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REVIEW

Predictors of early neurological deterioration in patients with intracerebral hemorrhage: a systematic review and meta-analysis

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Abstract

Background Early neurological deterioration, a common complication in patients with intracerebral hemorrhage, is associated with poor outcomes. Despite the fact that the prevalence and predictors of early neurological impairment are widely addressed, few studies have consolidated these findings. This study aimed to systematically investigate the prevalence and predictors of early neurological deterioration.

Methods The PubMed, Embase, Cochrane Library, CIHNAL, and Web of Science databases were systematically searched for relevant studies from the inception to December 2023. The data were extracted using a predefined worksheet. Quality assessment was conducted using the Newcastle–Ottawa Scale. Two reviewers independently performed the study selection, data extraction, and quality appraisal. The pooled effect size and 95% confidence intervals were calculated using the STATA 17.0 software package.

Results In total, 32 studies and 5,014 patients were included in this meta-analysis. The prevalence of early neurological deterioration was 23% (95% CI 21–26%, $p < 0.01$). The initial NIHSS score (OR = 1.24, 95% CI 1.17, 1.30, $p < 0.01$), hematoma volume (OR = 1.07, 95% CI 1.06, 1.09, $p < 0.01$), intraventricular hemorrhage (OR = 3.50, 95% CI 1.64, 7.47, $p < 0.01$), intraventricular extension (OR = 3.95, 95% CI 1.96, 7.99, $p < 0.01$), hematoma expansion (OR = 9.77, 95% CI 4.43, 17.40, $p < 0.01$), and computed tomographic angiography spot sign (OR = 5.77, 95% CI 1.53, 20.23, $p = 0.01$) were predictors of early neurological deterioration. The funnel plot and Egger's test revealed significant publication bias ($p < 0.001$).

Conclusions This meta-analysis revealed a pooled prevalence of early neurological deterioration of 23% in patients with intracerebral hemorrhage. The initial NIHSS score, hematoma volume, intraventricular hemorrhage, intraventricular expansion, hematoma expansion, and spot sign enhanced the probability of early neurological deterioration. These findings provide healthcare providers with an evidence-based basis for detecting and managing early neurological deterioration in patients with intracerebral hemorrhage.

Keywords Systematic review · Meta-analysis · Early neurological deterioration · Intracerebral hemorrhage · Predictors

Introduction

Spontaneous intracerebral hemorrhage is a devastating subtype of stroke with high rates of morbidity, disability and mortality [1]. In 2019, there were 3.41 million new intracerebral hemorrhage cases, accounting for 27.9% of all new strokes, and 2.89 million stroke deaths [2]. As known, the risk of intracerebral hemorrhage increases significantly with age. Despite improvements in public blood pressure regulation, intracerebral hemorrhage still remains a global public health concern as the population ages. [3]. Early neurological deterioration (END) is a common complication observed in patients with intracerebral hemorrhage and is typically defined as a ≥ 4-point increase in the National Institutes of

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Health Stroke Scale (NIHSS) score or a ≥ 2-point decrease in the Glasgow Coma Scale (GCS) score or death from baseline to 24 h [4]. Early neurological deterioration occurs in 7.47–40.99% of individuals after intracerebral hemorrhage [5] and is related to poor functional outcomes, increased mortality, and a greater risk of disability [6, 7]. Early identification of early neurological deterioration thus becomes essential for improving the outcomes of patients after intracerebral hemorrhage. However, early neurological deterioration is an underlying process that clinicians cannot see directly since continuous neuroimaging monitoring is difficult [8]. Identifying predictors of early neurological deterioration is thus crucial for detecting high-risk individuals and optimizing patient care and outcomes.

Several studies have demonstrated relationships between early neurological deterioration and sociodemographic variables, clinical characteristics, and neuroimaging parameters. In terms of sociodemographic factors, older age and male sex were found to be independent predictors of early neurological deterioration [6, 9]. For clinical characteristics, the NIHSS score on admission, anticoagulant medication, systolic blood pressure, plasma adrenomedullin, serum myeloperoxidase and other characteristics were found to be predictive of early neurological deterioration [10–13]. For neuroimaging parameters, hematoma volume, intraventricular hemorrhage, hematoma expansion, and intraventricular extension were reported to predict the occurrence of early neurological deterioration [4, 11]. However, most of those previous studies had small sample sizes and found contentious predictors of early neurological deterioration in patients with intracerebral hemorrhage.

A systematic review and meta-analysis can provide a comprehensive and up-to-date synthesis of the current evidence, assisting in the identification of predictors of early neurological deterioration in patients with intracerebral hemorrhage. Only one meta-analysis, which included 14 studies and 2,088 patients, has addressed the predictors of early neurological deterioration in patients with intracerebral hemorrhage [14]. This meta-analysis included studies with varying definitions of early neurological deterioration. For example, Delgado, Alvarez-Sabín [15] defined early neurological deterioration as an increase in the NIHSS score of ≥ 4 points within the first 48 h. Sykora, Diedler [16] used the definition of a 4-point increase in the NIHSSS score within the first 72 h. In addition, this meta-analysis performed a meta-analysis synthesis by merging the results from both multivariate and univariate logistic regression analyses, which may have overlooked significant confounders. The considerations stated above likely lead to partiality. Furthermore, numerous new studies providing additional predictors have emerged since the last meta-analysis. As a result, it is critical to undertake an updated systematic review that incorporates predictors derived only using multivariable logistic regression analysis with a similar definition of early neurological deterioration to reduce bias.

Therefore, this study aimed to conduct a systematic review and meta-analysis to identify the predictors of early neurological deterioration in patients with intracerebral hemorrhage. The findings of this study could provide an evidence-based foundation for healthcare providers to identify high-risk patients for early neurological deterioration and optimize management strategies.

Methods

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) declaration. This review's comprehensive protocol was registered with PROSPERO under the registration number CRD42023484527.

Search strategy

A comprehensive literature search was conducted in electronic databases, including PubMed, Embase, Web of Science, the Cochrane Library, and CINAHL, from inception to November 18, 2023. The search strategy was developed by combining the following free words and MeSH terms: "cerebral hemorrhage", "cerebrum hemorrhage*", "cerebral parenchymal hemorrhage*", "intracerebral hemorrhage*", "cerebral hemorrhage*", "cerebral brain hemorrhage*", "neurological worsening", "neurological deterioration", "neurologic worsening", and "neurologic deterioration". The exact search algorithms used in each electronic database are displayed in Supplementary Material 1. The literature search was restricted to human species and publications in English. Furthermore, reference lists were examined to identify additional references from the included articles as well as from previous reviews or meta-analyses.

Study selection

After removing duplicated articles with Endnote software, two reviewers independently reviewed the study titles and abstracts for eligibility using the inclusion and exclusion criteria. Once a study was deemed eligible by any reviewer, the full text was retrieved. The full texts of the retrieved publications were independently assessed by two reviewers for final inclusion. Any discrepancies were discussed to reach a consensus by two reviewers, with the participation of a third reviewer if necessary.

