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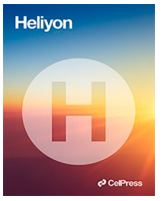

Research article

Efficacy and safety of standardized Ginkgo biloba extract as adjuvant therapy for intracerebral hemorrhage in China: A systematic review and meta-analysis

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ABSTRACT

Objective: The aim of this study was to systematically review the clinical efficacy and safety of standardized Ginkgo biloba extract (GBE) in the adjuvant treatment of intracerebral hemorrhage (ICH).
Methods: Relevant RCTs on GBE as adjuvant therapy for ICH were searched in seven Chinese and English databases. Data extraction of the included literature was performed after duplicate checking and screening, and Stata 15.1 software was applied for data analysis.
Results: With a total of 19 RCTs, the meta-analysis results showed that: Compared with conventional treatment alone, GBE combined with conventional treatment had a higher effective rate; NIHSS score and CSS score were lower; The residual hematoma was less. The volume of cerebral edema was smaller. ADL score was higher. MoCA score was higher. The serum levels of hs-CRP, TNF-α and IL-6 were lower; No significant difference was observed in the incidence of adverse reactions between conventional treatment alone and GBE combined with conventional treatment.
Conclusion: This study suggests that GBE as adjuvant therapy for ICH has better efficacy and is relatively safe compared with conventional treatment alone. However, due to the quality and quantity of included studies, further validation by more methodologically rigorous and multicenter studies with larger sample sizes is needed.

1. Background

Intracerebral hemorrhage (ICH), which refers to non-traumatic cerebral parenchymal hemorrhage, a type of hemorrhagic stroke, is the most severe and intractable type of stroke, accounting for 10%–15% of all strokes [1,2]. ICH, characterized by rapid onset, high mortality and high disability rate, affects approximately 2 million people worldwide each year with a mortality rate in the acute stage of 30%–50% and a disability rate of 75%, ranking first among all types of stroke [3–5]. The causes of brain injury due to ICH mainly

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include direct injury caused by the hematoma-occupying effect and a series of secondary injuries with complex mechanisms, which ultimately lead to neurological impairment [2,6,7]. Currently, the clinical therapeutic effect of ICH is not satisfactory and therefore the search for more appropriate adjuvant or alternative treatments has become a hotspot of ICH research [8,9].

According to the theory of traditional Chinese medicine (TCM), "Blood removed from the meridians becomes stasis", and blood stasis is considered to play an important role in the pathogenesis and progression of ICH. Some studies have shown that TCM which promotes blood circulation and resolves blood stasis has a certain guiding significance in the treatment of ICH [10]. TCM believes that Ginkgo biloba returns to the heart meridian, and has the effect of activating blood circulation and removing stasis, dredging collaterals, and relieving pain, especially good at treating heart and brain diseases. GBE is a mixture with various pharmacological effects extracted and processed from Ginkgo biloba leaves, and its main active ingredients are 24% flavonoids (baicalein, etc.), 6% terpene lactones (ginkgolide, bilobalide, etc.), organic acids and phenols [11,12]. In recent years, GBE has received wide attention from researchers and clinicians, and its effects of scavenging free radicals, anti-oxidation, inhibiting platelet aggregation, and vasodilating have been confirmed by some studies [13,14]. Some clinical studies have reported the efficacy of GBE as adjuvant therapy for ICH [15,16], but convincing evidence is still lacking. Therefore, this study is aim to conducted a systematic review and meta-analysis of the efficacy and safety of GBE as adjuvant therapy for ICH to provide a reference for the clinical treatment practice of ICH.

2. Methods

The systematic review and meta-analysis were performed in accordance with the PRISMA guidelines and the Cochrane Handbook, and this study was registered in the PROSPERO database (registration number: CRD 42022332298).

2.1. Literature retrieval

Seven Chinese and English databases, including PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Database of Chinese Sci-tech Periodicals (VIP), and Wanfang Database, were searched for randomized controlled trials (RCTs) on GBE as adjuvant therapy for ICH published from the inception of each database to July 1, 2022. The search terms included "Cerebral Hemorrhage", "Intracerebral Hemorrhage", "Brain Hemorrhage", "Ginkgo Biloba", "Ginko", "Ginkgo Biloba Extract", "Ginkgo Leaf Extract", and "Yinxingtiquwu", and mesh words in PubMed were used to expand the search scope. See the attachment for specific search strategies.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) Subjects: patients diagnosed with ICH by imaging; (2) Study type: randomized controlled trial; (3) Intervention measures: the control group received conventional treatment, including lowering blood pressure, maintenance of water-electrolyte balance, dehydration, use of neuroprotective agents, and prevention of complications, etc., while the observation group received GBE combined with conventional treatment; (4) The study involved one or more outcome measures: efficacy rate, NIH Stroke Scale (NIHSS), Chinese Stroke Scale (CSS), hematoma volume, cerebral edema volume, Activity of Daily Living (ADL), Montreal Cognitive Assessment (MoCA), Hypersensitive C-reactive Protein (hs-CRP), Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), and adverse reactions.

Exclusion criteria: (1) Reviews, animal experiments, systematic evaluation, case studies, conference abstracts, etc.; (2) Studies unable to obtain the full text or duplicate publications; (3) Studies with incomplete or incorrect data information; (4) Literature not in Chinese or English.

