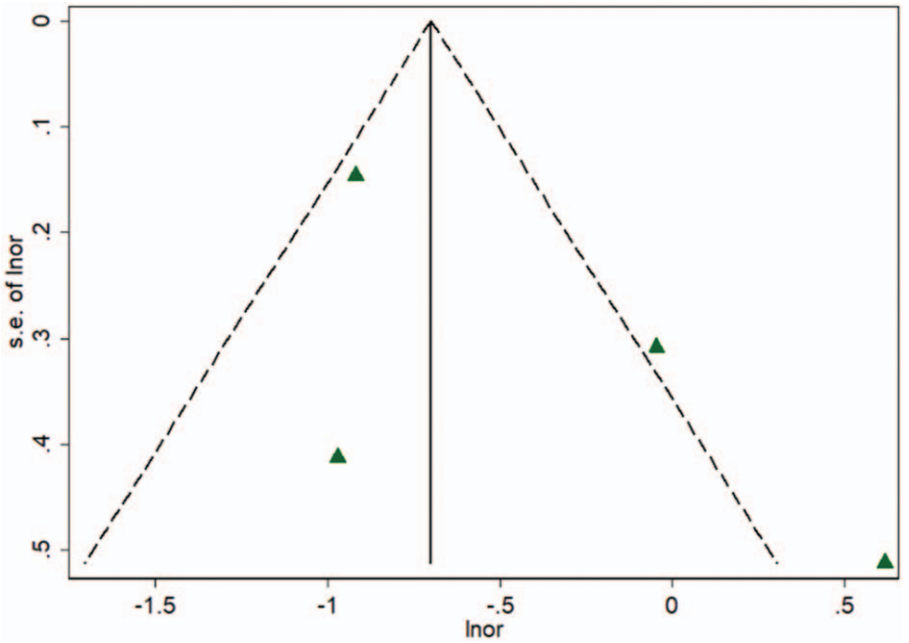

Figure 3. Funnel plot.

A meta-analysis by Zhang[18] evaluating the prognostic value of NLR in patients with ICH revealed that higher NLR was associated with higher risk of poor neurological functional outcome, but not higher mortality at 90-day. Another meta-analysis by Zengpanpan[19] showed that higher NLR predicted higher risk of 90-day mortality and in-hospital mortality, but not poor neurological functional outcome. These conclusions differed from the results of our meta-analysis. On account of

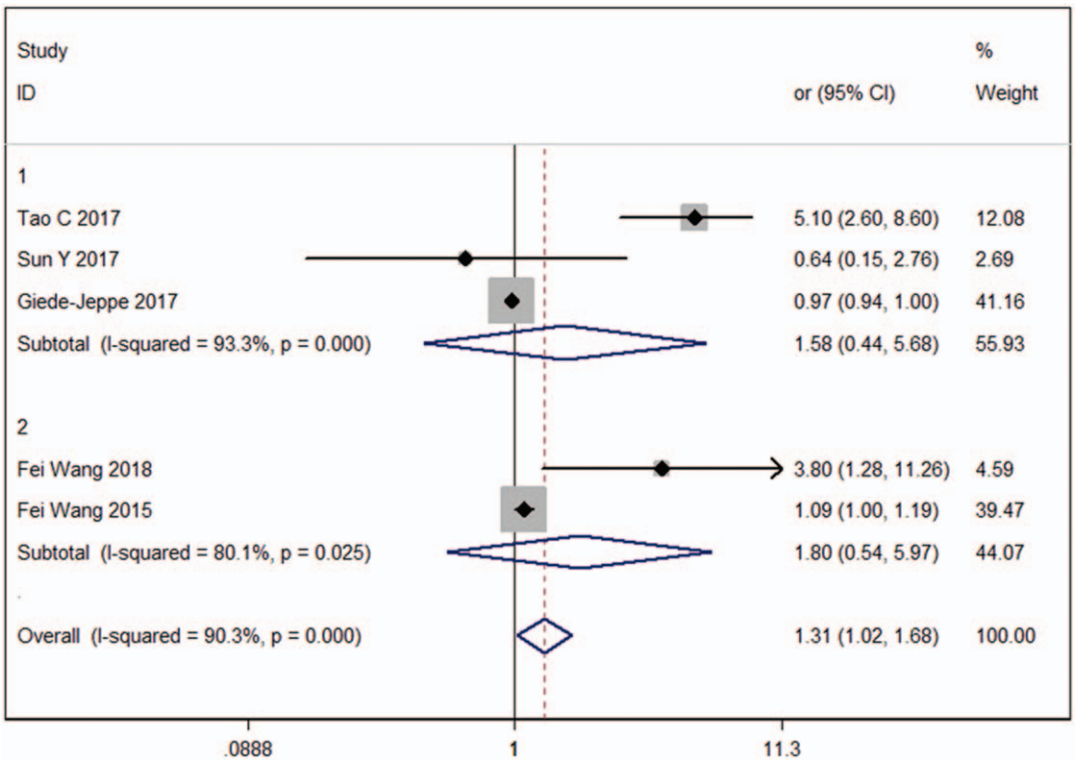

Figure 4. Forest plot for the association between NLR and short-term mortality. Pooled odds ratio of higher NLR for short-term mortality in patients with ICH.