The inclusion criteria following PECOs principles (P: participants; E: exposures; C: comparisons; O: outcomes; s: study design) were as follows: (1) P: patients diagnosed with spontaneous intracerebral hemorrhage by CT/MRI; (2)

E (exposures): study identifying at least one risk factor for early neurological deterioration using multivariate logistic regression; (3) O (outcomes): early neurological deterioration defined as an increase in the NIHSS score, a decrease in the GCS scores, or death from baseline to 24 h; and (4) S (study design): prospective or retrospective cohort studies. If numerous studies addressed the same cohort, only the most recent study with the largest sample size was included. The exclusion criteria were as follows: (1) younger than 18 years; (2) not an original study (review, conference abstract, or case report); (3) no interested outcomes; (4) data cannot be extracted; and (5) low-quality studies.

Data extraction

The data of the included studies were extracted by two reviewers independently. To reach a consensus, the two reviewers discussed any disagreements, and if needed, consulted a third reviewer. The following information was extracted from the included studies and coded: first author, publication year, location, study design, sample size, age, sex, presence or absence of early neurological deterioration, and predictors identified with *p* values, 95% confidence intervals (CIs), odds ratios (ORs), risk ratios (RRs), or hazard ratios (HRs). The extracted data were stored in Microsoft Excel.

Quality appraisal

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of the included studies [17]. The NOS for cohort studies consists of three dimensions, selection, comparability, and outcome, with a total of eight items. The maximum NOS score for a cohort study is nine points, which can be divided into three categories: low quality (≤ four points), moderate quality (five or six points), and high quality (≥ seven points)[18]. The quality appraisal procedure was independently conducted by two reviewers. Any disagreements were resolved through consultation with a third reviewer.

Data analysis

The meta-analysis in this study was conducted using the STATA 17.0 software package (Stata Corp LP, College Station, TX). The pooled prevalence and 95% confidence intervals (CIs) for early neurological deterioration were estimated. To assess predictors of early neurological deterioration, odds ratios (ORs) and their 95% CIs were synthesized. Heterogeneity was evaluated by the I^2 value and Q statistics. If there was low statistical heterogeneity ($p > 0.10$ and $I^2 \leq 50\%$), the fixed effects model was employed for meta-analysis; otherwise, the random effects model was utilized. A sensitivity analysis was conducted to examine the robustness of the overall findings by omitting the included studies one by one. Funnel plots and Egger's test were used to assess publication bias [19, 20]. If there was any publication bias, a trim-and-fill analysis was carried out [21]. Subgroup analysis was employed to examine variations in the prevalence and predictors of early neurological deterioration in subgroups categorized by study location and the baseline used to define early neurological deterioration.

Results

Study process

Figure 1 illustrates the flow diagram of the study screening process. The initial search yielded 3,051 documents from databases, 918 of which were duplicates. After evaluating the studies using the inclusion and exclusion criteria, a total of 32 studies were ultimately included.

Study characteristics

Table 1 displays the characteristics of the included studies. Among the 32 studies, five (15.6%) were retrospective cohort studies and twenty-seven (84.4%) were prospective studies. Only three studies (9.4%) were performed in multicenter settings. The included studies involved 5,014 patients, with 1,097 in the early neurological deterioration group and 3,683 in the case–control group (one study did not provide detailed data). The prevalence of early neurological deterioration ranged from 7.47% to 40.99%.

Quality assessment of the included studies

Thirty studies were of high quality, while two studies were of moderate quality according to the NOS. Supplementary Material 2 displays the detailed quality assessment results.

Prevalence of early neurological deterioration

The pooled prevalence in our meta-analysis involving 31 studies was 23% (95% CI 21–26%, $p < 0.01$), with high heterogeneity ($I^2 = 77.34\%$, $p < 0.01$). In subgroup analysis, the pooled prevalence showed no significant difference in subgroups stratified either by study location or by baseline used to define early neurological deterioration (Supplementary Figs. 1, 2).

Predictors of early neurological deterioration

Age

Only two studies provided data regarding the relationship between age and early neurological deterioration in patients

