Review Article

Association Between Baseline Serum Ferritin and Short-term Outcome of Intracerebral Hemorrhage: A Meta-Analysis

Mijuan Zhang, MSc,* Wei Li, MD,†,[1] Tao Wang, MD,†,[1] and Qian Zhang, MSc*

Background: Intracerebral hemorrhage is a devastating disease. In recent years, the association of between baseline serum ferritin and prognosis of intracerebral hemorrhage is an interesting issue. Although some of the studies have shown that baseline serum ferritin can predict the prognosis of intracerebral hemorrhage, there is no clear evidence that baseline serum ferritin can be used as an independent predictor of intracerebral hemorrhage. *Methods:* Electronic databases through November 2018 were searched to identify relevant studies that examined association between baseline serum ferritin and prognosis of intracerebral hemorrhage. *Results:* We found 7 eligible studies that included 411 participants. Our results showed that among them, 216 patients with intracerebral hemorrhage of poorer functional outcome were associated with elevated serum ferritin at admission. The results of 7 literature meta-analysis showed that intracerebral hemorrhage (ICH) patients with favorable shot-term functional outcome had lower baseline serum ferritin levels, with significant mean differences of −70.85 (95% confidence intervals −134.26, −7.43). *Conclusions:* This meta-analysis showed that baseline serum ferritin level at admission may predict the short-term prognosis of patients with ICH, and may provide a new target for intracerebral hemorrhage therapy.

Key Words: Intracerebral hemorrhage—serum ferritin—outcome—a meta-analysis

Introduction

Intracerebral hemorrhage (ICH) is a devastating disease and the incidence is 24.6/100,000 per year. It is roughly estimated that 40% of patients die and merely 12%-39% are independence after such an event.[1] After acute phase, ICH maybe occur a series of events, leading to secondary injury and serious neurological deficit.[2] In recent years, the association of between baseline serum ferritin and the prognosis of ICH is an interesting issue. Some relevant literatures have described the relationship between serum ferritin and functional outcome of ICH, possibly because the up-regulation of baseline serum ferritin level had neurotoxicity and this leaded to poor prognosis. But some investigators did not agree with this opinion, and they thought that serum ferritin was not associated with prognosis of ICH. Many prospective and retrospective studies have assessed the relationship between baseline serum ferritin and functional outcome of ICH with conflicting results.[3-9] Although some of the studies have shown that baseline serum ferritin can predict the prognosis of ICH, there is no clear evidence that baseline serum ferritin may be used as an independent predictor of ICH. Therefore, we conducted a systematic review and meta-analysis to search for the relationship between baseline serum ferritin and functional outcome of ICH.

From the *Xi'an Medical University, Xi'an City, Shaanxi Province, China; and †Department of Neurology, Shaanxi Province People's Hospital, Xi'an City, Shaanxi Province, China.

Received January 20, 2019; revision received February 23, 2019; accepted March 16, 2019.

Financial Disclosures: The research was funded by the program for tackling key problems in science and technology for social development. It is a plan project with Science and Technology Research and Development in Shaanxi province. The project number of the fund is S2015YFSF0325. But we declare that there is no conflict of interest.

Address correspondence to Wei Li, PhD, and Tao Wang, PhD, Department of Neurology, Shaanxi Province People's Hospital, Xi'an City, Shaanxi Province, China. E-mail: liwei.996@163.com.

[1]Now works at Shaanxi Province People's Hospital, Xi'an City, Shaanxi Province, China.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.03.037

Materials and Methods

Data Sources and Searches Strategies

Two researchers (Zhang and Wang) independently completed an extensive literature search through major database, including PubMed, Embase, Cochrane, clinicaltrials.gov, and the Chinese database (China National Knowledge Infrastructure and Wanfang databases) by the end of November 15, 2018. This article was performed through using Preferred Reporting Items about Systematic Reviews and Meta-Analyses guidelines to select relevant studies between baseline serum ferritin and functional outcome of ICH.[10] The search themes: 'ferritin,' 'iron,' 'cerebrovascular disease,' 'stroke,' 'intracerebral hemorrhage,' 'case-control study,' and 'meta-analysis' (see Fig 1 for the search strategy). During the retrieval process, the 2 researchers independently searched and cross-checked the result, and discussed in disagreements, and the third researcher (Li) consulted if necessary.

