Systematic Review and Meta-Analysis

Medicine®

OPEN

Prognostic impact of leukocytosis in intracerebral hemorrhage

A PRISMA-compliant systematic review and meta-analysis

Zhiyuan Yu, MD, Jun Zheng, MD, Rui Guo, MD, Lu Ma, MD, Chao You, MD*, Hao Li, PhD

Abstract

Background: Intracerebral hemorrhage (ICH) is correlated with high rate of death and poor outcome. Leukocytes participate in secondary brain injury in ICH. It is still not clear that whether leukocytosis can predict outcome in ICH. This study was performed to summarize that current evidences about the association between baseline leukocytosis and outcome in ICH patients in a systematic review and meta-analysis.

Methods: Published studies were searched in 5 databases. Original studies about association between baseline leukocytosis and outcome in ICH were included. Pooled odds ratios (ORs) and their 95% confidence intervals (CIs) were achieved to evaluate the association between leukocytosis and prognosis.

Results: A total of 19 eligible studies with 6417 patients were analyzed in this study. Meta-analysis showed baseline leukocyte count increase was significantly associated with worse overall (OR = 1.13, 95% CI 1.05–1.21, $P = .001$), short-term (OR = 1.20, 95% CI 1.05–1.38, $P = .009$), and long-term functional outcome (OR = 1.12, 95% CI 1.04–1.20, $P = .004$). Baseline leukocytosis defined by cut-off values had significant association with worse overall functional outcome (OR = 1.95, 95% CI 1.01–3.76, $P = .046$). Baseline leukocyte count increase was significantly associated with higher overall (OR = 1.10, 95% CI 1.02–1.18, $P = .011$) and long-term mortality (OR = 1.12, 95% CI 1.03–1.22, $P = .007$). Baseline leukocytosis defined by cut-off values was significantly associated with higher overall (OR = 1.67, 95% CI 1.23–2.27, $P = .001$) and short-term mortality (OR = 1.74, 95% CI 1.12–2.70, $P = .014$).

Conclusion: Baseline leukocytosis could be helpful in predicting prognosis in ICH patients. However, its prognostic value should be verified by further studies.

Abbreviations: CI = confidence interval, ICH = intracerebral hemorrhage, NOS = Newcastle–Ottawa Quality Assessment Scale, OR = odds ratio.

Keywords: intracerebral hemorrhage, leukocytosis, meta-analysis, prognosis, systematic review

1. Introduction

Intracerebral hemorrhage (ICH) is a devastating kind of stroke accounting for approximately 10% to 15% of all stroke cases.[1] ICH is related to high death rate and poor outcome throughout the world.[2] Inflammation has a crucial role in the secondary injury after occurrence of ICH, which can potentially be prognostic predictors for ICH patients.[3,4] Leukocytes participate in secondary brain injury in ICH.[5,6] After ICH, brain–blood barrier is disrupted and leukocytes infiltrating into perihematomal area.[7] Moreover, infiltrating leukocytes can release proinflammatory factors, activate microglia, and further damage blood–brain barrier.[8,9] Leukocytosis, which means the increased white blood cell count, can be observed at the early phase after ICH.[10] Early leukocytosis can be unrelated to infection and induced by stress after onset of ICH.[11] Moreover, a previous study using animal model has suggested that infiltrating leukocytes after ICH mainly originate from circulation.[12] Thus, baseline leukocytosis may represent the early inflammatory process in patients with ICH.[13] Although previous studies discussed the association between baseline leukocytosis and prognosis in patients with ICH, those studies had conflicting results.[10,13–16] Thus, this systematic review and meta-analysis was done to summarize that current evidences about the association between baseline leukocytosis and outcome in patients with ICH.

2. Material and methods

2.1. Study Search

This study was a systematic review and meta-analysis based on the current literature and ethical approval was not necessary. A systematic search of published studies was performed on September 5, 2018 in 2 international databases (PubMed and Embase) and 3 Chinese databases (CNKI, VIP, and Wanfang). The following items

Editor: Elena Cecilia Rosca.

This work was supported by Outstanding Subject Development 135 Project of West China Hospital, Sichuan University [grant number ZY2016102], National Natural Science Foundation of China [grant number 81801186].

The authors have no conflicts of interest to disclose.

Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China.

* Correspondence: Chao You, Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China (e-mail: youchaowchscu@163.com).

Medicine (2019) 98:28(e16281)

Received: 1 October 2018 / Received in final form: 13 February 2019 / Accepted: 7 June 2019

http://dx.doi.org/10.1097/MD.0000000000016281

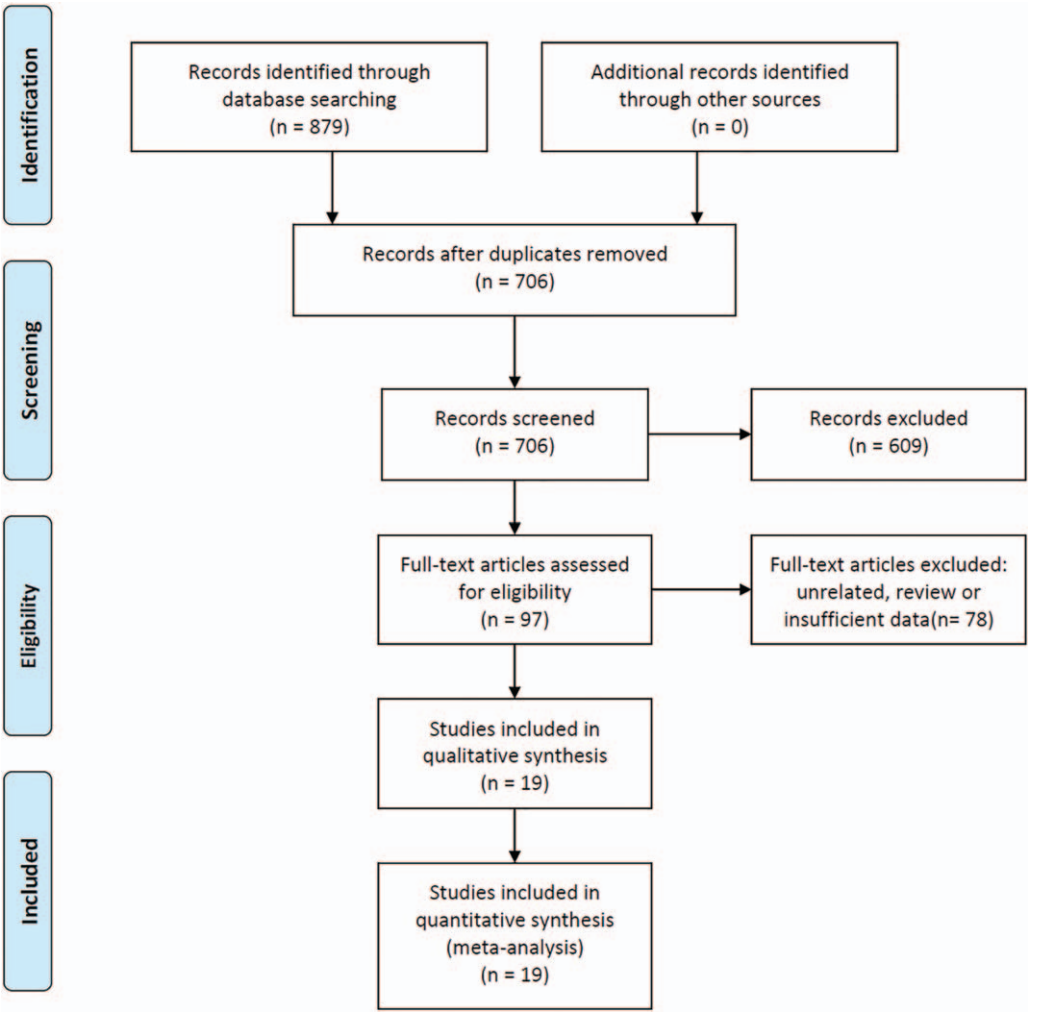

Figure 1. Flow chart of study selection.

were combined in search strategy: ("intracerebral hemorrhage" OR "brain hemorrhage" OR "cerebral hemorrhage") AND ("leukocyte" OR "white blood cell" OR "leukocytosis") AND ("prognosis" OR "outcome" OR "disability" OR "dependence" OR "mortality" OR "death" OR "survival"). The citation lists were manually checked for any study meeting criteria. Language restriction did exist in this search strategy.