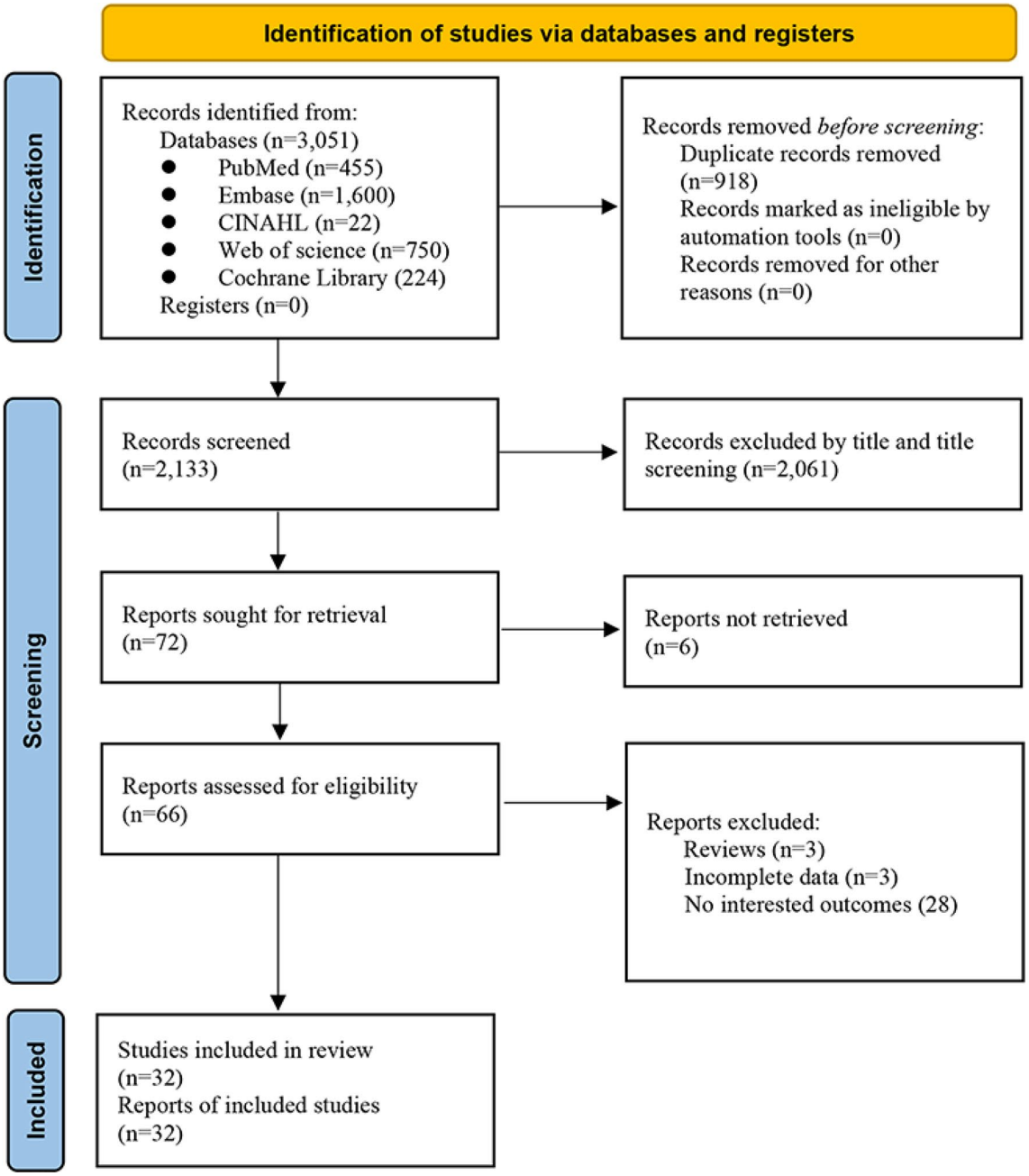

Fig. 1 Flow diagram of study selection

with intracerebral hemorrhage, yielding no statistically significant association (OR = 1.00, 95% CI 0.98, 1.03, $p = 0.88$), with no heterogeneity ($I^2 = 0.05\%$, $p = 0.72$) (Supplementary Fig. 3).

NIHSS score

Our meta-analysis included seventeen studies that examined the relationship between NIHSS score at admission and early neurological deterioration in patients with intracerebral hemorrhage. The meta-analysis revealed a 1.24-fold risk for early neurological deterioration when the NIHSS score increased by one point (OR = 1.24, 95% CI 1.17, 1.30, $p < 0.01$), with high heterogeneity ($I^2 = 67.65\%$, $p < 0.01$) (Fig. 2). Subgroup analysis revealed a significant difference in the pooled effect size of the NIHSS score among subgroups stratified by the baseline used to define early neurological deterioration. The sensitivity analysis revealed no statistically significant changes in the pooled effect size by eliminating studies by turns (Supplementary Figs. 4, 5).

Table 1 Characteristics of the included studies

Author, year	Location	Design/setting	Sample	Age	Male/female	END/non-END	Predictors identified
Ahn [36]	USA	P/S	161	59.7 ± 12.3	100/61	66/95	Spot sign under CTA, IVH
Behrouz [5]	Latin America, Europe, USA	R/M	375	67.1 ± 12.3	239/136	28/347	Hematoma expansion
Cai [37]	China	P/S	112	65.6 ± 10.5	67/45	23/89	NIHSS, plasma pNF-H
Chen [38]	China	P/S	110	61.7 ± 10.9	62/48	30/80	Serum sSRA, NIHSS, hematoma volume
Du [39]	China	P/S	102	66.2 ± 10.1	65/37	24/78	Hematoma volume, plasma leptin
Gu [40]	China	P/S	85	65.9 ± 9.5	47/38	20/65	Hematoma volume, plasma visfatin level
Gu [41]	China	P/S	104	59.9 ± 14.0	58/46	28/76	NIHSS, Hematoma volume, sTREM-1
Larsen [42]	Norway	R/S	295	–	–	107/188	Pulse pressure decrease
Li [43]	China	P/S	162	67.1 ± 14.2	94/68	35/127	Plasma osteopontin, NIHSS, hematoma volume
Li [44]	China	P/S	148	60.6 ± 13.0	94/54	44/104	NIHSS, hematoma volume, serum NLRC4
Li [45]	China	P/S	135	61.3 ± 12.6	83/52	40/95	NIHSS, serum RvD1
Lord [4]	USA	R/M	376	65.9 ± 13.1	230/146	81/295	Hematoma expansion, hematoma volume, GCS, IVH
Lv [46]	China	P/S	299	61.1 ± 13.3	205/94	38/261	uIVHG, hematoma volume, hematoma expansion
Ovesen [12]	Denmark	R/S	224	–	–	–	Anticoagulation treatment, IVH extension, hematoma volume, spot sign under CTA
Qiu [47]	China	P/S	128	66.3 ± 9.8	77/51	21/107	Serum signal peptide-Cub-Egf domain- containing protein-1
Qiu [48]	China	P/S	101	61.2 ± 13.6	58/43	29/72	NIHSS, hematoma volume, serum S100A12
Rodriguez-Luna, [30]	Canada, USA, Germany,	P/M	157	–	–	34/123	Ultra-early hematoma growth
Rodriguez-Luna [9]	Poland, India, Spain	P/S	117	71.2 ± 12.2	68/49	25/92	Hematoma volume, SBP variability, SBP 180-load
Rodriguez-Luna [49]	Spain	P/S	108	71.6 ± 11.5	62/46	22/86	LDL-C, hematoma volume, intraventricular extension
Rodriguez-Luna [50]	Spain	P/S	133	71.7 ± 11.8	77/56	30/103	Ultra-early hematoma growth, intraventricular extension
Shentu [51]	China	P/S	185	62.3 ± 10.4	108/77	49/136	NIHSS, hematoma volume, serum ITIH4
Tsou [11]	Taiwan	R/S	168	72.0 ± 9.2	96/72	36/132	Prehospital SBP increase, hematoma size, CT markers of hematoma expansion, intraventricular extension
Wang [13]	China	P/S	114	65.7 ± 10.5	69/45	23/91	NIHSS, plasma adrenomedullinp
Wang [52]	China	P/S	126	59.6 ± 10.9	70/56	36/90	Annexin A7

Table 1 (continued)

Author, year	Location	Design/setting	Sample	Age	Male/female	END/non-END	Predictors identified
Wang [53]	China	P/S	115	62.9 ± 12.0	65/50	30/85	NIHSS, hematoma volume, serum Nrf2
Wang [54]	China	P/S	162	64.7 ± 13.5	90/72	32/130	NIHSS, hematoma volume, serum TNC
Yan [55]	China	P/S	106	64.0 ± 11.0	60/46	24/82	Serum VILIP-1, NIHSS, hematoma volume
Zhang [56]	China	P/S	124	61.5 ± 12.2	69/55	33/91	NIHSS, hematoma volume, serum MANF
Zhang [57]	China	P/S	124	61.7 ± 13.2	70/54	34/90	NIHSS, hematoma volume, serum pannexin-1
Zhang [58]	China	P/S	89	64.5 ± 10.9	54/35	22/67	NIHSS, plasma copeptin
Zheng [10]	China	P/S	128	66.3 ± 9.8	77/51	21/107	Serum myeloperoxidase
Zhuge [59]	China	P/S	141	58.3 ± 13.9	73/58	32/99	NIHSS, hematoma volume, serum SUR1

P: prospective cohort study; R: retrospective cohort study; S: single center; M: multi-center; CTA: computed tomography angiography; IVH: intraventricular hemorrhage; NIHSS: National Institute of Health stroke scale; pNF-H: phosphorylated axonal neurofilament subunit H; sSRA: soluble scavenger receptor A; sTREM-1: soluble triggering receptor expressed on myeloid cells-1; NLRC4: caspase activation and recruitment domain-containing protein 4; RvD1: resolvin D1; GCS: Glasgow Coma Scale; uIVHG: ultraearly intraventricular hemorrhage growth; SBP: systolic blood pressure; LDL-C: Low-Density Lipoprotein Cholesterol; ITIH4: inter-alpha-trypsin inhibitor heavy chain 4; TNC: tenascin-C; VILIP-1: visinin-like protein-1; MANF: mesencephalic astrocyte-derived neurotrophic factor; SUR1: Sulfonylurea Receptor-1