2.3. Literature screening and data extraction

Two researchers independently scanned the titles and abstracts for preliminary screening, then read the full text for re-screening according to the inclusion and exclusion criteria, and cross-checked the screening results. Data from the included literature were extracted independently by the two researchers, and disagreements were resolved by discussion with a third researcher. The extracted information included: (1) Study characteristics: first author, and publication year; (2) Patient baseline: sample size, gender, age, course of disease, intervention measures, and course of treatment; (3) Outcome measures: efficacy rate, NIH Stroke Scale (NIHSS), Chinese Stroke Scale (CSS), hematoma volume, cerebral volume, Activity of Daily edema Living (ADL), Montreal Cognitive Assessment (MoCA), Hypersensitive C-Reactive Protein (HS-CRP), Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), and adverse reactions.

2.4. Quality assessment

The methodological quality of each study was assessed by two investigators using the risk of bias assessment tool for RCTs by Cochrane Collaboration, and discrepancies were resolved by discussion with a third investigator. The specific evaluation items included random sequence generation, allocation concealment methods, blinding of the investigators, subjects and outcome assessors, completeness of the outcome data, selective reporting of study results, and the presence of other biases. The risk of bias maps and risk of bias summary maps were created using RevMan 5.4.1 software.

2.5. Statistical analysis

Statistical analysis was performed using Stata 15.1 software. Relative risk (RR) and weighted mean difference (WMD) were used as the effect value for dichotomous variables and continuous variables, respectively, with the 95% confidence interval (*95% CI*) calculated for both. The heterogeneity of the included studies was tested by Q test and I^2 test. If $P > 0.10$ or $I^2 < 50\%$, the heterogeneity among studies was small, and the fixed-effects model was adopted; otherwise, the random-effects model was employed. Sensitivity analysis was conducted to evaluate the stability of the results. Begg's test and Egger's test were used to quantify publication bias. $P < 0.05$ was considered to indicate a significant difference between the two groups.

3. Results

3.1. Literature screening results

A total of 830 studies were retrieved from the databases, including 20 studies from PubMed, 119 from Embase, 16 from Cochrane, 193 from Web of Science, 145 from CNKI, 161 from VIP, and 176 from Wanfang Database. After the exclusion of duplicate literature, 296 non-Chinese and non-English RCTs of reviews, animal experiments, case studies, and systematic evaluations were removed by reading the titles and abstracts, and 71 studies that did not meet the requirements of study subjects, intervention measures, and outcome measures were excluded after reading the full text. A total of 19 studies [17–35] were finally included, as shown in Fig. 1.

3.2. Basic characteristics of the included literature

A total of 11,692 patients with ICH were included in the 19 studies, including 5805 in the treatment group and 5887 in the control

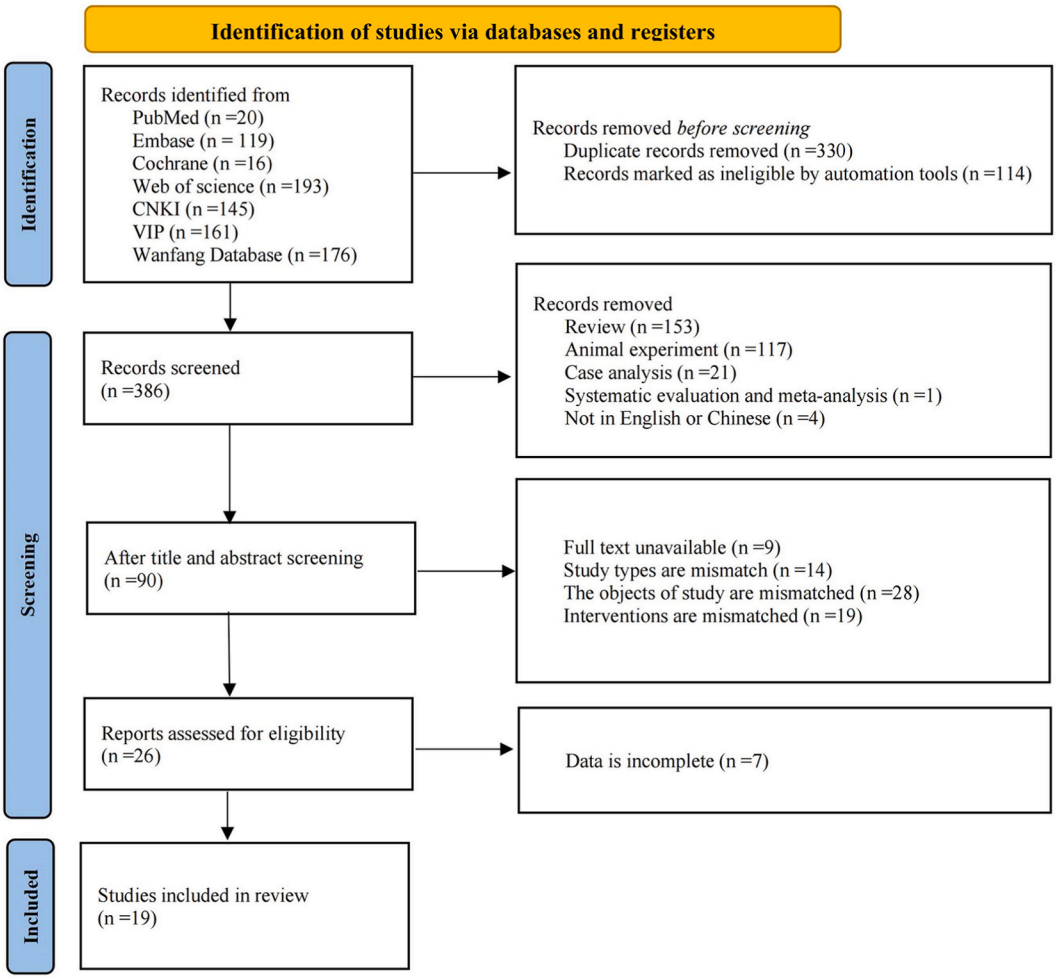

Fig. 1. The flow diagram of the included studies.

