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...
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. 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. 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. To stability of the results were evaluated in sensitivity analysis. Publication bias was assessed with funnel plot. Statistical

![Flow chart of study selection.](image_url)
### 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 x 10^9/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 x 10^9/L              | Mortality         | Death                 | 30 days         | Sex, warfarin, IWH, ICH volume, BG, anemia                                                   |
| Zweifel (2010)   | Switzerland | 40   | 2006–2007       | RS           | Per 10^9/L increase       | Mortality         | Mortality, functional outcome | 30 days         | NA                                                                                           |
| De Napoli (2011) | Argentina | 210   | 2005–2009       | PS           | Per 10^9/L increase       | Mortality         | Death                 | 30 days         | Time of blood sample delay, GCS, ICH volume, IWH, ICH location, age, midline shift, hydrocephalus |
| Rodriguez-Yáñez (2012) | Spain | 185   | 2008–2010       | PS           | Per 10^9/L increase       | Mortality         | mRS >2                | 3 months        | NA                                                                                           |
| Palm (2013)      | Germany   | 152   | 2006–2010       | PS           | Per 10^9/L increase       | Mortality         | Mortality, functional outcome | 1 year          | Age, sex, do-not resuscitate order                                                          |
| Zhang (2013)     | China     | 120   | NA              | PS           | Per 10^9/L increase       | Mortality         | Mortality, functional outcome | 90 days         | GCS, Hemphill score, ICH volume, copeptin                                                   |
| Behrouz (2015)   | USA       | 128   | 2011–2013       | PS           | >11 x 10^9/L              | Mortality         | Death; mRS >3         | 6 months        | NA                                                                                           |
| Ma (2015)        | China     | 150   | 2013–2013       | PS           | Per 10^9/L increase       | Mortality         | Death                 | At discharge     | NA                                                                                           |
| Hansen (2016)    | Sweden    | 261   | 2001–2007       | PS           | >11 x 10^9/L              | Mortality         | mRS >3                | 30 days         | Sex, age, IWH, modified Graeb score, ICH volume, GCS, ICH location, age, SBP, SBP variability |
| Lattanzi (2016)  | Italy     | 177   | 2008–2015       | RS           | Per 10^9/L increase       | Functional outcome| mRS >2                | 3 months        | Age, sex, NIHSS, ICH volume, ICH location, NIHSS, ICH volume, ICH location, IWH, SBP, SBP variability |
| Tapia-Pérez (2016) | Germany | 43    | 2010–2011       | PS           | >12.5 x 10^9/L            | Mortality         | Death                 | 30 days; 90 days | NA                                                                                           |
| Yu (2016)        | International | 2630 | 2008–2012       | PS           | >10.20 x 10^9/L           | Mortality         | mRS >3                | 90 days         | Age, sex, country, lipid lowering agent, body temperature, GCS, ICH volume, ICH location, NIHSS, ICH volume, ICH location, IWH, SBP, SBP variability |
| Kim (2017)       | Korea     | 538   | 2008–2015       | RS           | >12.8 x 10^9/L; per 10^9/L increase | Mortality         | Death                 | 30 days         | Age, sex, NIHSS, ICH volume, ICH location, IWH, SBP, SBP variability |
| Tao (2017)       | China     | 336   | 2010–2013       | RS           | >12.2 x 10^9/L; >11.88 x 10^9/L increase | Mortality         | Mortality, functional outcome | 90 days         | Age, SBP, GCS, ICH location, ICH volume, ICH location, IWH, SBP, SBP variability |
| 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, IWH, osteopontin                                                                |
| Lattanzi (2018)  | Italy     | 208   | 2008–2017       | PS           | Per 10^9/L increase       | Functional outcome| mRS >2                | 30 days         | Age, NIHSS, ICH volume, ICH location, IWH, SBP                                             |
| Qian (2018)      | China     | 182   | 2013–2016       | PS           | Per 10^9/L increase       | Mortality         | Death                 | 30 days         | Age, NIHSS, ICH volume, ICH location, IWH, SBP                                             |

BG = blood glucose, CT = computed tomography, GCS = Glasgow Coma Scale, ICH = intracerebral hemorrhage, IWH = 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.

| Study                  | Selection | Comparability | Outcome |
|------------------------|-----------|---------------|---------|
|                        | Is the case definition adequate? | Study controls for selecting the most important factor | Study controls for any additional factor | Ascertainment 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      |
| Rodriguez-Yáñez (2012) | ☆         | ☆             | ☆       | -       | ☆               | -              | 7      |
| Palm (2013)            | ☆         | ☆             | ☆       | -       | ☆               | -              | 6      |
| Zhang (2013)           | ☆         | ☆             | ☆       | -       | ☆               | -              | 6      |
| Behnouz (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.
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\textsuperscript{[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 $10 \times 10^9$ to $12.8 \times 10^9$/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 3. Sensitivity analysis of studies about association between baseline leukocyte count increase and functional outcome.

Figure 4. Funnel plot of studies about association between baseline leukocyte count increase 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 (I² = 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 (I² = 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 (I² = 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 (I² = 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. Notably, disruption of blood–brain barrier occurs after ICH. Normal blood–brain barrier can prevent circulating cells and molecules...
from infiltrating into central nervous system. However, when blood–brain barrier is damaged after ICH, leukocytes and inflammatory agents can infiltrate into perihematomal area. Moreover, leukocytes can further damage blood–brain barrier, which deteriorates secondary brain injury. 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. Number of polymorphonuclear neutrophils was observed to increase significantly in brain parenchyma in first 2 weeks after ICH. Neutrophils can cause damage to brain tissue via direct cellular injury or monocyte recruitment. Blood-derived inflammatory monocytes were identified after ICH in brain tissue and increased disability in mice. Reduction of lymphocyte infiltration improved outcome in experimental ICH. In an animal study, infiltrating leukocytes are found to be mainly from circulation after experimental ICH. 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 8. Forest plot of studies about association between baseline leukocyte count increase and mortality.

| Study ID | OR (95% CI) | % Weight |
|----------|-------------|----------|
| Zweifel (2010) | 0.87 (0.63, 1.19) | 4.10 |
| Di Napoli (2011) | 6.02 (0.89, 40.57) | 0.14 |
| Kim (2017) | 1.02 (1.01, 1.03) | 24.78 |
| Kayhanian (2017) | 1.19 (1.04, 1.36) | 12.81 |
| Qian (2018) | 1.12 (0.99, 1.26) | 14.67 |
| Subtotal (I² = 65.2%, p = 0.022) | 1.08 (0.97, 1.20) | 56.51 |

Long-term mortality

| Study ID | OR (95% CI) | % Weight |
|----------|-------------|----------|
| Palm (2013) | 1.16 (1.05, 1.28) | 16.67 |
| Zhang (2013) | 1.21 (1.01, 1.43) | 9.89 |
| Ma (2015) | 1.05 (0.95, 1.15) | 16.93 |
| Subtotal (I² = 34.2%, p = 0.219) | 1.12 (1.03, 1.22) | 43.49 |
| Overall (I² = 68.1%, p = 0.003) | 1.10 (1.02, 1.18) | 100.00 |

NOTE: Weights are from random effects analysis

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

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,[15–17] some other studies had the conflicting results.[22,27,28] The results of this meta-analysis suggested baseline leukocyte count increase was significantly associated with overall mortality and long-term mortality, 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.

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