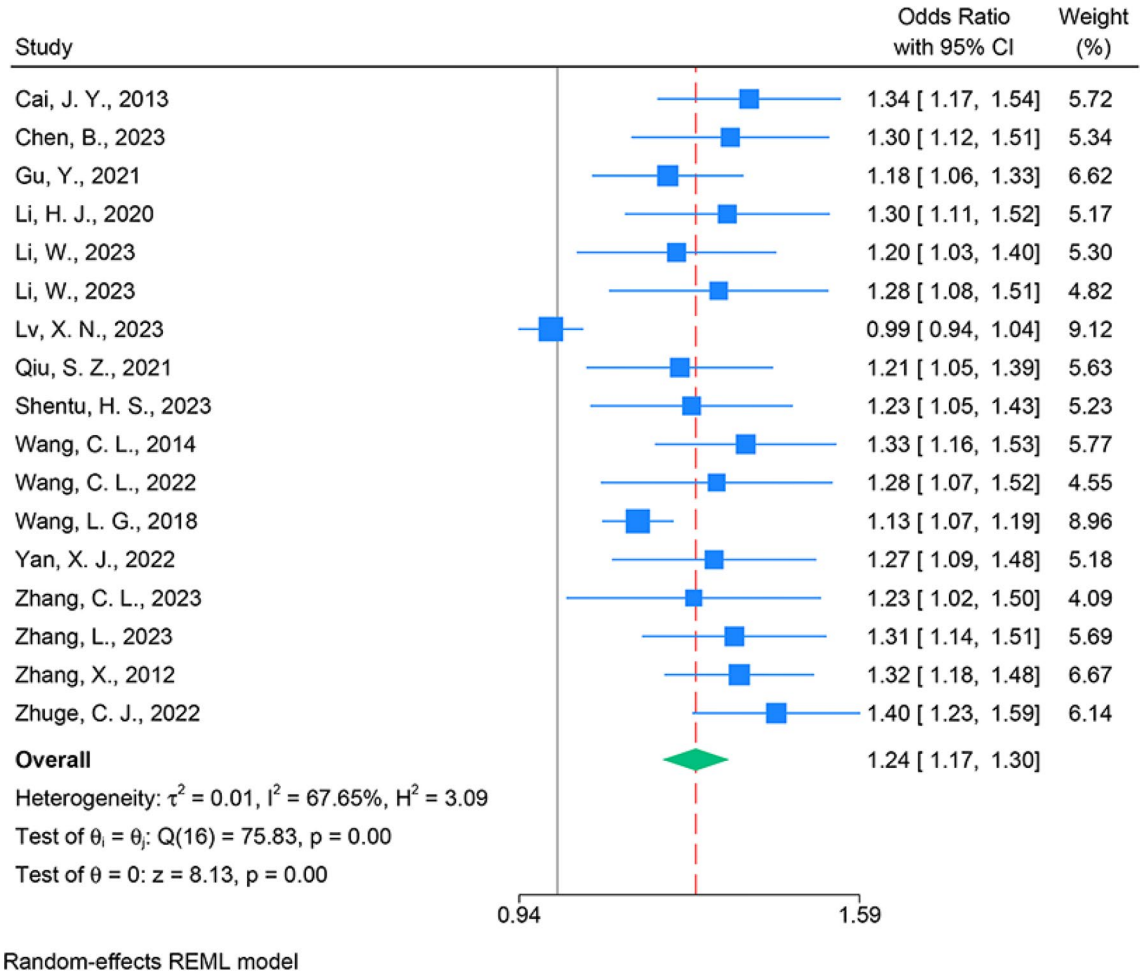

Fig. 2 Odds ratio of NIHSS for early neurological deterioration

Hematoma volume

Eighteen studies provided data examining the relationship between hematoma volume and early neurological deterioration, revealing a 7% increase in risk for early neurological deterioration with increasing hematoma volume (OR = 1.07, 95% CI 1.06, 1.09, $p < 0.01$), with high heterogeneity ($I^2 = 59.52\%$, $p < 0.01$) (Fig. 3). Subgroup analysis revealed that the pooled effect size significantly differed among in subgroups based on the baseline used in defining early neurological deterioration. No statistically significant differences were found among the subgroups based on study location. The sensitivity analysis revealed no statistically significant changes in the pooled effect size by eliminating studies by turns (Supplementary Figs. 6–8).

Intraventricular hemorrhage

Three studies provided data examining the relationship between intraventricular hemorrhage and early neurological deterioration. This meta-analysis found that the patients with intraventricular hemorrhage had a 3.5-fold greater risk of early neurological deterioration (OR = 3.50, 95% CI 1.64, 7.47, $p < 0.01$), with high heterogeneity ($I^2 = 54.87\%$, $p = 0.11$) (Fig. 4A). Subgroup analysis revealed no statistically significant differences in the pooled effect size. The sensitivity analysis indicated no statistically significant changes in the pooled effect size by eliminating studies by turns (Supplementary Figs. 9–11).

Intraventricular extension

Three studies provided data examining the relationship between intraventricular extension and early neurological deterioration. The meta-analysis found a 3.95-fold increase