Study Selection

We included in the studies: (1) patients diagnosed ICH, and admitted to hospital within 7 days of symptom onset; (2) measured of serum ferritin within 24 hours of admission; (3) patients with short-term prognosis of ICH; (4) reported in Chinese or English language. We excluded criteria: (1) patients with severe disease, such as inflammation, infection, blood diseases, and tumors; (2) duplicated studies and review articles or case reports; (3) took drugs that affect serum ferritin; (4) lacked of relevant data in published results.

Data Extraction and Quality Assessment

Two researchers (Zhang and Wang) independently extracted data from the included studies using predesigned forms (see Table 1), and cross-checked whether the data was consistent. When faced with conflicts, they together discussed, and the third (Li) negotiated if necessary. If the data was incomplete, we tried to obtain the data by contacting the original author. For each study, we needed to extract information include: literature subject, the first author's name, year of publication, sample size, age, sex, history of risk factors (hypertension, diabetes, cardiovascular disease, and smoking, drinking), National Institutes of Health Stroke Scale score at admission, hematoma volume at admission, admission time, serum ferritin acquisition time and methods, multiple factors correlation analysis, article source sites, quality score, type of study, follow-up duration, and assessment scale (see Table 1). The quality of the included studies was assessed by 2 researchers (Zhang and Wang) and discrepancies resolved by another (Li) using the Newcastle-Ottawa Scale. The maximum number of stars in each study is a total of 9 stars, and more than 5 "stars" are relatively high quality articles. The scale has been confirmed to be reliable and valid.[11]

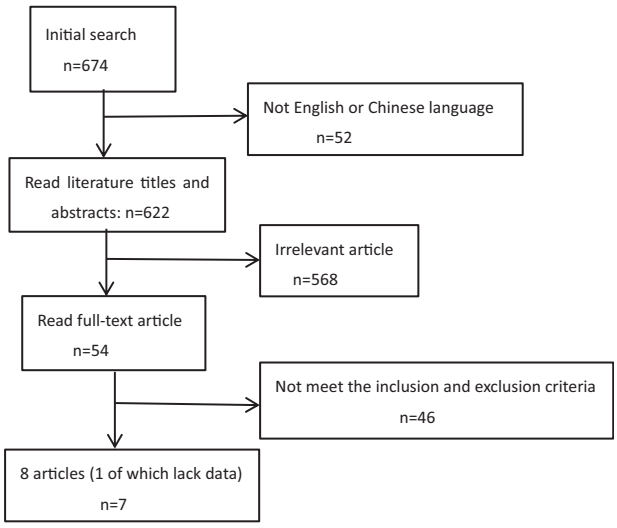

Figure 1. *Flow chart of study inclusion.*

Statistical Analysis

The outcomes of included studies were conducted using the Review Manager software version 5.3 (Cochrane collaboration, Oxford, United Kingdom). Heterogeneity was represented using the I^2 statistics. When I^2 statistic was less than 50%, heterogeneity was acceptable. *P* values less than .05 were used statistically significant, and 95% confidence intervals were reported for all results. The mean and standard deviation were used for continuous variables, and a fixed effects model was used for meta-analysis. Sensitivity analysis was used to explore the sources of heterogeneity, and we discovered the causes of high heterogeneity through speculation.[12]

Results

Our study selection process is shown in Fig 1. Initially, we searched 674 literatures, and a total of 7 literatures were ultimately included with a pooled sample of 411 patients. The main characteristics of the study are shown in Table 1. Six studies were prospective, whereas one was retrospective. Among the 7 studies, 4 were in China and the other not in China. At the time of reporting the multivariate analysis, all included studies adjusted the severity of baseline ICH by National Institutes of Health Stroke Scale score, the meanwhile adjusted the effects of age. All studies were assessed by Newcastle-Ottawa Scale from 6 to 9. All baseline serum ferritin levels (within 24 hours at admission) was measured using immunoradiation or electroluminescence, and the mean of baseline serum ferritin levels was ranged from 45.9 to 270.6 ng/mL. The follow-up time of the included study was within 3 months after admission and mRS was used to evaluate the functional outcomes of ICH.