2.2. Study selection

Studies were included if: published original studies enrolling ICH patients; evaluating association between baseline leukocyte count and outcome; availability of odd ratio (OR) and its 95% confidence interval (CI). The studies were excluded if: reviews, case reports, or letters; secondary intracerebral hemorrhage, subarachnoid hemorrhage, traumatic brain injury, or ischemic stroke; insufficient data; duplicated data. Titles and abstracts of all records were inspected by 2 independent assessors. Ineligible records were excluded, and full papers of remaining studies were screened by 2 assessors independently. Disagreements were solved by discussion. When studies contained the same cohort of patients, only the study reporting data of more patients was included.

2.3. Quality assessment and data extraction

Quality of included studies was assessed using Newcastle–Ottawa Quality Assessment Scale (NOS) by 2 assessors independently.[17] With a data extraction sheet, 2 authors independently collected the following information: first author, publication year, study duration, country, design of study, number of included patients, characteristics of patients, leukocytosis definition, outcome definition, time for follow-up, adjusted confounding factors, adjusted or unadjusted ORs and 95% CIs for association between leukocytosis and outcome. All data were then checked by the third author.

2.4. Statistical analysis

ORs and their 95% CIs were pooled with DerSimonian and Laird method and random-effects model to evaluate the association between baseline leukocytosis and prognosis.[18] Outcome beyond 30 days was considered as long-term outcome and outcome within 30 days was defined as short-term outcome. Heterogeneity among included studies was assessed with Higgins I^2 and $I^2 > 50\%$ was considered as substantial heterogeneity.[19] To stability of the results were evaluated in sensitivity analysis. Publication bias was assessed with funnel plot.[20,21] Statistical

Table 1

Information of included studies.

Study	Country	N	Study duration	Study design	Definition of leukocytosis	Outcome	Definition of outcome	Follow-up time	Adjusted confounding factors
Chen (2006)	China	196	2001–2003	RS	$>10\times10^9$/L	Mortality	Death	30 days	Age, conscious disturbance, body temperature, BG, blood urea nitrogen, coronary heart disease
Kumar (2009)	USA	685	1999–2005	RS	$>10\times10^9$/L	Mortality	Death	30 days	Sex, warfarin, IVH, ICH volume, BG, anemia
Zweifel (2010)	Switzerland	40	2006–2007	PS	Per 10^9/L increase	Mortality; functional outcome	Death; mRS>2	30 days; 90 days	NA
Di Napoli (2011)	Argentina	210	2005–2009	PS	Per 10^9/L increase	Mortality	Death	30 days	Time of blood sample delay, GCS, ICH volume, IVH, ICH location, age, midline shift, hydrocephalus
Rodríguez-Yáñez (2012)	Spain	185	2008–2010	PS	Per 10^9/L increase	Functional outcome	mRS >2	3 months	NA
Palm (2013)	Germany	152	2006–2010	PS	Per 10^9/L increase	Mortality; functional outcome	Death; mRS >3	1 year	Age, sex, do-not resuscitate order
Zhang (2013)	China	120	NA	PS	Per 10^9/L increase	Mortality; functional outcome	Death; mRS >2	90 days	GCS, Hemphill score, ICH volume, copeptin
Behrouz (2015)	USA	128	2011–2013	RS	$>11\times10^9$/L	Functional outcome	mRS >4	At discharge	NA
Ma (2015)	China	150	2013–2013	PS	Per 10^9/L increase	Mortality	Death	6 months	NA
Hansen (2016)	Sweden	261	2001–2007	PS	$>11\times10^9$/L	Mortality; functional outcome	Death; mRS >3	30 days	Sex, age, IVH, modified Graeb score, ICH volume, GCS, ICH location, hypertension, diabetes mellitus, ischemic heart disease, atrial fibrillation, hypercholesterolemia, previous transient ischemic attack, smoking, C-reactive protein, anticoagulant therapy, antiplatelet therapy
Lattanzi (2016)	Italy	177	2008–2015	RS	Per 10^3/L increase	Functional outcome	mRS >2	3 months	Age, sex, NIHSS, ICH volume, ICH location, IVH, SBP, SBP variability
Tapia-Pérez (2016)	Germany	43	2010–2011	PS	$>12.5\times10^9$/L	Mortality	Death	30 days; 90 days	NA
Yu (2016)	International	2630	2008–2012	PS	$>10.20\times10^9$/L	Mortality; functional outcome	Death; mRS >3	90 days	Age, sex, country, lipid lowering agent, body temperature, BG, SBP, heart rate, NIHSS, ICH volume, ICH location, IVH, time from onset to CT, treatment
Kim (2017)	Korea	538	2008–2015	RS	$>12.8\times10^9$/L; per 10^9/L increase	Mortality	Death	30 days	Age, sex, ICH volume, diabetes, alcohol drinking, antithrombotics, sodium, chloride, BG, platelet
Tao (2017)	China	336	2010–2013	RS	$>12.2\times10^9$/L; $>11.88\times10^9$/L	Mortality; Functional outcome	Death; mRS >2	90 days	Age, SBP, GCS, ICH location, midline shift, SAH, IVH, ICH volume, BG, treatment
Kayhanian (2017)	UK	113	2009–2011	RS	Per 10^9/L increase	Mortality	Death	At discharge	Sex, BG, pre-morbid mRS
Xiang (2017)	China	63	2014–2016	PS	Per 10^9/L increase	Functional outcome	mRS >3	90 days	ICH volume, IVH, osteopontin
Lattanzi (2018)	Italy	208	2008–2017	RS	Per 10^3/L increase	Functional outcome	mRS >2	30 days	Age, NIHSS, ICH volume, ICH location, IVH, SBP
Qian (2018)	China	182	2013–2016	PS	Per 10^9/L increase	Mortality	Death	30 days	NA

BG = blood glucose, CT = computed tomography, GCS = Glasgow Coma Scale, ICH = intracerebral hemorrhage, IVH = intraventricular hemorrhage, mRS = modified Rankin Scale, n = number of patients, NA = not available, NIHSS = National Institutes of Health Stroke Scale, PS = prospective study, RS = retrospective study, SAH = subarachnoid hemorrhage, SBP = systolic blood pressure.

Table 2

Quality assessment using Newcastle–Ottawa scale.

	Selection				Comparability		Outcome			
Study	Is the case definition adequate?	Representa-tiveness of the cases	Selection of controls	Definition of controls	Study controls for select the most important factor	Study controls for any additional factor	Ascertain-ment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total
Chen (2006)	☆	–	☆	☆	☆	–	–	☆	–	5
Kumar (2009)	☆	☆	☆	☆	–	☆	–	☆	–	6
Zweifel (2010)	☆	–	☆	☆	☆	☆	☆	☆	–	7
Di Napoli (2011)	☆	–	☆	☆	☆	☆	–	☆	–	6
Rodríguez-Yáñez (2012)	☆	–	☆	☆	☆	☆	☆	☆	–	7
Palm (2013)	☆	–	☆	☆	☆	–	☆	☆	–	6
Zhang (2013)	☆	–	☆	☆	–	☆	☆	☆	–	6
Behrouz (2015)	☆	–	☆	☆	☆	–	☆	☆	–	6
Ma (2015)	☆	–	☆	☆	☆	☆	–	☆	–	6
Hansen (2016)	☆	–	☆	☆	☆	☆	☆	☆	–	7
Lattanzi (2016)	☆	–	☆	☆	☆	☆	–	☆	–	6
Tapia-Pérez (2016)	☆	–	☆	☆	☆	–	☆	☆	–	6
Yu (2016)	☆	☆	☆	☆	☆	–	☆	☆	–	7
Kim (2017)	☆	☆	☆	☆	☆	☆	–	☆	–	7
Tao (2017)	☆	☆	☆	☆	☆	–	☆	☆	–	7
Kayhanian (2017)	☆	–	☆	☆	☆	☆	–	☆	–	6
Xiang (2017)	☆	–	☆	☆	–	☆	–	☆	–	5
Lattanzi (2018)	☆	–	☆	☆	☆	☆	–	☆	–	6
Qian (2018)	☆	–	☆	☆	☆	☆	–	☆	–	6