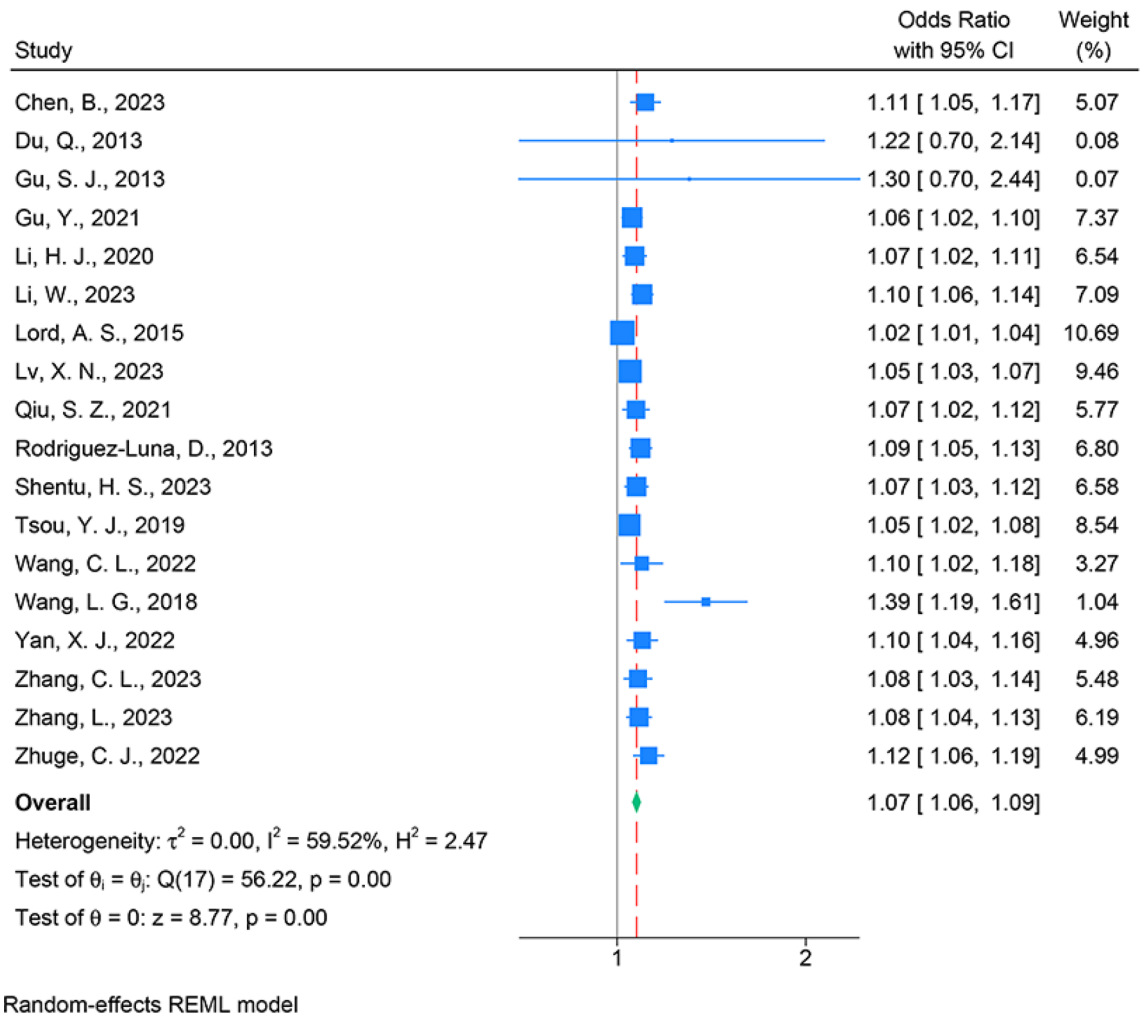

Fig. 3 Odds ratio of hematoma volume for early neurological deterioration

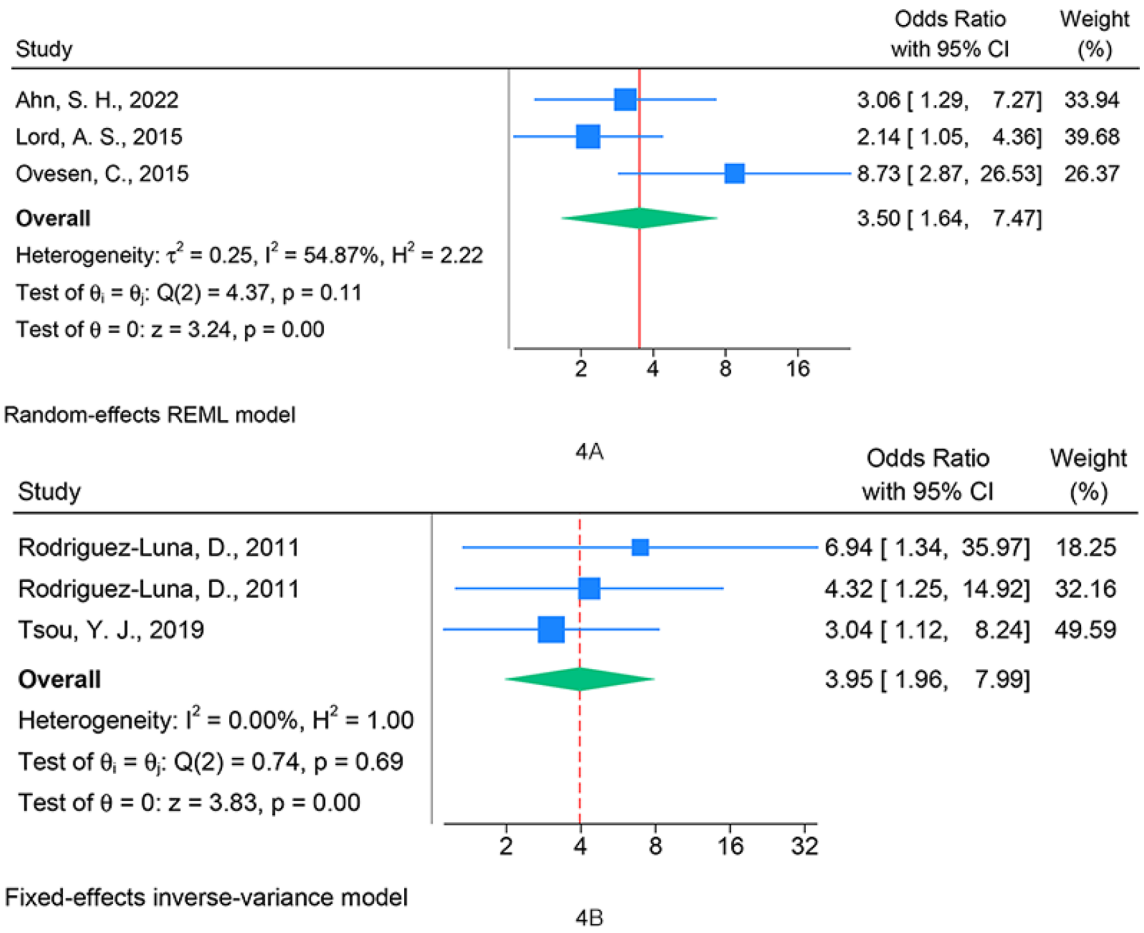

Fig. 4 A Odds ratio of intraventricular hemorrhage for early neurological deterioration; **B** Odds ratio of intraventricular extension for early neurological deterioration

in the risk of early neurological deterioration in patients with intraventricular extension (OR = 3.95, 95% CI 1.96, 7.99, $p < 0.01$), with no heterogeneity ($I^2 = 0$, $p = 0.69$) (Fig. 4B). Subgroup analysis revealed no statistically significant differences in the pooled effect size. The sensitivity analysis indicated no statistically significant changes in the pooled effect size by eliminating studies by turns (Supplementary Figs. 12–14).

Hematoma expansion

Four studies provided data examining the relationship between hematoma expansion and early neurological deterioration. The meta-analysis found an 8.77-fold increase in the risk of early neurological deterioration in patients with hematoma expansion (OR = 9.77, 95%CI 4.43, 17.40, $p < 0.01$), with high heterogeneity ($I^2 = 50.03\%$, $p = 0.11$) (Fig. 5A). Subgroup analysis found no statistically significant differences in the pooled effect size. The sensitivity analysis indicated no statistically significant changes in the pooled effect size by eliminating studies by turns (Supplementary Figs. 15–17).

Spot sign under computed tomographic angiography (CTA)

Only two studies provided data examining the relationship between spot sign and early neurological deterioration. The meta-analysis found that patients with spot sign under CTA had a 5.77-fold greater risk of early neurological deterioration (OR = 5.77, 95%CI 1.53, 20.23, $p = 0.01$), with high heterogeneity ($I^2 = 79.37\%$, $p = 0.03$) (Fig. 5B).