group. The control group received conventional treatment, including lowering blood pressure, maintenance of water-electrolyte balance, dehydration, use of neuroprotective agents, and prevention of complications; the observation group was treated with GBE combined with conventional treatment for 7 d to 20 d. The specific study characteristics, patient baseline, and outcome measures of the included studies are shown in Table 1.

3.3. Risk of bias assessment results

The risk of bias assessment tool provided by Cochrane Collaboration was used to assess the 19 included studies. As for randomization methods, with randomized grouping mentioned in 19 studies, five studies [18,20,21,24,25] used a random number table, one study [23] used the randomized block design, and one study [26] adopted a random sampling method, which were assessed as low risk; the remaining studies did not specify the specific randomization method and were assessed as uncertain risk. None of the 19 studies mentioned allocation concealment methods, and thus were assessed as uncertain risk. In terms of blinding, none of the 19 studies applied blinding methods to investigators, subjects, and outcome assessors, but four of them [22,24,28,30] had outcomes unlikely to be affected by the lack of blinding and were assessed as low risk, while the remaining studies were assessed as high risk. All 19 studies had complete outcome data, all of which reported prespecified outcome indicators with no other bias observed, so they were assessed as low risk. The detailed risk of bias assessment chart is shown in Fig. 2AB.

Table 1
Characteristics of the included studies.

Author (Year)	Group	Number (M/F)	Age (year)	Time course	Intervening measure	Treatment course	Outcomes
Zuo et al. (2021)	Observation	50 (29/21)	59.16 ± 6.74	2 ~ 36 h	CT + GBE 20 ml/d	14 d	①②④⑥⑧⑪
	Control	50 (29/21)	60.02 ± 5.97	2 ~ 35 h	CT	14 d	
Zhong et al. (2021)	Observation	43 (30/13)	60.16 ± 2.61	2 ~ 24 h	CT + GBE 17.5 mg/d	14 d	②③⑧⑨⑩⑪
	Control	43 (29/14)	60.13 ± 2.57	2 ~ 24 h	CT	14 d	
Yang (2020)	Observation	36 (23/13)	60.48 ± 6.43	2 ~ 24 h	CT + GBE	14 d	②④⑤⑥
	Control	36 (24/12)	62.61 ± 6.85	2 ~ 24 h	CT	14 d	
Teng (2020)	Observation	39 (22/17)	69.12 ± 4.30	3 ~ 45 h	CT + GBE 17.5 mg/d	14 d	③④⑤⑧⑨⑩
	Control	39 (20/19)	67.36 ± 3.24	3 ~ 45 h	CT	14 d	
Li (2020)	Observation	35 (18/17)	68.29 ± 5.77	1 ~ 6 h	CT + GBE 17.5 mg/d	14 d	②⑥⑦
	Control	35 (20/15)	68.25 ± 5.74	1 ~ 7 h	CT	14 d	
Chen (2020)	Observation	5000 (2570/2430)	56.8 ± 11.5	NA	CT + GBE 20 ml/d	14 d	⑩
	Control	5000 (2600/2400)	55.7 ± 10.5	NA	CT	14 d	
Ma et al. (2019)	Observation	105 (55/50)	76.54 ± 4.92	NA	CT + GBE 17.5 mg/d	14 d	①②④⑤⑥⑦⑪
	Control	105 (57/48)	77.12 ± 4.63	NA	CT	14 d	
Luo et al. (2019)	Observation	46 (30/16)	54.5 ± 12.5	NA	CT + GBE	14 d	④⑤
	Control	46 (22/24)	59.5 ± 14.5	NA	CT	14 d	
Ni et al. (2018)	Observation	49 (30/19)	58.97 ± 4.51	1 ~ 35 h	CT + GBE 20 ml/d	14 d	①②⑥⑧⑨⑩⑪
	Control	49 (28/21)	59.27 ± 4.62	1 ~ 35 h	CT	14 d	
Cao (2017)	Observation	20 (10/10)	71.62 ± 8.34	NA	CT + GBE 20 ~ 50 ml/d	20 d	①②④
	Control	20 (11/9)	71.66 ± 8.38	NA	CT	20 d	
Min et al. (2016)	Observation	41 (31/10)	61.55 ± 11.47	2 ~ 48 h	CT + GBE 17.5 mg/d	14 d	③④⑤⑪
	Control	41 (30/11)	62.52 ± 10.30	2 ~ 48 h	CT	14 d	
Wang et al. (2015)	Observation	34 (19/15)	63.7	0.5 ~ 8 h	CT + GBE 20 ml/d	14 d	④⑤
	Control	31 (20/11)	62.3	0.5 ~ 7.5 h	CT	14 d	
Cui et al. (2015)	Observation	48 (26/22)	64.9 ± 11.6	1 ~ 48 h	CT + GBE 20 ml/d	14 d	④
	Control	44 (24/20)	67.8 ± 11.9	1 ~ 48 h	CT	14 d	
Guo (2013)	Observation	41	NA	1 ~ 24 h	CT + GBE 20 ml/d	7 d	④
	Control	41	NA	1 ~ 24 h	CT	7 d	
Zhou et al. (2012)	Observation	158 (89/69)	61.4 ± 7.8	NA	CT + GBE 10 ~ 20 ml/d	7 d	①②⑪
	Control	82 (58/24)	63.2 ± 5.9	NA	CT	7 d	
Yuan et al. (2012)	Observation	45 (24/21)	58.61	1 ~ 24 h	CT + GBE 20 ml/d	14 d	①②④
	Control	43 (22/21)	59.24	1 ~ 24 h	CT	14 d	
Song et al. (2009)	Observation	40 (21/19)	61.2	1 ~ 24 h	CT + GBE 87．5 mg/d	18 d	②④
	Control	41 (21/20)	62.3	1 ~ 24 h	CT	18 d	
Liu (2007)	Observation	27 (19/8)	51 ± 3.6	0.5 ~ 72 h	CT + GBE 15 ml/d	15 d	④⑤
	Control	29 (21/8)	52 ± 4.1	0.5 ~ 72 h	CT	15 d	
Wang et al. (2004)	Observation	30	NA	1 ~ 72 h	CT + GBE 6 ml/d	14 d	②④
	Control	30	NA	1 ~ 72 h	CT	14 d	