Because of the high heterogeneity ($I^2 = 93\%$, $P = .03$), we chose random effect model. The results of 7 literature

Table 1. *Characteristics of 7 studies*

First author's name (year of publication)	Bakhshayesh[3] (2014)		Dong[4] (2014)		Garton[5] (2017)		De la Ossa[6] (2010)	
	Favorable outcome	Unfavorable outcome	Favorable outcome	Unfavorable outcome	Favorable outcome	Unfavorable outcome	Favorable outcome	Unfavorable outcome
Sample size	16	30	25	15	20	21	41	51
Age	66.19 ± 9.49	67.87 ± 10.81	63 [47-85]	78 [34-85]	42.2 ± 17.6	67.9 ± 14.8	66.6 ± 10	69.7 ± 10
Female (%)	38.1	61.9	66.7	87.5	60	42	31.7	30.3
History of risk factors, %								
Hypertension	40.6	59.4	N	N	N	N	78.0	74.5
Diabetes	11.1	88.9	N	N	N	N	24.4	27.5
CHD	14.3	85.7	N	N	N	N	N	N
Smoking	N	N	N	N	N	N	14.6	15.7
Drinking	N	N	N	N	N	N	29.3	25.5
NIHSS score at admission	9.44 ± 6.98	13.2 ± 5.89	8.48 ± 3.85	19.2 ± 4.28	9.5 ± 8.2	21.3 ± 11.7	7 [5-10]	17 [13-20]
Hematoma volume at admission	14.38 ± 7.67	24.5 ± 15.22	11.16 ± 5.52	23.00 ± 9.2	18.2 ± 16.6	28.1 ± 28.2	9.0 [3.3-16.1]	26.3 [12.0-48.2]
Admission time	Less than 24 hours of the onset of symptoms		Less than 24 hours of the onset of symptoms		N		Within the first 12 hours from onset of symptoms	
Serum ferritin acquisition time and methods	On admission; immunoassay method		On days 1,5 and 14; electrochemiluminescenc immunoassay		On days 1 and 7 post-admission; immunoassay technique		On admission and at 24 and 72 hours; electrochemiluminescence immunoassay	
Multiple factors correlation analysis	Yes		No		Yes		Yes	
Article source sites	Iran		China		America		Spain	
Quality score	7 stars		8 stars		7 stars		7 stars	
Type of study	Prospective		Prospective		Retrospective		Prospective	
Follow-up duration and assessment scale	Using mRS at 3 months; Good (<3), Bad (≥3)		Using mRS at 1 month after onset of symptoms; Good (≤2), Bad (>2)		Using mRS at 3 and 12 months follow-up; Good (0-3), Bad (4-6)		Using mRS at 3 months; Good (≤2), Bad (>2)	

First author's name (year of publication)	Wu[7] (2017)		Zhang[8] (2015)		Zhu[9] (2014)	
	Favorable outcome	Unfavorable outcome	Favorable outcome	Unfavorable outcome	Favorable outcome	Unfavorable outcome
Sample size	34	26	41	59	18	14
Age	64 ± 9	76 ± 7	55 ± 8	56 ± 12	65 [46-80]	77 [62-82]
Female (%)	N	N	26.9	28.8	33.33	42.86

(*Continued*)

Table 1. (*Continued*)