Publication bias

Supplementary Fig. 18 displays the funnel plot, which indicates significant publication bias. Additionally, Egger's test also revealed significant publication bias ($p < 0.001$). The trim-and-fill analysis revealed that there were no statistically significant changes in the pooled effect size after seven studies were imputed.

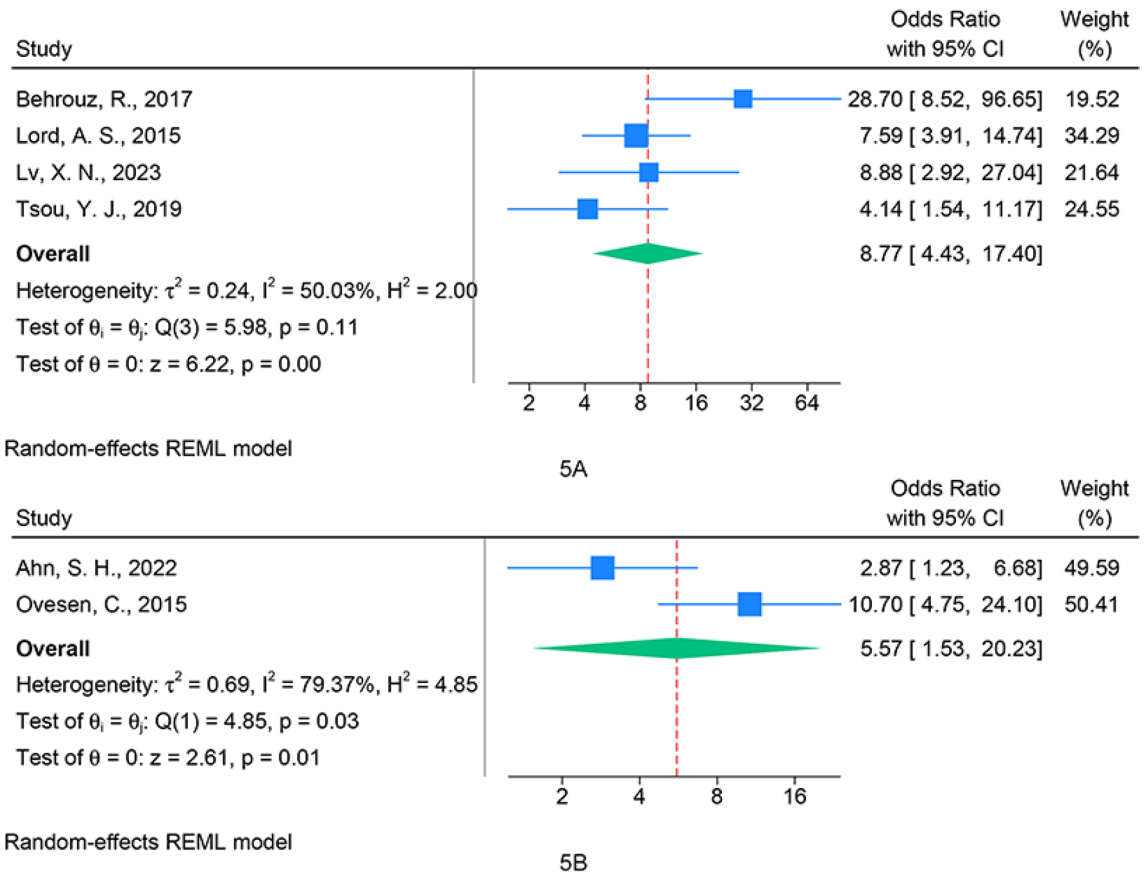

Fig. 5 **A** Odds ratio of hematoma expansion for early neurological deterioration; **B** Odds ratio computed tomographic angiography for early neurological deterioration

Discussion

This meta-analysis conducted a comprehensive search of multiple databases to identify relevant studies. Ultimately, data from a total of 32 studies and 5,014 patients were included. The pooled prevalence of early neurological deterioration was determined to be 23%. Six variables, including the NIHSS score at admission, hematoma volume, intraventricular hemorrhage, intraventricular extension, hematoma expansion, and spot sign under CTA, were found to be significantly associated with early neurological deterioration in patients with intracerebral hemorrhage.

This meta-analysis revealed that the initial NIHSS score and hematoma volume, which are usually thought to be strong predictive variables for mortality and functional outcomes [22], were also predictors of early neurological deterioration in patients with intracerebral hemorrhage. Specifically, patients with higher NIHSS scores and larger hematoma volumes were found to be at a higher risk of early neurological deterioration. These findings support previous models proposed by Law [7] and He [6], which included both the NIHSS score and hematoma volume as predictors of neurological deterioration in patients with intracerebral hemorrhage. However, given that most intracerebral hemorrhage patients have depressed consciousness, routine evaluation of the NIHSS score may be limited. To expedite assessment and anticipate early neurological deterioration in the future, it may be advantageous to employ alternate severity tools, such as the ICH score and GCS [23, 24], which are widely used and validated. Notably, subgroup analysis revealed differences in the pooled effect sizes of the NIHSS score and hematoma volume among subgroups stratified by the baseline used to define early neurological deterioration. As a result, future research must define early neurological deterioration in precise terms.

This meta-analysis revealed that the presence of intraventricular hemorrhage and intraventricular extension were also predictive factors for early neurological deterioration. Intraventricular hemorrhage and intraventricular extension following intracerebral hemorrhage are hypothesized to be related to inflammation, hydrocephalus, and the neurotoxic effects of blood products on the diencephalon, thus contributing to early neurological deterioration [7, 25, 26]. These findings emphasize the necessity of early

neuroimaging scans with CT/MRI in patients with intracerebral hemorrhage, as well as the need for a follow-up scan within 24 h for patients who have stable examination and consciousness [27].

Our meta-analysis also found that hematoma expansion is associated with an increased risk of early neurological deterioration. Hematoma expansion has been attributed to continued bleeding caused by original etiologies or subsequent vascular injury in 30–40% of intracerebral hemorrhage patients within 6 h of onset [28, 29]. Changes in hemodynamics may contribute to early neurological deterioration. Rodriguez-Luna, Coscojuela [30] also reported that the rate of hematoma expansion was a predictor of early neurological impairment. These findings highlight the clinical significance of predicting, monitoring, and stopping hematoma expansion in the early stage of intracerebral hemorrhage. The non-contrast computed tomography (NCCT) markers, such as heterogeneous densities within the hematoma or irregularities at its margins, have been reported as reliable predictors of hematoma expansion [27]. These markers help to improve the triage strategy and monitoring density in clinical practice.