Annotation: M: male; F: female; NA: not applicable; CT: conventional treatment (mainly including decreasing blood pressure, dehydration detumescence, maintaining water and electrolyte balance, neuroprotective agent and prevention of complications); Outcomes: ①Efficacy rate、②-NIHSS、③CSS、④Hematoma volume、⑤Cerebral edema volume、⑥ADL、⑦MoCA、⑧hs-CRP、⑨TNF-α、⑩IL-6、⑪Adverse reactions.

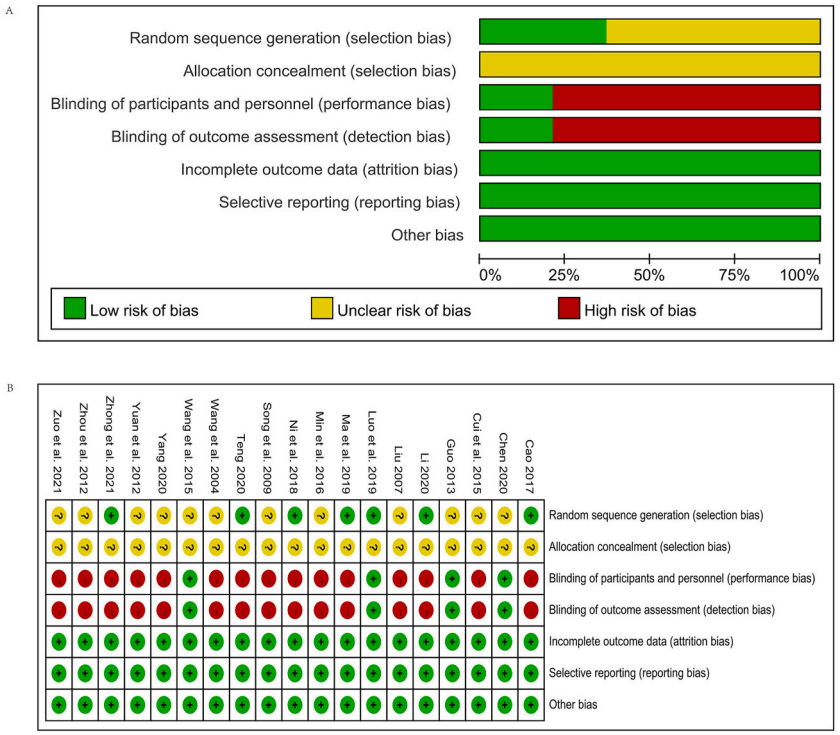

Fig. 2. (A) Methodological quality summary about the risk of bias of included studies (B) Methodological quality graph of included studies.

3.4. Meta-analysis results

3.4.1. Efficacy rate

A total of six studies [17,23,25,26,31,32] reported data on the clinical efficacy rate with low heterogeneity among studies ($P = 0.175$, $I^2 = 34.9\%$), and a meta-analysis was performed using a fixed-effects model. The results suggested that GBE combined with conventional treatment had a higher clinical efficacy rate than conventional treatment alone ($RR = 1.29$, 95% CI:1.18~1.41, $P < 0.05$), as shown in Fig. 3.