First author's name (year of publication)	Wu[7] (2017)		Zhang[8] (2015)		Zhu[9] (2014)	
	Favorable outcome	Unfavorable outcome	Favorable outcome	Unfavorable outcome	Favorable outcome	Unfavorable outcome
History of risk factors, %						
Hypertension	N	N	60.9	60.8	72.22	78.57
Diabetes	N	N	7.3	15.2	16.67	14.29
CHD	N	N	2.4	6.7	N	N
Smoking	N	N	36.6	42.3	72.22	42.86
Drinking	N	N	26.8	28.8	72.22	50
NIHSS score at admission	9	14	6 [0-18]	16 [5-22]	10 [5-8]	15 [10-28]
Hematoma volume at admission	5 ± 1	23 ± 6	20.1 ± 14.4	43.7 ± 21.8	4.5 [1-24]	24 [6-64]
Time interval	Less than 24 hours of the onset of stroke symptoms		Less than 48 hours of the onset of stroke symptoms		Less than 24 hours of the onset of stroke symptoms	
Serum ferritin acquisition time and methods	On admission and at 3,7,14 days; electrochemiluminescence immunoassay		On admission and at 3,7,14,21 days; chemiluminescence		On admission and at 3,7,14 days; immunoluminescence	
Multiple factors correlation analysis	Yes		No		Yes	
Article source sites	China		China		China	
Quality score	6 stars		7 stars		6 stars	
Type of study	Prospective		Prospective		Prospective	
Follow-up duration and assessment scale	Using mRS at 3 months after onset of symptoms; Good (≤2), Bad (>2)		Using mRS at 3 months; Good (0-2), Bad (3-6)		Using mRS at 3 months after admission; Good (≤2), Bad (>2)	

Abbreviations: CHD, cardiovascular disease; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; Good, good outcome, Bad, bad outcome.
Values were presented as proportions, mean ± standard deviation (SD), or median [quartiles].

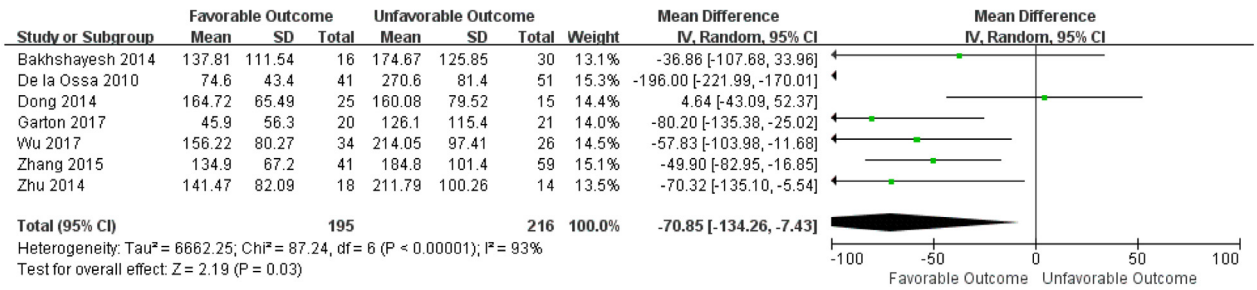

Figure 2. *The relationship between baseline serum ferritin and short-term functional outcome of ICH with 7 studies.*

showed that ICH patients with favorable outcomes compared with unfavorable outcomes had lower baseline serum ferritin levels, with significant mean differences of −70.85 (95% CI:−134.26, −7.43; Fig 2). By using the sensitivity analysis, we found that the one study[6] caused high heterogeneity. After excluding the one study, the remaining 6 studies showed lower heterogeneity ($I^2 = 25\%$, $P < .00001$), and pooled mean differences was −46.81 (95% CI −66.46, −27.16; Fig 3), and meanwhile we used the fixed effect model.

According to the different of the article sources, the objects of study were classified by China and not China, and the results (Figs. 4 and 5) showed that four studies came from China ($I^2 = 41\%$, $P = .0002$) and two not China ($I^2 = 0$, $P = .004$; Figs. 4 and 5).