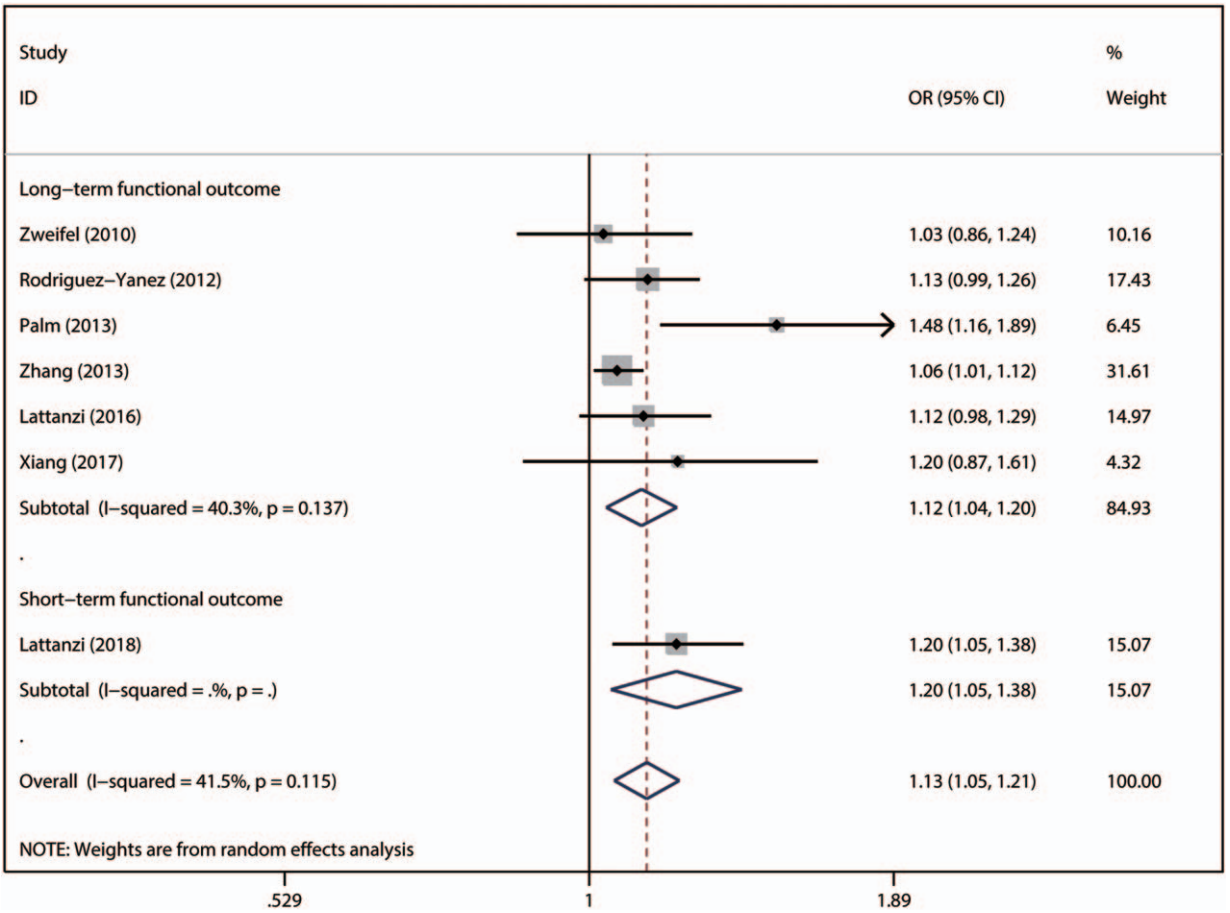

Figure 2. Forest plot of studies about association between baseline leukocyte count increase and functional outcome.

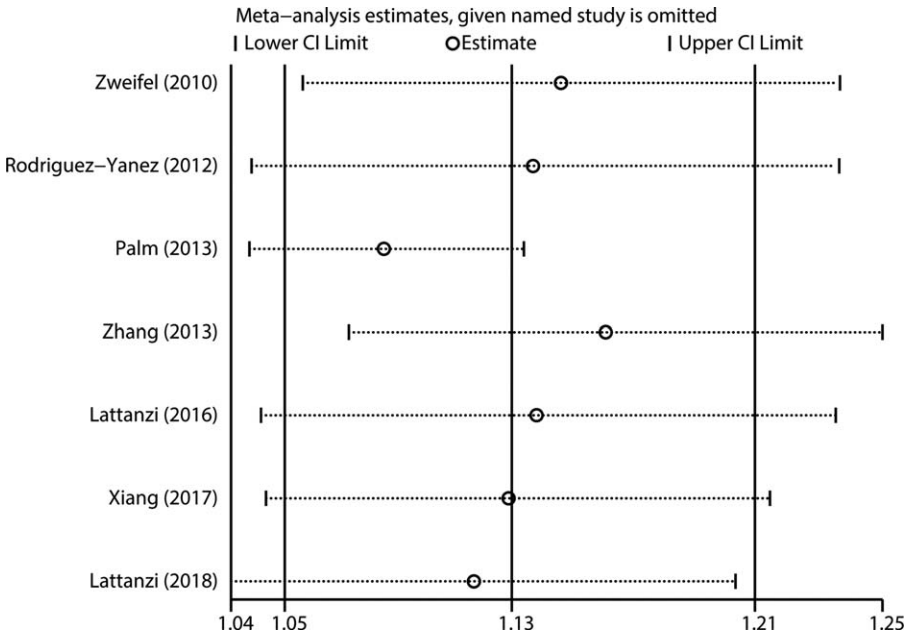

Figure 3. Sensitivity analysis of studies about association between baseline leukocyte count increase and functional outcome.

significance was considered if $P < .05$. Statistical analyses in this systematic review and meta-analysis were completed using STATA version 12.0 software (StataCorp., College Station, TX).

3. Results

3.1. Information of included studies

Finally, 19 eligible studies with 6417 patients were included[10,13,14,16,22–36] (Fig. 1). The definitions of leukocytosis in these studies are various. Seven studies used a cut-off value to define leukocytosis, 11 studies treated leukocyte count as a continuous variable, and another study discussed leukocytosis using both cut-off value and continuous variable. The cut-off values of leukocytosis were slightly different in included studies, ranging from 10×10^9 to 12.8×10^9/L. Outcome measures were also different in these studies. Eight studies reported mortality, 5 studies discussed functional outcome, and another 6 studies investigated both mortality and functional outcome. The follow-up time points were also various in these included studies (Table 1). The results of quality assessment are shown in Table 2.