3.4.2. NIH Stroke Scale (NIHSS)

A total of 10 studies [17–19,21,23,25,26,31–33] reported data on NIHSS scores with high heterogeneity among studies ($P < 0.01$, $I^2 = 83.5\%$), and the meta-analysis was performed using a random-effects model. The results indicated that GBE combined with conventional treatment reduced patients' NIHSS scores compared with conventional treatment alone ($WMD = -4.81$, 95%CI: 6.30~-3.31, $P < 0.05$). Subgroup analysis based on treatment duration showed that when treatment duration ≤1w, there was no statistically significant difference between GBE combined with conventional treatment and conventional treatment alone ($WMD =$

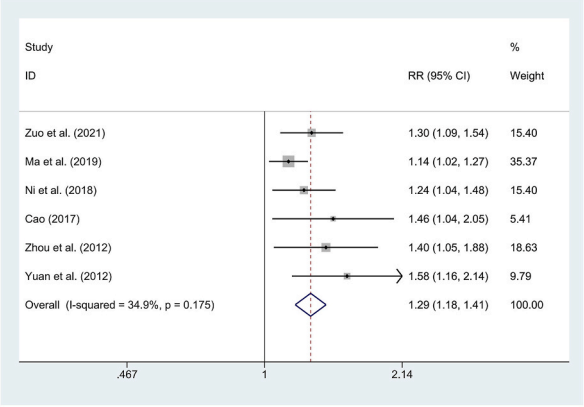

Fig. 3. Forest plot of efficacy rate in the two groups.

-1.20, 95%CI: 3.13-0.73, P = 0.222), while when treatment duration ≥2w, inter-study heterogeneity was small, indicating that treatment duration may be the source of heterogeneity, as shown in Fig. 4.

3.4.3. Chinese Stroke Scale (CSS)

A total of three studies [18,20,27] reported data on CSS scores with low heterogeneity among studies ($P = 0.434$, $I^2 = 0\%$), and a fixed-effects model was adopted for meta-analysis. The results suggested that GBE combined with conventional treatment reduced patients' CSS scores compared with conventional treatment alone (*WMD = -4.16, 95%CI: 5.11~-3.20, P < 0.05*), as shown in Fig. 5.

3.4.4. Hematoma volume

A total of 14 studies [17,19,20,23,24,26–30,32–35] reported data on hematoma volume with low heterogeneity among studies ($P = 0.671$, $I^2 = 0\%$), and a fixed-effects model was used for meta-analysis. The results suggested that GBE combined with conventional treatment reduced the hematoma volume in patients compared with conventional treatment alone (*WMD = -4.96, 95%CI: 5.52~-4.39, P < 0.05*), as shown in Fig. 6.

3.4.5. Cerebral edema volume

A total of six studies [19,20,23,24,28,34] reported data on cerebral edema volume with high heterogeneity among studies ($P < 0.01$, $I^2 = 77.9\%$), and a meta-analysis was performed using a random-effects model. The results revealed that GBE combined with conventional treatment reduced the cerebral edema volume in patients compared with conventional treatment alone (*WMD = -5.05, 95%CI: 7.16~-2.94, P < 0.05*). Subgroup analysis based on the treatment duration showed significant results for all subgroups but little change in heterogeneity, indicating that treatment duration was not the source of heterogeneity, as shown in Fig. 7.

3.4.6. Activity of Daily Living (ADL)

A total of five studies [17,19,21,23,25] reported data on ADL scores with high heterogeneity among studies ($P = 0.025$, $I^2 = 64.1\%$), and a meta-analysis was performed using a random-effects model. The results suggested that GBE combined with conventional treatment improved patients' ADL scores compared with conventional treatment alone (*WMD = 11.50, 95%CI: 9.65~13.35, P < 0.05*), as detailed in Fig. 8.

3.4.7. Montreal Cognitive Assessment (MoCA)

Data on MoCA scores were reported in three studies [18,20,27] with high heterogeneity among studies ($P = 0.017$, $I^2 = 82.4\%$), and a meta-analysis was performed using a random-effects model. The results indicated that GBE combined with conventional treatment improved patients' ADL scores compared with conventional treatment alone (*WMD = 7.19, 95%CI: 5.68~8.17, P < 0.05*), as shown in Fig. 9.

3.4.8. Serum inflammatory factors hs-CRP, TNF-α, IL-6

A total of four studies [17,18,20,25] reported data on hs-CRP, with high heterogeneity among studies ($P < 0.01$, $I^2 = 94.5\%$); three studies [18,20,25] reported data on TNF-α, with high heterogeneity among studies ($P < 0.01$, $I^2 = 96.7\%$); four studies [18,20,22,25] reported data on IL-6 with high heterogeneity among studies ($P < 0.01$, $I^2 = 97.9\%$), all of which were meta-analyzed using a random-effects model. The results suggested that, compared with conventional treatment alone, GBE combined with conventional treatment could reduce the levels of serum inflammatory factors hs-CRP, TNF-α, and IL-6 in patients ($WMD_{hs\text{-}CRP} = -8.30$, *95%CI: 12.00~-4.61, P < 0.05*; $WMD_{TNF\text{-}\alpha} = -17.62$, *95%CI: 34.13~-1.12, P < 0.05*; $WMD_{IL\text{-}6} = -10.35$, *95%CI: 16.61~-4.08, P < 0.05*). Forest plots of hs-CRP, TNF-α, and IL-6 are shown in Figs. 10–12, respectively.

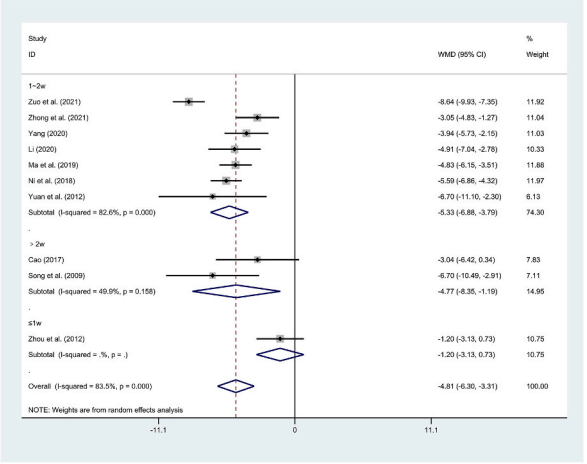

Fig. 4. Subgroup analysis of NIHSS in the two groups.