Discussion

Many epidemiological studies about the association of serum ferritin and ICH have been published in those years. Our meta-analysis showed that elevated baseline serum ferritin levels were associated with statistically significant unfavorable functional outcomes in patients with ICH. This indicated that baseline serum ferritin maybe a potential prognostic factor in patients with ICH. However, the exact mechanism of baseline serum ferritin elevation after ICH remains unclear.

It is well known that iron is essential in normal brain function, but excess iron may cause a lot of damage.[13] The study found that iron overload played an important role in mediating delayed perihematoma edema (PHE) formation and neuronal injury after ICH.[14] Iron, that comes from the release of ferritin stores and hemoglobin degradation when erythrocyte lysis, was neurotoxic by promoting oxidative stress and catalyzing hydroxyl radical formation.[15] As a reliable and stable indicator of body iron load, serum ferritin was connected with relative PHE volume,[16] and was a vital predictor of clinical functional outcome for patients with ICH.[3,17]

Recent reviews[18] indicated that secondary damage after ICH can cause to the inflammation, the continued bleeding, and also cerebral edema compound brain injury. It was not clear how ICH causes the stage of secondary brain injury, but they assumed that those were associated with erythrolysis, iron exposure, and neural toxicity. In addition, the study[19] found that upregulation of serum ferritin will come secondary to acute phase response, and there was no relevant in ischemic stroke between the acute phase reactants and serum ferritin. A retrospective study[20] observed the relationship between PHE volume and serum ferritin in patients of ICH. They came to the conclusion that high serum ferritin had a positive association with increased PHE growth. Then they inferenced iron maybe involved in delayed PHE formation and neuronal injury. Meanwhile De la Ossa et al[6] found that serum ferritin was associated with long-term outcome. However, Bakhshayesh et al[3] found that meaningless correlation between serum ferritin and 3-month functional outcome, but they thought iron overload really may contribute to in-hospital mortality by increasing PHE growth. For Garton et al,[5] their finding led them to a complex inference that higher ferritin, collecting on day 1 and day 7, were associated with poorer outcomes at 3

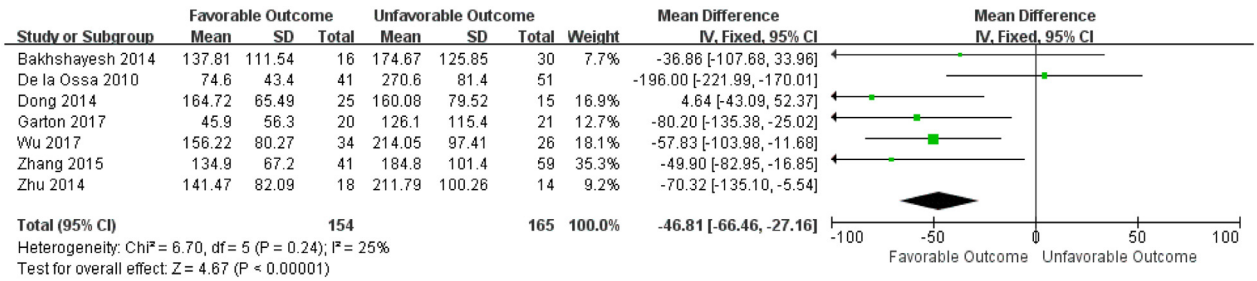

Figure 3. *The relationship between baseline serum ferritin and short-term functional outcome of ICH with 6 studies.*