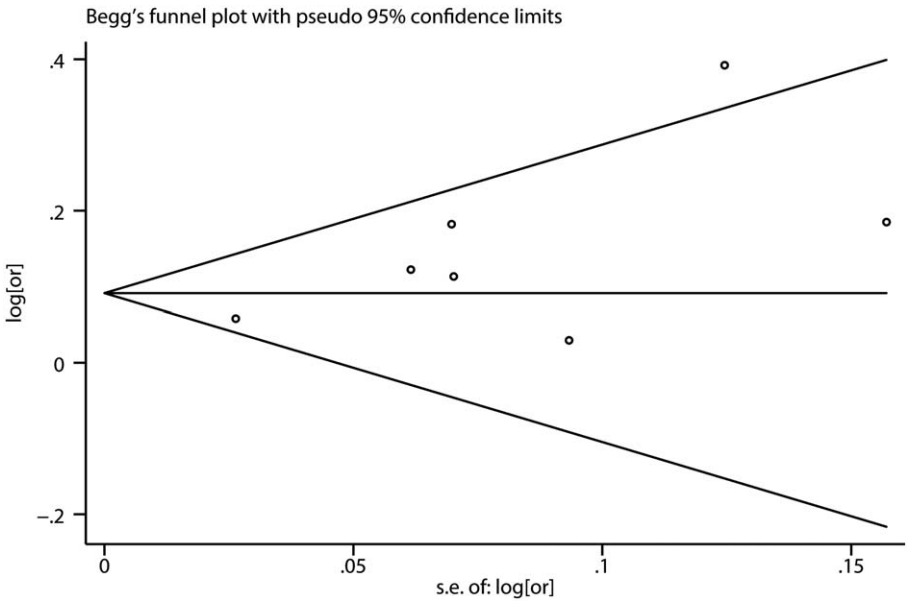

Figure 4. Funnel plot of studies about association between baseline leukocyte count increase and functional outcome.

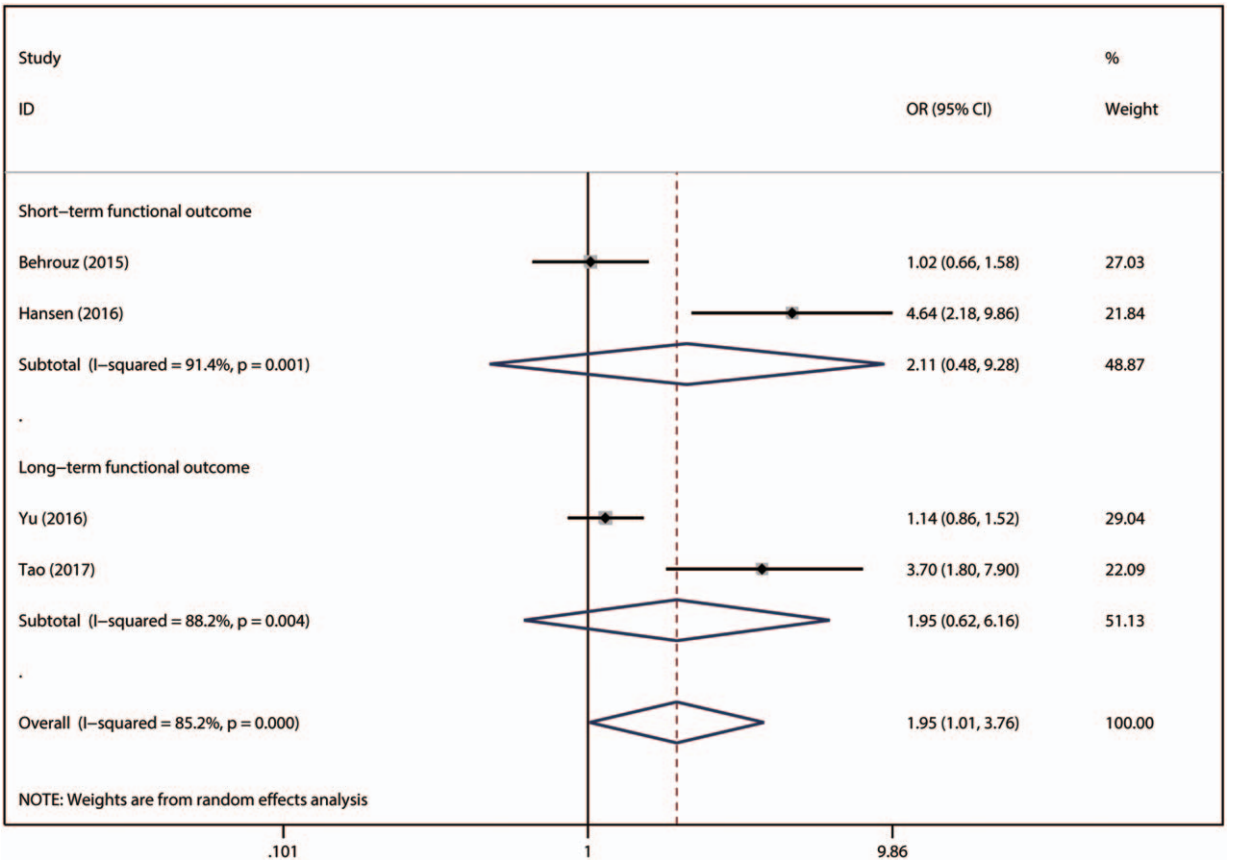

Figure 5. Forest plot of studies about association between baseline leukocytosis defined by cutoff values and functional outcome.

3.2. Baseline leukocytosis and functional outcome in ICH

Seven studies about leukocyte count increase and functional outcome were analyzed. Baseline leukocyte count increase had significant association with overall poor functional outcome (OR = 1.13, 95% CI 1.05–1.21, $P = .001$). Moreover, baseline leukocyte count increase remained significantly associated with both short-term (OR = 1.20, 95% CI 1.05–1.38, $P = .009$) and long-term functional outcome (OR = 1.12, 95% CI 1.04–1.20, $P = .004$). No substantial heterogeneity was found ($I^2 = 41.5\%$) (Fig. 2) the stability of the results was confirmed in sensitivity analysis (Fig. 3). Obvious publication bias was not shown in funnel plot (Fig. 4).

Only 4 studies were analyzed for the association between baseline leukocytosis defined using cut-off values and poor functional outcome. Overall, baseline leukocytosis defined by cut-off values had significant association with poor functional outcome (OR = 1.95, 95% CI 1.01–3.76, $P = .046$). However, no significant association was found when discussing short-term (OR = 2.11, 95% CI 0.48–9.28, $P = .325$) or long-term functional outcome (OR = 1.95, 95% CI 0.62–6.16, $P = .255$) separately. There was substantial heterogeneity among these 4 studies ($I^2 = 85.2\%$) (Fig. 5). Sensitivity analysis suggested the result could be influenced when omitting the individual studies (Fig. 6). Obvious publication bias was not shown in funnel plot (Fig. 7).

3.3. Baseline leukocytosis and mortality in ICH

Eight studies were analyzed for the association between baseline leukocyte count increase and mortality. Meta-analysis suggested the significant association between baseline leukocyte count increase and higher overall mortality (OR = 1.10, 95% CI 1.02–1.18, $P = .011$). Baseline leukocyte count increase remained significantly associated with long-term mortality (OR = 1.12, 95% CI 1.03–1.22, $P = .007$) but not with short-term mortality (OR = 1.08, 95% CI 0.97–1.20, $P = .179$). There was substantial heterogeneity among included studies ($I^2 = 68.1\%$) (Fig. 8). Sensitivity analysis showed the results were stable (Fig. 9). Obvious publication bias was not shown in funnel plot (Fig. 10).

Seven studies were analyzed for the association between baseline leukocytosis defined by cut-off values and mortality. Baseline leukocytosis defined by cut-off values had significant association with higher overall mortality (OR = 1.67, 95% CI 1.23–2.27, $P = .001$). It still had significant association with short-term mortality (OR = 1.74, 95% CI 1.12–2.70, $P = .014$), but not with long-term mortality (OR = 1.69, 95% CI 0.93–3.08, $P = .083$). Substantial heterogeneity was found among included studies ($I^2 = 65.9\%$) (Fig. 11). Sensitivity analysis showed the results were stable (Fig. 12). Obvious publication bias was not shown in funnel plot (Fig. 13).