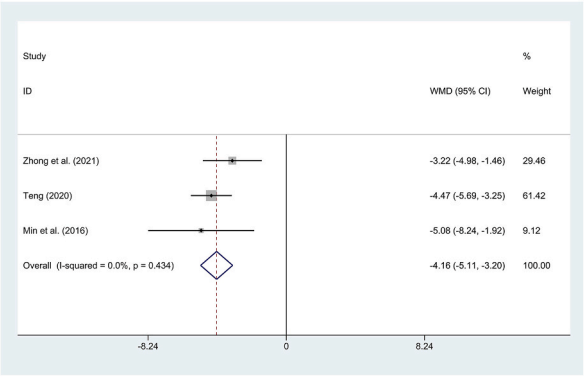

Fig. 5. Forest plot of CSS in the two groups.

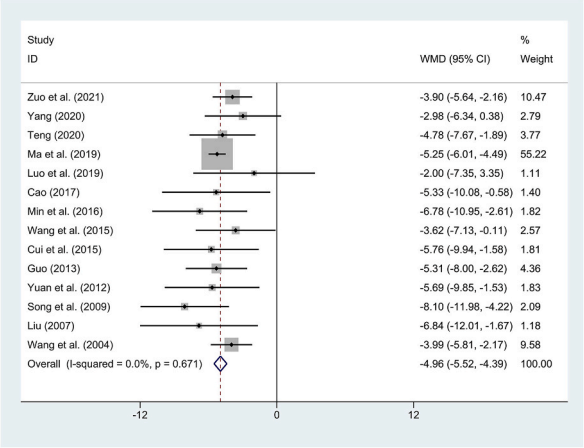

Fig. 6. Forest plot of hematoma volume in the two groups.

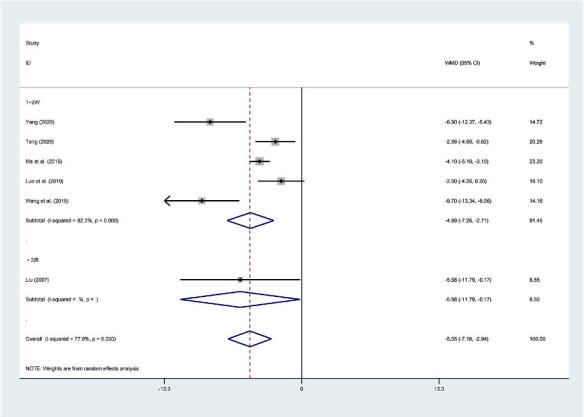

Fig. 7. Subgroup analysis of cerebral edema volume in the two groups.

3.4.9. Adverse reactions

A total of five studies [17,18,23,27,31] reported data on the occurrence of adverse reactions, with low heterogeneity among studies ($P = 0.699$, $I^2 = 0\%$), and a meta-analysis was performed using a fixed-effects model. The results indicated that there was no statistically significant difference in the incidence of adverse reactions between conventional treatment alone and GBE combined with conventional treatment ($RR = 0.95$, 95%CI: 0.52~1.74, $P = 0.873$), as shown in Fig. 13.

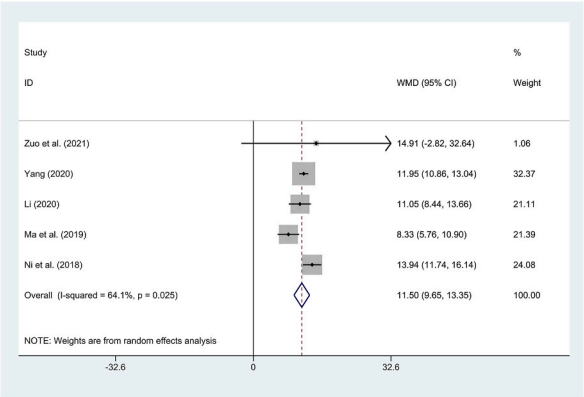

Fig. 8. Forest plot of ADL scores in the two groups.

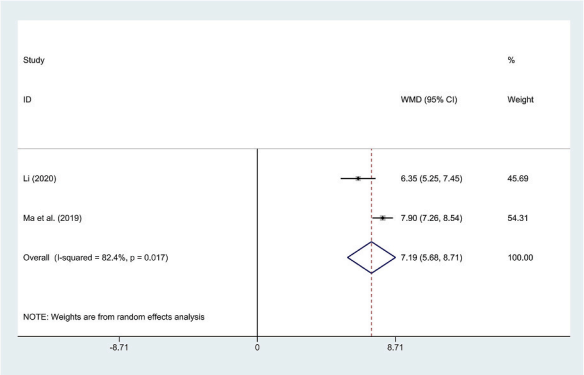

Fig. 9. Forest plot of MoCA scores in the two groups.