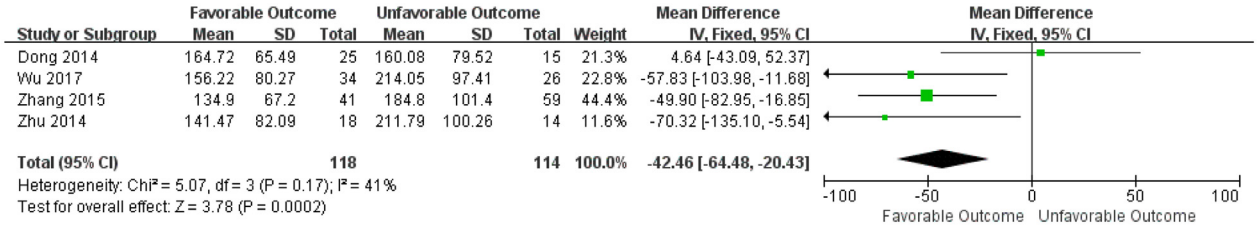

Figure 4. *The relationship between baseline serum ferritin and short-term functional outcome of ICH with 4 Chinese studies.*

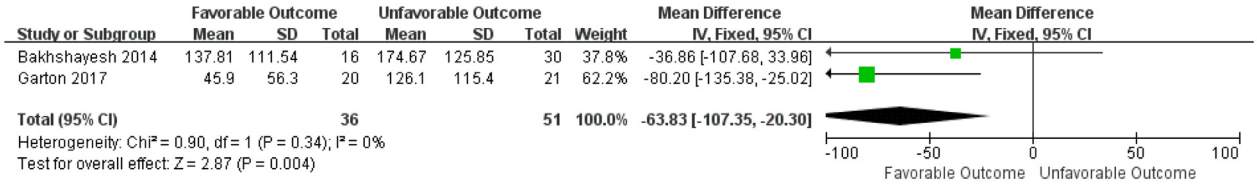

Figure 5. *The relationship between baseline serum ferritin and short-term functional outcome of ICH with 2 not Chinese studies. CIs, confidence intervals; SD, standard deviation.*

months, but this was not found to the same degree at 12 months. Interestingly, when controlling for other prognosticators, logistic regression analysis showed that serum ferritin was only trend-level associated with for 3 months outcomes with independently significance for 12 months. They considered it support that iron exposure caused to damage for longer periods of time. These studies suggested that elevated baseline serum ferritin contributed to hematoma formation and hemorrhagic inflammation, which can predict short-term functional outcomes.

Furthermore, treatment with iron chelator has been shown to reduce ICH-induced iron handling proteins and perihematomal iron overload, and it further reduced brain edema neurological deficits and delayed brain atrophy.[21-23] Iron overload and up-regulation of ferritin in the brain after ICH showed that iron may be a target of ICH therapy. Since most of erythrocytes began to lyse within a few days after ICH, this potentially delayed window of time for injury may be useful for treatment.[24]

The limitations of our study should be admitted. Firstly, the sample size included in each study was relatively small, which cannot well-represent the situation of a large range of patients. Secondly, due to the differences in the design, inclusion and exclusion of objects, analysis methods or other factors, the results of the combined analysis may not be rigorous. Thirdly, serum ferritin was measured only at the beginning of admission in most of the studies, without dynamic detection over time, and there was also a lack of serum ferritin in patients before cerebral hemorrhage, so the interpretation of single serum ferritin may be problematic. Fourthly, our meta-analysis only included Chinese and English literatures, which resulted in incomplete retrieval of literatures and produce bias. Finally, because participant data of included studies were unavailable, we only used and observed aggregate data as reported. The common approach could not better find and may not solve to affect the primary studies of methodological problems. In addition, our study also had some advantages. First, the inherent advantages of meta-analysis were seen. It overcame selective and potentially biased inclusion studies and weighing of studies' results when explaining the evidence. This made the combined results even more reliable and convincing. Then it was of great significance for finding biomarkers to predict the prognosis of cerebral hemorrhage.

Conclusions

In summary, elevated serum ferritin at admission was associated with poorer short-term functional outcome of patients with ICH, which indicated that serum ferritin level at admission may predict the prognosis of patients with ICH. In the future, we will need more epidemiological and experimental data to draw clearer conclusions. Whether iron consumption or chelating agents may be used to treat patients with ICH will require extensive, well-designed prospective, interventional studies.

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