4. Discussion

After onset of ICH, a series of complicated mechanisms lead to secondary brain injury, such as direct cellular toxicity, disrupted blood–brain barrier, and upregulated inflammation.[37] Notably, disruption of blood–brain barrier occurs after ICH.[38] Normal blood–brain barrier can prevent circulating cells and molecules

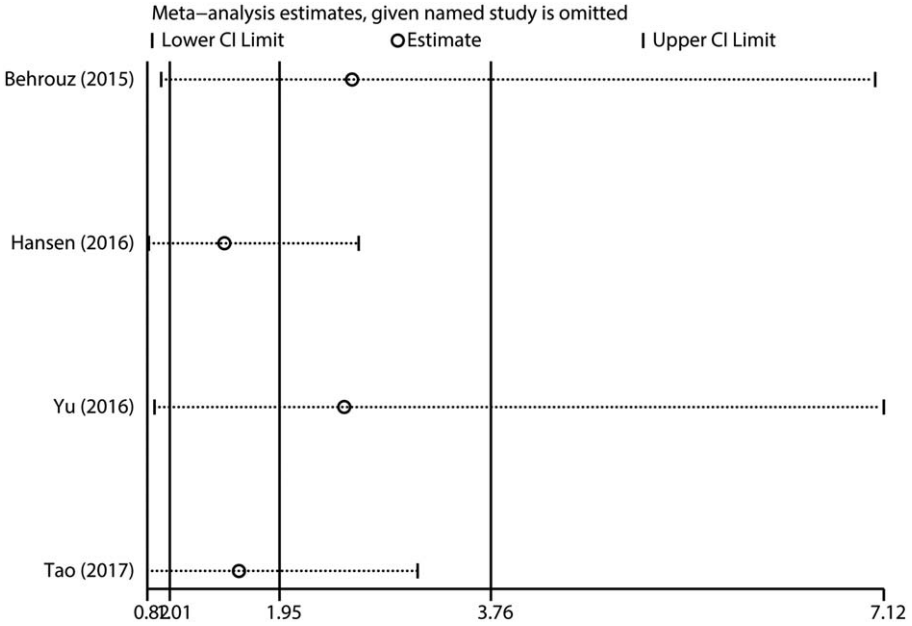

Figure 6. Sensitivity analysis of studies about association between baseline leukocytosis defined by cutoff values and functional outcome.

from infiltrating into central nervous system.[39] However, when blood–brain barrier is damaged after ICH, leukocytes and inflammatory agents can infiltrate into perihematomal area.[7] Moreover, leukocytes can further damage blood–brain barrier, which deteriorates secondary brain injury.[40] As the subtype of leukocytes, neutrophils enter brain very early after onset of ICH and are related to blood vessel damage, blood–brain barrier disruption, microglial reaction, and neuronal apoptosis.[41,42] Number of polymorphonuclear neutrophils was observed to increase significantly in brain parenchyma in first 2 weeks after ICH.[43] Neutrophils can cause damage to brain tissue via direct cellular injury or monocyte recruitment.[44] Blood-derived inflammatory monocytes were identified after ICH in brain tissue and increased disability in mice.[45] Reduction of lymphocyte infiltration improved outcome in experimental ICH.[46] In an animal study, infiltrating leukocytes are found to be mainly from circulation after experimental ICH.[12] Thus, leukocytes has a crucial role in secondary brain injury after ICH. However, the association between baseline leukocytosis and outcome in patients with ICH is still unclear. Thus, this study was

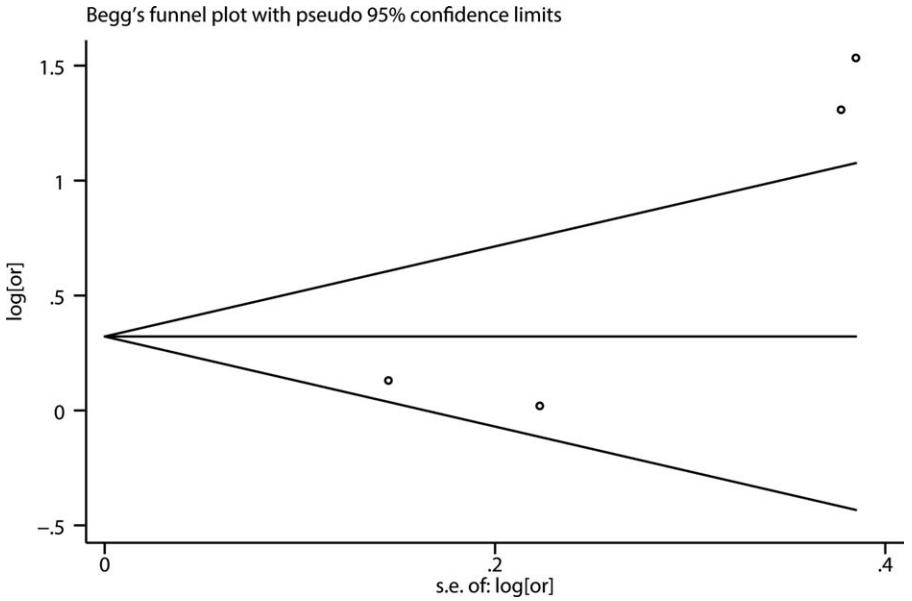

Figure 7. Funnel plot of studies about association between baseline leukocytosis defined by cutoff values and functional outcome.

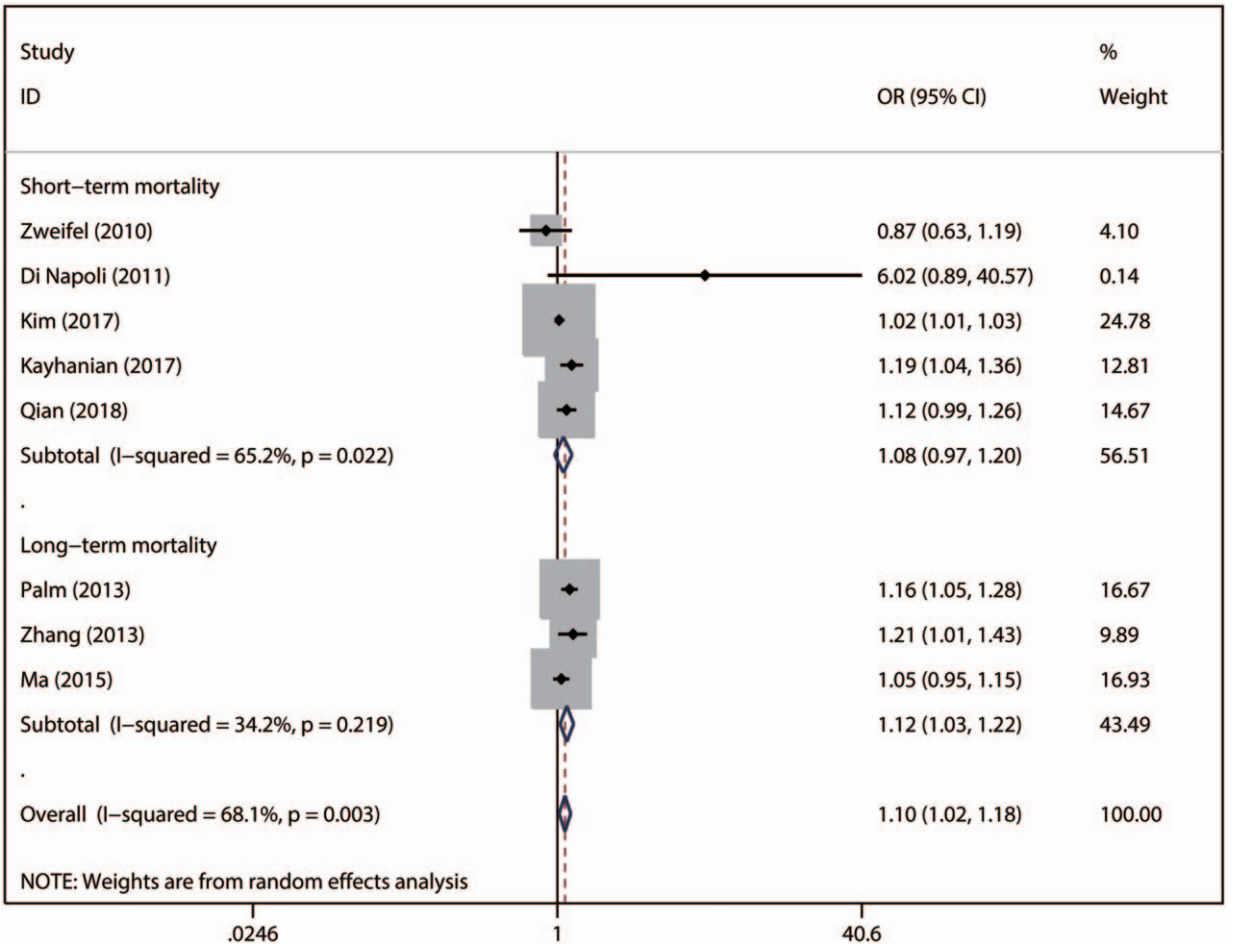

Figure 8. Forest plot of studies about association between baseline leukocyte count increase and mortality.