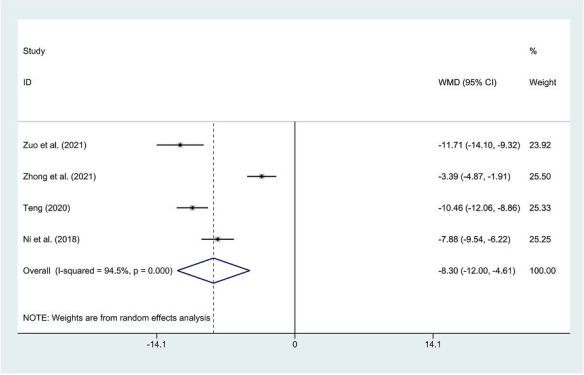

Fig. 10. Forest plot of hs-CRP in the two groups.

3.5. Sensitivity analysis and publication bias

Sensitivity analysis of all outcome measures by removing each study one by one demonstrated that the results were relatively stable. See the attachment for sensitivity analysis chart. The NIHSS score and hematoma volume were reported in over 10 included studies as outcome indicators, and publication bias was quantified using Begg's funnel plot and Egger's linear regression test. The results showed that about the NIHSS score, Egger's $P = 1.000$ and Begg's $P = 0.466$, indicating that there was no significant publication bias; as for hematoma volume, Egger's $P = 0.443$ and Begg's $P = 0.894$, suggesting no significant publication bias, as shown in Fig. 14AB.

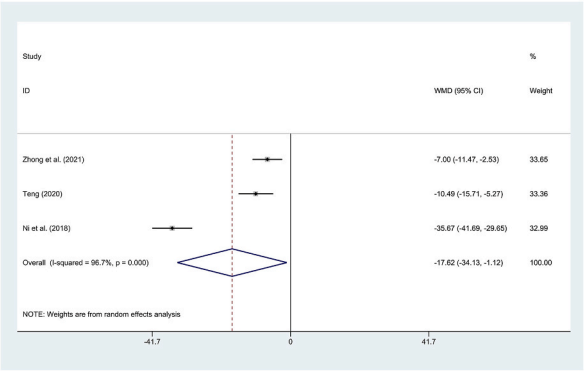

Fig. 11. Forest plot of TNF-α in the two groups.

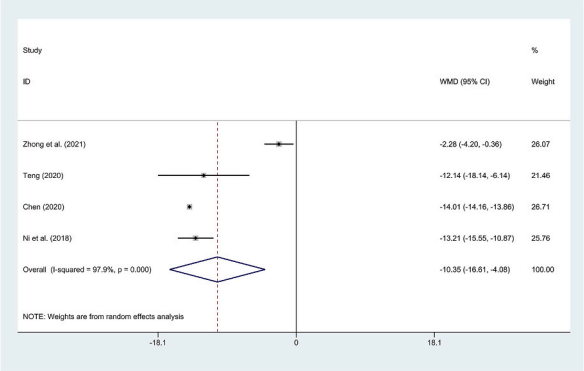

Fig. 12. Forest plot of IL-6 in the two groups.

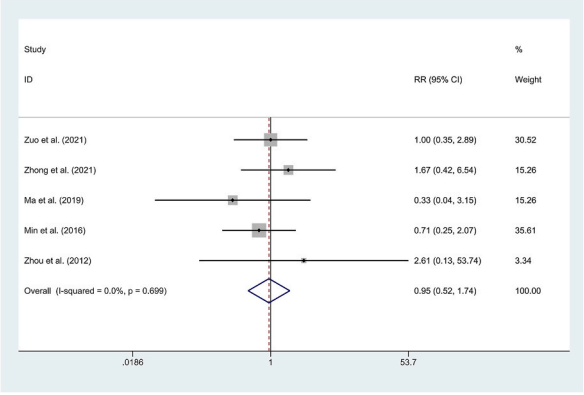

Fig. 13. Forest plot of adverse reactions in the two groups.

4. Discussion

ICH is a common cerebrovascular disease with acute conditions and poor prognosis, which seriously threatens the life safety and quality of life of patients, mainly manifesting as headache, vomiting, motor and speech impairment, and in severe cases, confusion and coma. The compressive effect of hematoma after the occurrence of ICH directly leads to the formation of cerebral edema by elevated pressure in the surrounding brain tissue, which in turn causes a decrease in local cerebral blood flow, resulting in ischemia and hypoxia in the patient's brain tissue [36]. In addition, toxic products of hematoma metabolism, disruption of the blood-brain barrier, and inflammatory reactions are also involved in brain tissue damage and worsen with time [37]. GBE can act simultaneously against multiple pathological aspects of ICH and can protect brain tissue by antioxidation and anti-inflammatory effects, scavenging oxygen

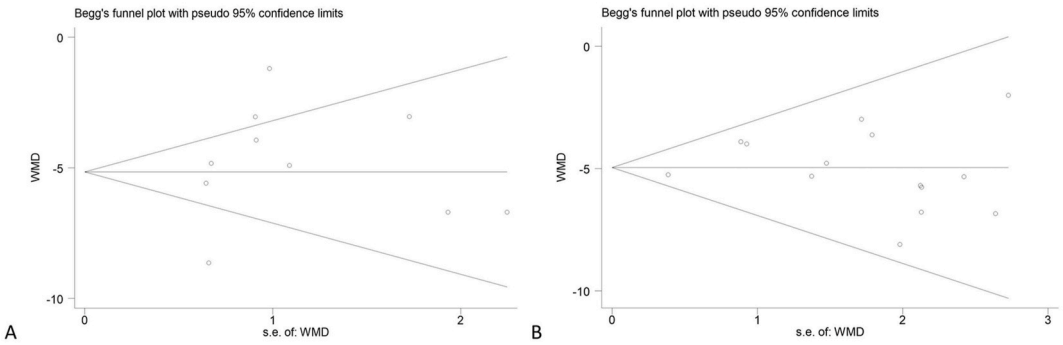

Fig. 14. A: Funnel plot of publication bias for the NIHSS score B: Funnel plot of publication bias for hematoma volume.