In our meta-analysis, the spot sign observed by computed tomographic angiography was also revealed to be a predictor of early neurological deterioration. The computed tomographic angiography spot sign denotes contrast leakage into the hematoma. Previous research has revealed that the spot sign on computed tomographic angiography is related to persistent bleeding or rebleeding caused by coagulopathy within hematomas, systemic coagulopathy, or a reaction to rapid consumption of hemostatic substances [31, 32]. Continuous bleeding increases the risk of hematoma expansion and intraventricular hemorrhage [31, 33, 34], both of which can result in early neurological deterioration. This result, however, should be regarded with caution because this meta-analysis included data from only two studies with 385 individuals. More large-scale studies are needed in the future to investigate the predictive value of the spot sign for early neurological deterioration.

Our meta-analysis did not find a statistically significant association between age and early neurological deterioration in patients with intracerebral hemorrhage, in contrast to common perceptions [35]. More studies on the association between age and early neurological deterioration are needed. In fact, numerous variables, such as plasma leptin, visfatin, osteopontin, adrenomedullin, low-density lipoprotein cholesterol (LDL-C) levels, and anticoagulation treatment (Table 1), were identified as predictors of early neurological deterioration. These variables could not be synthesized in this meta-analysis because each variable was reported in only one study. However, these findings still offer new insights for healthcare providers to predict early neurological deterioration in patients with intracerebral hemorrhage and to guide further studies.

There are strengths and limitations in this study. This review was conducted using systematic and rigorous approaches. Only high-quality studies adjusted for relevant confounders and identified predictors using multivariate logistic regression analyses were included. Subgroup analysis and sensitivity analysis were used to address heterogeneity and increase the robustness of the pooled results. This meta-analysis has several limitations. First, several factors, such as plasma leptin, visfatin, and osteopontin levels were not further analyzed since they were reported in a small number of studies. Second, this study excluded unpublished articles and studies that did not employ multivariate logistic regression analyses, which may have introduced publication bias, especially influencing the pooled prevalence of early neurological deterioration. Third, the publication language was limited to English, which limited the comprehensiveness of the included studies. As a result, future research should overcome these limitations and examine predictors of early neurological deterioration in a more comprehensive manner.

Conclusion

This systematic review and meta-analysis found that the pooled prevalence of early neurological deterioration was 23%. Such a high prevalence emphasizes the importance of early neurological deterioration in patients with intracerebral hemorrhage. This meta-analysis also found that the initial NIHSS score, hematoma volume, hematoma expansion, intraventricular hemorrhage, intraventricular extension, and spot sign were all predictors of early neurological deterioration. By identifying these factors, healthcare providers may be better prepared to identify and manage high-risk patients, thereby improving outcomes. However, it is important to take publication bias into consideration when interpreting the findings. Further research and validation of these predictors in clinical practice are needed to fully integrate these findings into therapeutic practice.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-024-12230-6.

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Author contributions Wei Zhu: resources, methodology, formal analysis, writing—review and editing. Jiehong Zhou: investigation, formal analysis, writing—original draft. Buyun Ma: data curation, validation, supervision. Chaofen Fan: conceptualization, methodology, data curation, formal analysis.

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Data availability The data supporting the findings of this study are available on request from the corresponding author.

Declarations

Conflict of interests The authors have no competing interests to declare that are relevant to the content of this article.

Ethical pproval Not applicable.

Consent to participate Not applicable.

Consent to publish All authors have agreed to publish this article and this article in part and whole has not been considered for publication elsewhere.

References

1. Kim JY, Bae HJ (2017) Spontaneous intracerebral hemorrhage: management. J Stroke 19(1):28–39. https://doi.org/10.5853/jos.2016.01935
2. Feigin VL et al (2021) Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Neurol 20(10):795–820. https://doi.org/10.1016/S1474-4422(21)00252-0
3. Jolink WM et al (2015) Time trends in incidence, case fatality, and mortality of intracerebral hemorrhage. Neurology 85(15):1318–1324. https://doi.org/10.1212/wnl.0000000000002015
4. Lord AS et al (2015) Time course and predictors of neurological deterioration after intracerebral hemorrhage. Stroke 46(3):647–652. https://doi.org/10.1161/strokeaha.114.007704
5. Behrouz R et al (2017) Clinical course and outcomes of small supratentorial intracerebral hematomas. J Stroke Cerebrovasc Dis 26(6):1216–1221. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.01.010
6. He Q et al (2022) Prediction of neurological deterioration after intracerebral hemorrhage: the SIGNALS score. J Am Heart Assoc 11(15):e026379. https://doi.org/10.1161/jaha.122.026379
7. Law ZK et al (2021) Predictors and outcomes of neurological deterioration in intracerebral hemorrhage: results from the TICH-2 randomized controlled trial. Transl Stroke Res 12(2):275–283. https://doi.org/10.1007/s12975-020-00845-6
8. Li Q, Goldstein JN (2022) Neurological deterioration in intracerebral hemorrhage: can we predict it, and what would we do if we could? J Am Heart Assoc 11(15):e026760. https://doi.org/10.1161/jaha.122.026760
9. Rodriguez-Luna D et al (2013) Impact of blood pressure changes and course on hematoma growth in acute intracerebral hemorrhage. Eur J Neurol 20(9):1277–1283. https://doi.org/10.1111/ene.12180
10. Zheng GR et al (2018) Serum myeloperoxidase concentrations for outcome prediction in acute intracerebral hemorrhage. Clin Chim Acta 487:330–336. https://doi.org/10.1016/j.cca.2018.10.026
11. Tsou YJ, Lan KP, Fan JS (2019) Relationship between changes in prehospital blood pressure and early neurological deterioration in spontaneous intracerebral hemorrhage. Adv Emerg Nurs J 41(2):163–171. https://doi.org/10.1097/tme.0000000000000239
12. Ovesen C et al (2015) Prediction and prognostication of neurological deterioration in patients with acute ICH: a hospital-based cohort study. BMJ Open 5(7):e008563. https://doi.org/10.1136/bmjopen-2015-008563
13. Wang CL et al (2014) Blood levels of adrenomedullin on admission predict outcomes after acute intracerebral hemorrhage. Peptides 54:27–32. https://doi.org/10.1016/j.peptides.2014.01.005
14. Specogna AV et al (2014) Factors associated with early deterioration after spontaneous intracerebral hemorrhage: a systematic review and meta-analysis. PLoS ONE 9(5):e96743. https://doi.org/10.1371/journal.pone.0096743
15. Delgado P et al (2006) Plasma d-dimer predicts poor outcome after acute intracerebral hemorrhage. Neurology 67(1):94–98. https://doi.org/10.1212/01.wnl.0000223349.97278.e0
16. Sykora M et al (2009) Subacute perihematomal edema in intracerebral hemorrhage is associated with impaired blood pressure regulation. J Neurol Sci 284(1–2):108–112. https://doi.org/10.1016/j.jns.2009.04.028
17. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9):603–605. https://doi.org/10.1007/s10654-010-9491-z
18. Guo Y et al (2023) Risk factors for delirium among hospitalized adults with COVID-19: a systematic review and meta-analysis of cohort studies. Int J Nurs Stud 148:104602. https://doi.org/10.1016/j.ijnurstu.2023.104602
19. Irwig L et al (1998) Bias in meta-analysis detected by a simple, graphical test. Graphical test is itself biased. BMJ (Clin Res ed) 316(7129):470 (**authorreply 470-471**)
20. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50(4):1088–1101. https://doi.org/10.2307/2533446
21. Duval S, Tweedie R (2000) Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56(2):455–463. https://doi.org/10.1111/j.0006-341x.2000.00455.x
22. Hemphill JC et al (2015) Guidelines for the management of spontaneous intracerebral hemorrhage. Stroke 46(7):2032–2060. https://doi.org/10.1161/STR.0000000000000069
23. Hemphill JC, Farrant M, Neill TA Jr (2009) Prospective validation of the ICH Score for 12-month functional outcome. Neurology 73(14):1088–1094. https://doi.org/10.1212/WNL.0b013e3181b8b332
24. van Asch CJ et al (2013) External validation of the secondary intracerebral hemorrhage score in The Netherlands. Stroke 44(10):2904–2906. https://doi.org/10.1161/strokeaha.113.002386
25. Ziai WC et al (2019) Intracranial hypertension and cerebral perfusion pressure insults in adult hypertensive intraventricular hemorrhage: occurrence and associations with outcome. Crit Care Med 47(8):1125–1134. https://doi.org/10.1097/ccm.0000000000003848
26. Bhattathiri PS et al (2006) Intraventricular hemorrhage and hydrocephalus after spontaneous intracerebral hemorrhage: results from the STICH trial. Acta Neurochir Suppl 96:65–68. https://doi.org/10.1007/3-211-30714-1_16
27. Greenberg SM et al (2022) 2022 Guideline for the Management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. Stroke 53(7):e282–e361. https://doi.org/10.1161/str.0000000000000407
28. Kazui S et al (1996) Enlargement of spontaneous intracerebral hemorrhage incidence and time course. Stroke 27(10):1783–1787. https://doi.org/10.1161/01.str.27.10.1783
29. Sheth KN (2022) Spontaneous Intracerebral Hemorrhage. N Engl J Med 387(17):1589–1596. https://doi.org/10.1056/NEJMra2201449
30. Rodriguez-Luna D et al (2016) Ultraearly hematoma growth in active intracerebral hemorrhage. Neurology 87(4):357–364. https://doi.org/10.1212/wnl.0000000000002897