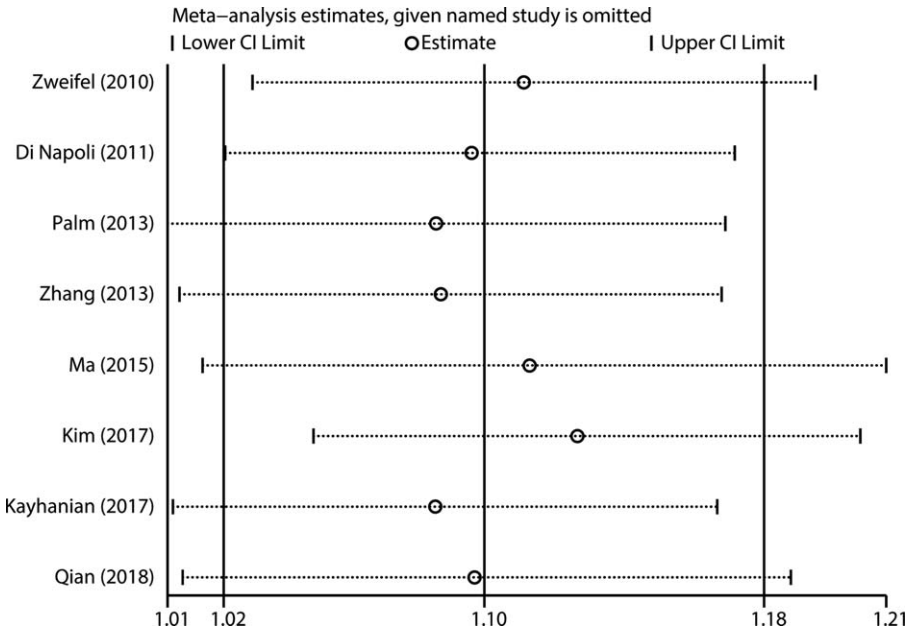

Figure 9. Sensitivity analysis of studies about association between baseline leukocyte count increase and mortality.

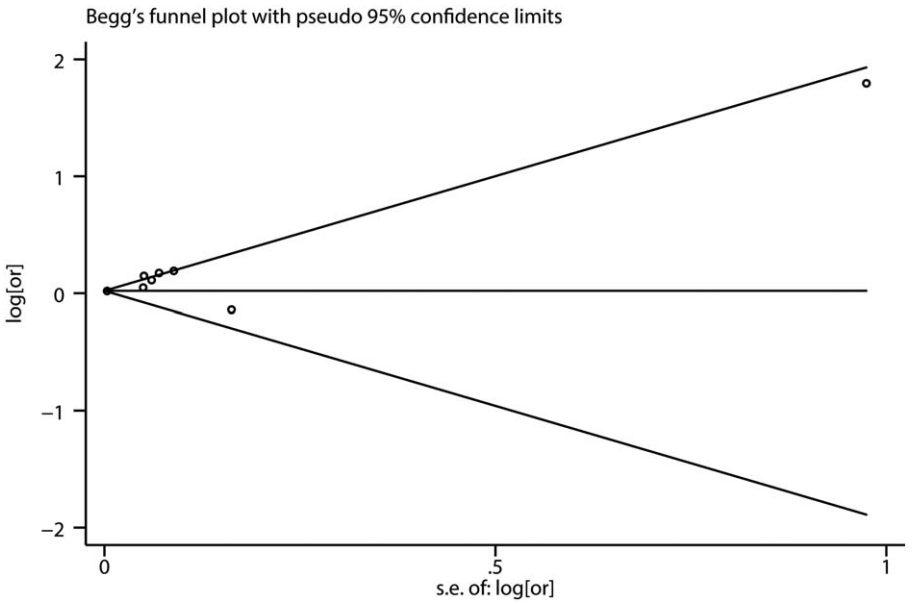

Figure 10. Funnel plot of studies about association between baseline leukocyte count increase and mortality.

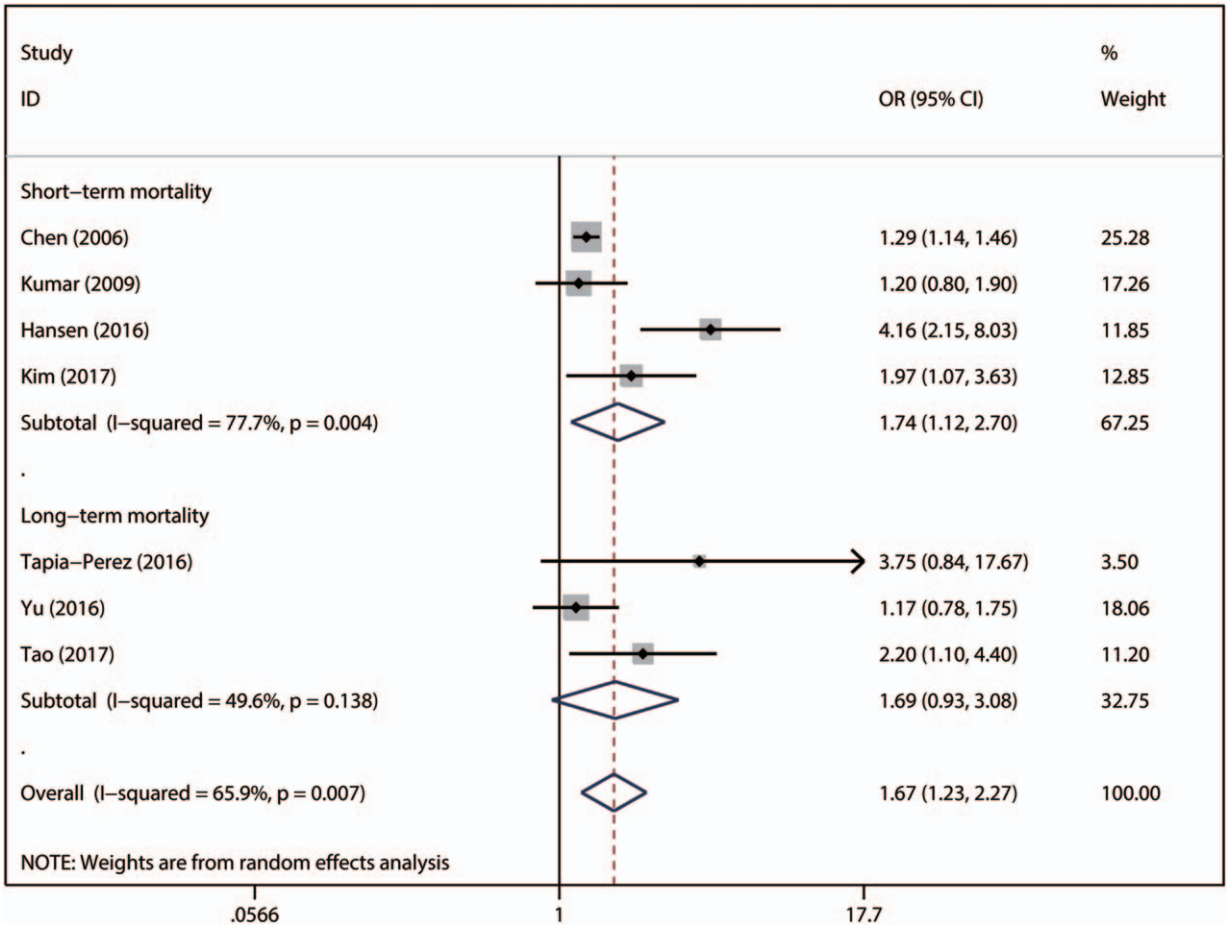

Figure 11. Forest plot of studies about association between baseline leukocytosis defined by cutoff values and mortality.