free radicals, inhibiting lipid peroxidation, and preventing neuronal apoptosis [38,39]. GBE can also reduce blood viscosity and dilate blood vessels of patients, thus achieving the purpose of improving microcirculation and brain injury after ischemia [40,41]. Moreover, GBE can protect the damaged blood-brain barrier and help restore neurological function, so it is widely used clinically in cardiovascular and cerebrovascular diseases. Animal experiments have further proved that GBE can restore nerve function, relieve vasospasm and cerebral edema in rats with cerebral hemorrhage, and is considered as a neuroprotective agent with multiple targets and effects [42,43].

Although some clinical studies have found that GBE adjuvant therapy for ICH has a certain effect, there is still no convincing evidence-based medical evidence. Therefore, this study is the first systematic evaluation and meta-analysis of the efficacy and safety of GBE as an adjunctive therapy for ICH. The results showed that: Intracerebral hemorrhage can lead to brain tissue damage, involving surrounding tissues and causing edema, which further aggravates cerebral circulation and metabolic disorders. GBE adjuvant therapy can effectively reduce hematoma volume and edema volume, and then reduce brain damage. The NIHSS score, CSS score, ADL score, and MoCA score are used to evaluate neurological impairment, daily living ability and cognitive function, which are important prognostic indicators. GBE adjuvant therapy can effectively improve the prognosis of patients by improving their neurological function, cognitive function and ability of daily living activities. The hematoma component after the onset of ICH can trigger inflammatory pathways leading to brain edema and neurological dysfunction, while inflammatory factors such as hs-CRP, TNF-α, and IL-6 show a positive correlation with the degree of brain injury and are commonly used to assess the condition [44]. GBE adjuvant therapy can effectively promote the absorption of inflammatory factors and reduce the inflammatory response of brain tissue. The incidence of adverse reactions was used as an indicator of safety, and the results of this study showed no statistically significant difference in the probability of adverse reactions between conventional treatment alone and GBE combined with conventional treatment. Taken together, GBE combined with conventional treatment increased clinical efficiency, improved neurological function, improved daily living ability and cognition, reduced serum inflammatory index levels, and had a good safety profile compared with conventional treatment alone. As sensitivity analysis showed the results were stable and there was no publication bias. This study meticulously followed the standards of Cochrane Collaborative network systematic review and meta-analysis, which not only provided reliable evidence-based medical evidence for the clinical application of GBE in ICH patients, but also played a role in promoting the clinical use of TCM preparations. This study is of great significance.

Nevertheless, this study still has some limitations: (1) The methodological quality of the included studies was generally low, with 12 studies not describing in detail how the randomized sequences were generated; all studies did not specify whether allocation concealment schemes were used, which may lead to some selection bias; 15 studies did not mention the specific implementation of blinding, which may result in certain selection bias. (2) The heterogeneity among studies of some outcome measures (NIHSS score, edema volume, ADL score, MoCA score, hs-CRP, TNF-α, IL-6) was too high, which may be related to the sample size, study subjects, and treatment duration, etc. Further expansion of the sample size may help to eliminate the heterogeneity. (3) In this study, subgroup analysis based on treatment duration did not reveal a significant difference among subgroups, so the sample size should be further expanded to refine the analysis. (4) The clinical adaptability is limited. All the patients included in the study were Chinese patients, which affected the reliability of the results to a certain extent. Hence, larger sample sizes are required to include more patients from different regions and countries for further analysis.

5. Conclusion

Compared with conventional therapy alone, GBE adjuvant therapy for ICH has better efficacy and is relatively safe. This study provides more detailed and reliable evidence-based medical evidence for the use of GBE as adjuvant therapy for ICH, and some guiding suggestions for promoting the better clinical application of TCM preparations in ICH patients. However, given the limitations of this study, the long-term efficacy and safety of GBE for ICH need to be validated by more large-sample, multi-center, methodologically rigorous studies.

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Data availability statement

All data generated or analyzed during this study are included in this published article (and its Supplementary Information files).

Ethics approval and consent to participate

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

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CRediT authorship contribution statement

Shikai Chen: Writing – original draft, Methodology, Data curation, Conceptualization. **Shufa Tan:** Methodology, Investigation, Formal analysis, Data curation. **Wen Hou:** Investigation, Funding acquisition, Formal analysis, Data curation. **Xu Chen:** Investigation, Funding acquisition, Formal analysis, Data curation. **Lei Bai:** Investigation, Funding acquisition, Formal analysis, Data curation. **Yingying Zou:** Methodology, Investigation, Formal analysis, Data curation. **Weitong Sun:** Investigation, Funding acquisition, Formal analysis, Data curation. **Zhao Zhang:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Yi Zhang:** Writing – review & editing, Supervision, Resources, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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