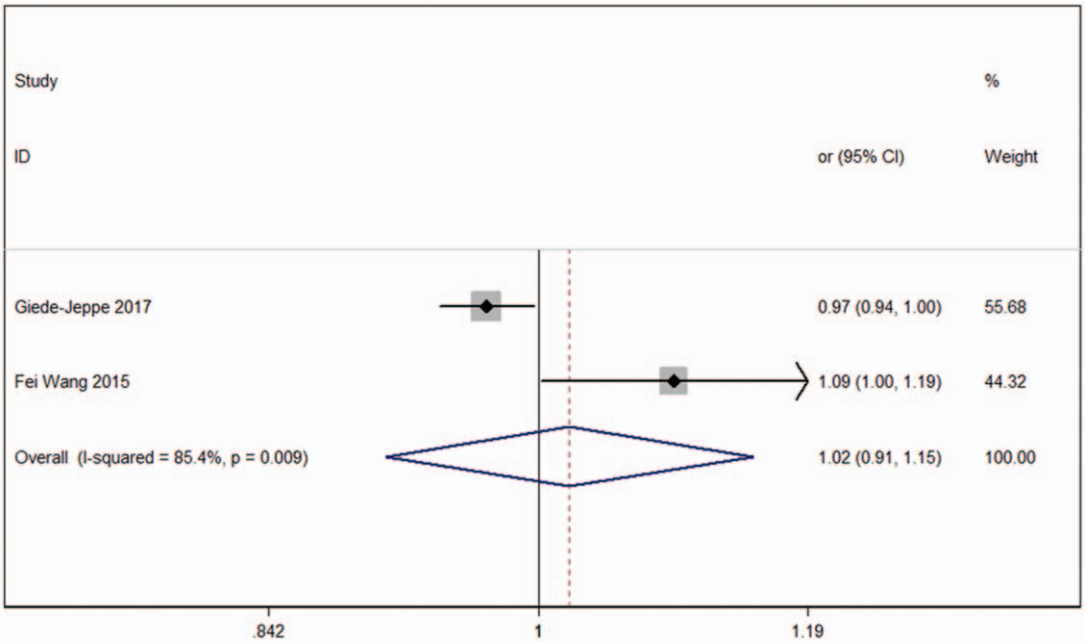

Figure 5. Forest plot for the association between NLR and in-hospital mortality. Pooled odds ratio of higher NLR for in-hospital mortality in patients with ICH.

more studies and patients included in our research, we are convinced that our findings are more dependable. The 2 meta-analyses written by Zhang and Zengpanpan both pointed out the limited amount of studies included and called for more articles to further research this issue. Our meta-analysis not only included the same trials with Zengpanpan's meta-analysis but also included 2 recent studies reported in 2017 and 2018. Consequently, we reduced the amount of bias and increased the statistical power in comparison with the previous meta-analyses, which made our finding more reliable.

The NLR is the ratio of the neutrophil count to lymphocyte count. Studies have shown that neutrophils can induce and activate inflammatory responses while lymphocytes have anti-inflammatory and endothelial protective functions.[13] The compromised balance between them is the basis of the inflammatory reaction. The higher the overall NLR, the more intense the inflammatory response.[13] The pathogenesis of ICH is an inflammatory process. In the early stage, cytokines regulate the increased migration of leukocytes to the hematoma and facilitate secondary brain injury.[24,29] Acute brain injury also causes the inactivation of lymphocytes, which greatly weaken host immune system.[18] Eventually, it may result in infectious complications, which are the main cause of poor prognosis in ICH patients.[18] Therefore, higher NLR represents elevated neutrophils (intense inflammatory response) or decreased lymphocytes (impairment of host defense), which would lead to a poor outcome in ICH.

NLR is an inexpensive and readily available marker. Our meta-analysis showed that higher NLR could predict major disability in ICH patients. It is in accordance with several previous articles and could be applied in clinical work.[16,17,26,28] There are similar studies put forward the prognostic role of NLR in patients with acute ischemic stroke (AIS), which is also an inflammatory process.[30–32]

Anti-inflammatory therapy has been supposed as a new therapy for ICH and AIS. In some experimental models, inhibition of neutrophils can improve clinical outcomes in mice with AIS.[33,34] Nowadays, due to its anti-inflammatory effect, hypothermia has been wildly studied as a method to treat ICH and AIS. In ICH model of rats, therapeutic hypothermia provides considerable neuroprotective effect.[35] However, potential complications may occur, such as infection and increased blood pressure.[9] Thus, anti-inflammatory therapy for ICH is still in question. It may become a new direction in the future.

In our study, several limitations must be emphasized. First, this study was on account of small amount of studies. Second, all studies included were retrospective studies. Missing data and selection bias were inevitable. Third, there were differences between the included studies, such as the blood sampling time and cut-off values of NLR. Finally, significant heterogeneity between studies was present. Therefore, our results should be used with caution. Specifically, we look forward more large-scale studies to assess the predictive value of NLR for ICH patients.

5. Conclusion

Our meta-analysis proves that higher NLR is a predictor of major disability at 90-day and higher mortality at short term in patients with ICH, but not a predictor of in-hospital mortality. NLR could be applied in the prognosis of ICH in clinical work.

Author contributions

Conceptualization: Weiduan Zhuang.
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Formal analysis: Shuo Liu.
Methodology: Shuo Liu, Shuying Chen, Yingxiu Xiao.
Project administration: Weiduan Zhuang.
Software: Shuo Liu, Xiaoqiang Liu.
Supervision: Yingxiu Xiao, Weiduan Zhuang.
Writing – original draft: Shuo Liu, Xiaoqiang Liu.

Writing – review & editing: Shuo Liu, Shuying Chen, Weiduan Zhuang.

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