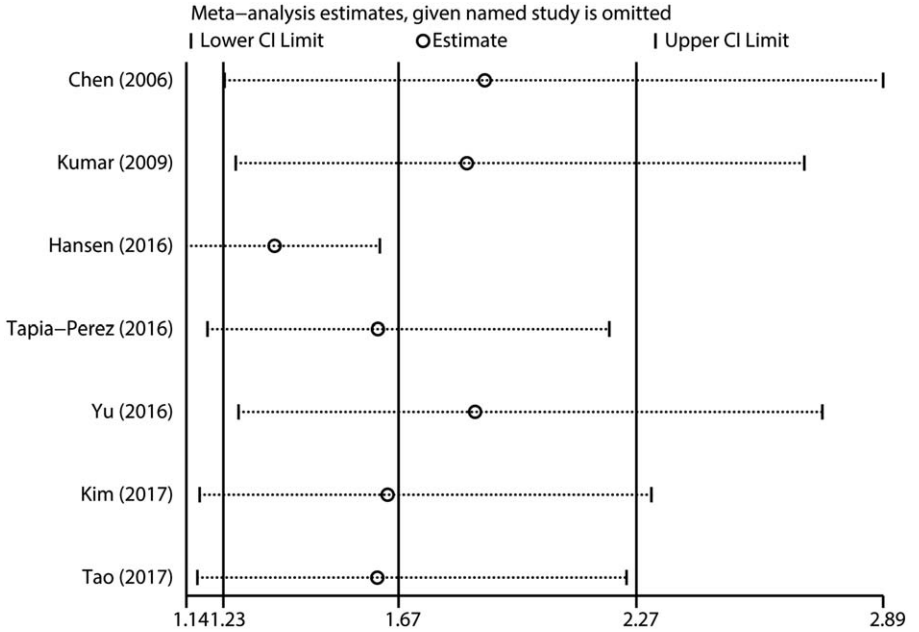

Figure 12. Sensitivity analysis of studies about association between baseline leukocytosis defined by cutoff values and mortality.

performed and a total of 19 studies with 6417 patients were included finally in this systematic review and meta-analysis.

Although some studies did not suggest increase of baseline leukocyte count was significantly associated with functional outcome,[24,26] other studies suggested the association between baseline leukocyte count increase and functional outcome.[27,28] This meta-analysis demonstrated that baseline leukocyte count increase was significantly associated with overall poor functional outcome. In addition, it had significant association with both short-term and long-term functional outcome. Baseline leukocyte count increase may be a helpful predictor for functional outcome in ICH patients. Significant association was found between baseline leukocytosis defined by cut-off values and functional outcome in Hansen et al's and Tao's studies.[16,30] However, Yu et al[10] did not find this significant association based on INTERACT cohort. This study showed that baseline leukocytosis defined by cut-off values was significantly associated with poor functional outcome overall, but it did not remain significant association when discussing short-term or long-term functional outcome separately. Moreover, sensitivity analysis also suggested the result was unstable. This could be caused by the small number of included studies. In addition, the cut-off values for leukocytosis

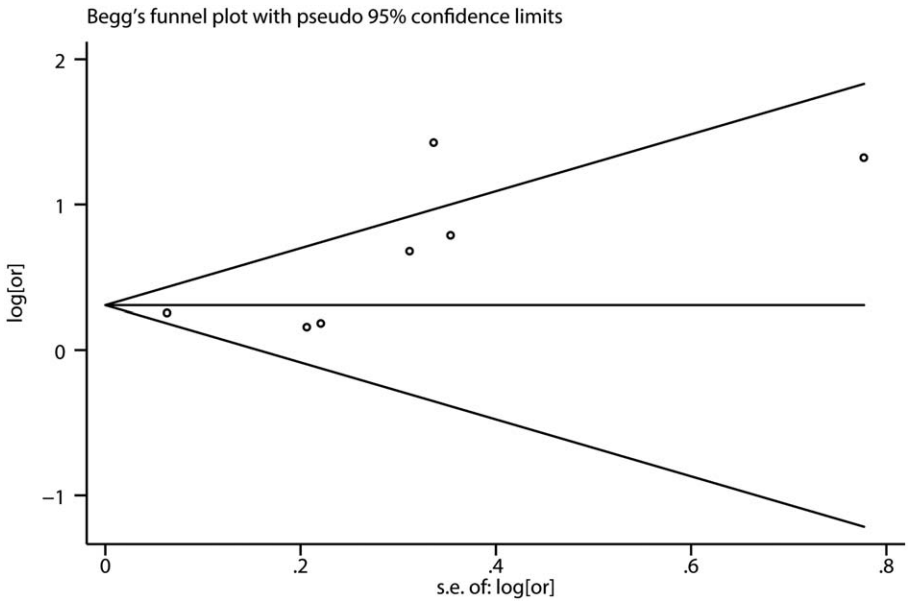

Figure 13. Funnel plot of studies about association between baseline leukocytosis defined by cutoff values and mortality.

were also different in these studies, which could increase the heterogeneity and influence the accuracy of the results. Further original studies are still necessary to confirm the role of leukocytosis defined by cut-off values in predicting functional outcome in ICH patients.

Although no significant association was reported between baseline leukocyte count increase and mortality in some studies,[24,25,29,33] some other studies had the conflicting results.[27,28] The results of this meta-analysis suggested baseline leukocyte count increase was significantly associated with overall mortality and long-term morality, but not short-term mortality, which could be caused by the relatively small number of included studies and relatively high heterogeneity among these studies. Several other studies discussed the association between baseline leukocytosis defined by cut-off values and mortality. Some of them reported the significant association between leukocytosis and mortality,[16,30,33] but some others showed the opposite results.[10,31] This meta-analysis suggested baseline leukocytosis defined by cut-off values had significant association with higher overall and short-term mortality, but did not reach significant association with long-term mortality, which could be caused by the small number of included studies and various cut-off values for leukocytosis in different studies. Thus, baseline leukocytosis could help the prediction of mortality in ICH patients, but its role should be verified in further studies.

Several limitations exist in this study. First of all, only studies reporting ORs and their 95% CIs were included, which decrease the accuracy of this study. Second, sensitivity analysis showed instability of some results, which suggested the meta-analysis should be strengthened by further studies. Moreover, the cut-off values of leukocytosis were various in different studies. Since this meta-analysis was performed based on the published studies, the cut-off values of leukocytosis were directly adopted as defined in these studies, which contributed to heterogeneity and decreased the accuracy of the results. The optimal cut-off value of leukocytosis should be explored in further studies. Furthermore, the definitions of functional outcome were also various in different studies, which could cause heterogeneity among these studies. In addition, 6 studies only reported unadjusted results and adjusted confounding factors were also different in the other studies, which potentially reduced the reliability of the results.

In conclusion, this systematic review and meta-analysis suggested baseline leukocytosis could be helpful in predicting prognosis in ICH patients. However, its prognostic value should be verified by further studies.

Author contributions

Conceptualization: Hao Li.
Data curation: Zhiyuan Yu, Jun Zheng, Rui Guo.
Formal analysis: Zhiyuan Yu, Jun Zheng.
Funding acquisition: Chao You, Jun Zheng.
Project administration: Rui Guo.
Resources: Lu Ma.
Software: Lu Ma.
Supervision: Chao You.
Writing – original draft: Zhiyuan Yu.
Writing – review & editing: Jun Zheng, Hao Li.

References

[1] Grysiewicz RA, Thomas K, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. Neurol Clin 2008;26:871–95. vii.
[2] Chan S, Hemphill JC3rd. Critical care management of intracerebral hemorrhage. Crit Care Clin 2014;30:699–717.
[3] Zhou Y, Wang Y, Wang J, et al. Inflammation in intracerebral hemorrhage: from mechanisms to clinical translation. Prog Neurobiol 2014;115:25–44.
[4] Brunswick AS, Hwang BY, Appelboom G, et al. Serum biomarkers of spontaneous intracerebral hemorrhage induced secondary brain injury. J Neurol Sci 2012;321:1–0.
[5] Hammond MD, Ambler WG, Ai Y, et al. alpha4 integrin is a regulator of leukocyte recruitment after experimental intracerebral hemorrhage. Stroke 2014;45:2485–7.
[6] Wang J. Preclinical and clinical research on inflammation after intracerebral hemorrhage. Prog Neurobiol 2010;92:463–77.
[7] Keep RF, Xiang J, Ennis SR, et al. Blood-brain barrier function in intracerebral hemorrhage. Acta Neurochir Suppl 2008;105:73–7.
[8] Wang J, Dore S. Heme oxygenase-1 exacerbates early brain injury after intracerebral haemorrhage. Brain 2007;130(pt 6):1643–52.
[9] Joice SL, Mydeen F, Couraud PO, et al. Modulation of blood-brain barrier permeability by neutrophils: in vitro and in vivo studies. Brain Res 2009;1298:13–23.
[10] Yu S, Arima H, Heeley E, et al. White blood cell count and clinical outcomes after intracerebral hemorrhage: the INTERACT2 trial. J Neurol Sci 2016;361:112–6.
[11] Wang J, Dore S. Inflammation after intracerebral hemorrhage. J Cereb Blood Flow Metab 2007;27:894–908.
[12] Mracsko E, Javidi E, Na SY, et al. Leukocyte invasion of the brain after experimental intracerebral hemorrhage in mice. Stroke 2014;45:2107–14.
[13] Behrouz R, Hafeez S, Miller CM. Admission leukocytosis in intracerebral hemorrhage: associated factors and prognostic implications. Neurocrit Care 2015;23:370–3.
[14] Lattanzi S, Cagnetti C, Provinciali L, et al. Neutrophil-to-lymphocyte ratio predicts the outcome of acute intracerebral hemorrhage. Stroke 2016;47:1654–7.
[15] Sun W, Peacock A, Becker J, et al. Correlation of leukocytosis with early neurological deterioration following supratentorial intracerebral hemorrhage. J Clin Neurosci 2012;19:1096–100.
[16] Tao C, Hu X, Wang J, et al. Admission neutrophil count and neutrophil to lymphocyte ratio predict 90-day outcome in intracerebral hemorrhage. Biomark Med 2017;11:33–42.
[17] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[18] DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015;45(pt A):139–45.
[19] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
[20] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[21] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[22] Chen QM, Zhou CP, Xia YL, et al. Risk factors for early death in patients with intracerebral hemorrhage. Clin Med J China 2006;2:59–61.
[23] Kumar MA, Rost NS, Snider RW, et al. Anemia and hematoma volume in acute intracerebral hemorrhage. Crit Care Med 2009;37:1442–7.
[24] Zweifel C, Katan M, Schuetz P, et al. Copeptin is associated with mortality and outcome in patients with acute intracerebral hemorrhage. BMC Neurol 2010;10:34.
[25] Di Napoli M, Godoy DA, Campi V, et al. C-reactive protein level measurement improves mortality prediction when added to the spontaneous intracerebral hemorrhage score. Stroke 2011;42:1230–6.
[26] Rodriguez-Yanez M, Brea D, Arias S, et al. Increased expression of Toll-like receptors 2 and 4 is associated with poor outcome in intracerebral hemorrhage. J Neuroimmunol 2012;247:75–80.
[27] Palm F, Henschke N, Wolf J, et al. Intracerebral haemorrhage in a population-based stroke registry (LuSSt): incidence, aetiology, functional outcome and mortality. J Neurol 2013;260:2541–50.
[28] Zhang A, Li J, Li X, et al. The prognostic value of copeptin for acute intracerebral hemorrhage patients. Exp Ther Med 2013;5:467–70.

[29] Ma BQ, Zhang M, Ba L. Plasma pituitary adenylate cyclase-activating polypeptide concentrations and mortality after acute spontaneous basal ganglia hemorrhage. Clin Chim Acta 2015;439:102–6.
[30] Hansen BM, Morgan TC, Betz JF, et al. Intracerebral hemorrhage: the modified graeb scale improves outcome prediction in lund stroke register. Neuroepidemiology 2016;46:43–50.
[31] Tapia-Perez JH, Karagianis D, Zilke R, et al. Assessment of systemic cellular inflammatory response after spontaneous intracerebral hemorrhage. Clin Neurol Neurosurg 2016;150:72–9.
[32] Kayhanian S, Weerasuriya CK, Rai U, et al. Prognostic value of peripheral leukocyte counts and plasma glucose in intracerebral haemorrhage. J Clin Neurosci 2017;41:50–3.
[33] Kim Y, Han MH, Kim CH, et al. Increased short-term mortality in patients with spontaneous intracerebral hemorrhage and its association with admission glucose levels and leukocytosis. World Neurosurg 2017;98:503–11.
[34] Xiang ST, Xiao H, Chen AN. Diagnostic and prognostic values of serum osteopontin in acute intracerebral hemorrhage. Chongqing Med 2017;46:4838–41.
[35] Lattanzi S, Cagnetti C, Rinaldi C, et al. Neutrophil-to-lymphocyte ratio improves outcome prediction of acute intracerebral hemorrhage. J Neurol Sci 2018;387:98–102.
[36] Qian SQ, He SR, Li BB, et al. Serum S100A12 and 30-day mortality after acute intracerebral hemorrhage. Clin Chim Acta 2018;477:1–6.
[37] Belur PK, Chang JJ, He S, et al. Emerging experimental therapies for intracerebral hemorrhage: targeting mechanisms of secondary brain injury. Neurosurg Focus 2013;34:E9.
[38] Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. Lancet Neurol 2012;11:720–31.
[39] Zhang X, Liu W, Yuan J, et al. T lymphocytes infiltration promotes blood-brain barrier injury after experimental intracerebral hemorrhage. Brain Res 2017;1670:96–105.
[40] Keep RF, Zhou N, Xiang J, et al. Vascular disruption and blood-brain barrier dysfunction in intracerebral hemorrhage. Fluids Barriers CNS 2014;11:18.
[41] Ziai WC. Hematology and inflammatory signaling of intracerebral hemorrhage. Stroke 2013;44(6 suppl 1):S74–8.
[42] Moxon-Emre I, Schlichter LC. Neutrophil depletion reduces blood-brain barrier breakdown, axon injury, and inflammation after intracerebral hemorrhage. J Neuropathol Exp Neurol 2011;70: 218–35.
[43] Zhao X, Sun G, Zhang H, et al. Polymorphonuclear neutrophil in brain parenchyma after experimental intracerebral hemorrhage. Transl Stroke Res 2014;5:554–61.
[44] Sansing LH, Harris TH, Kasner SE, et al. Neutrophil depletion diminishes monocyte infiltration and improves functional outcome after experimental intracerebral hemorrhage. Acta Neurochir Suppl 2011; 111:173–8.
[45] Hammond MD, Taylor RA, Mullen MT, et al. CCR2+ Ly6C(hi) inflammatory monocyte recruitment exacerbates acute disability following intracerebral hemorrhage. J Neurosci 2014;34:3901–9.
[46] Rolland WB, Lekic T, Krafft PR, et al. Fingolimod reduces cerebral lymphocyte infiltration in experimental models of rodent intracerebral hemorrhage. Exp Neurol 2013;241:45–55.