31. Delgado Almandoz JE et al (2009) Systematic characterization of the computed tomography angiography spot sign in primary intracerebral hemorrhage identifies patients at highest risk for hematoma expansion: the spot sign score. Stroke 40(9):2994–3000. https://doi.org/10.1161/strokeaha.109.554667
32. Wada R et al (2007) CT angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. Stroke 38(4):1257–1262. https://doi.org/10.1161/01.STR.0000259633.59404.f3
33. Tran TT, Veldman A, Malhotra A (2012) Does risk-based coagulation screening predict intraventricular haemorrhage in extreme premature infants? Blood Coagul Fibrinolysis 23(6):532–536. https://doi.org/10.1097/MBC.0b013e3283551145
34. Gladstone DJ et al (2019) Effect of recombinant activated coagulation factor vii on hemorrhage expansion among patients with spot sign-positive acute intracerebral hemorrhage: The SPOTLIGHT and STOP-IT randomized clinical trials. JAMA Neurol 76(12):1493–1501. https://doi.org/10.1001/jamaneurol.2019.2636
35. Amer HA et al (2023) Clinical and paraclinical predictors of early neurological deterioration and poor outcome in spontaneous intracerebral hemorrhage. Egypt J Neurol Psychiatr Neurosurg 59(1):74. https://doi.org/10.1186/s41983-023-00675-x
36. Ahn SH et al (2022) The spot sign and intraventricular hemorrhage are associated with baseline coagulopathy and outcome in intracerebral hemorrhage. Neurocrit Care 37(3):660–669. https://doi.org/10.1007/s12028-022-01537-9
37. Cai JY et al (2013) Predictive value of phosphorylated axonal neurofilament subunit H for clinical outcome in patients with acute intracerebral hemorrhage. Clin Chim Acta 424:182–186. https://doi.org/10.1016/j.cca.2013.06.019
38. Chen B et al (2023) Prognostic and predictive significance of serum soluble scavenger receptor A in acute primary basal ganglia hemorrhage: a prospective cohort study. Clin Chim Acta 539:7–17. https://doi.org/10.1016/j.cca.2022.11.023
39. Du Q et al (2013) Plasma leptin level predicts hematoma growth and early neurological deterioration after acute intracerebral hemorrhage. Peptides 45:35–39. https://doi.org/10.1016/j.peptides.2013.04.017
40. Gu SJ et al (2013) Admission plasma visfatin level strongly correlates with hematoma growth and early neurologic deterioration in patients with acute spontaneous basal ganglia hemorrhage. Clin Chim Acta 425:85–89. https://doi.org/10.1016/j.cca.2013.07.025
41. Gu Y et al (2021) Soluble triggering receptor expressed on myeloid cells-1 as a serum biomarker of early neurologic deterioration and prognosis in acute supratentorial intracerebral hemorrhage. Clin Chim Acta 523:290–296. https://doi.org/10.1016/j.cca.2021.10.010
42. Larsen KT et al (2022) Prehospital blood pressure and clinical and radiological outcomes in acute spontaneous intracerebral hemorrhage. Stroke 53(12):3633–3641. https://doi.org/10.1161/STROKEAHA.121.038524
43. Li HJ et al (2020) Plasma osteopontin acts as a prognostic marker in acute intracerebral hemorrhage patients. Clin Chim Acta 500:208–212. https://doi.org/10.1016/j.cca.2019.10.018
44. Li W et al (2023) Prognostic significance of serum NLRC4 in patients with acute supratentorial intracerebral hemorrhage: a prospective longitudinal cohort study. Front Neurol. https://doi.org/10.3389/fneur.2023.1125674
45. Li W et al (2023) Prognostic significance of serum resolvin D1 levels in patients with acute supratentorial intracerebral hemorrhage: a prospective longitudinal cohort study. Clin Chim Acta. https://doi.org/10.1016/j.cca.2023.117446
46. Lv XN et al (2023) Ultraearly intraventricular hemorrhage growth predicts early neurologic deterioration and poor functional outcome after acute intracerebral hemorrhage. J Am Heart Assoc. https://doi.org/10.1161/JAHA.123.031214
47. Qiu SZ et al (2016) The prognostic value of serum signal peptide-Cub-Egf domain-containing protein-1 concentrations in acute intracerebral hemorrhage. Clin Chim Acta 461:103–109. https://doi.org/10.1016/j.cca.2016.08.001
48. Qiu SZ et al (2021) High serum s100a12 levels predict poor outcome after acute primary intracerebral hemorrhage. Neuropsychiatr Dis Treat 17:3245–3253. https://doi.org/10.2147/NDT.S337041
49. Rodriguez-Luna D et al (2011) Serum low-density lipoprotein cholesterol level predicts hematoma growth and clinical outcome after acute intracerebral hemorrhage. Stroke 42(9):2447–2452. https://doi.org/10.1161/STROKEAHA.110.609461
50. Rodriguez-Luna D et al (2011) Ultraearly hematoma growth predicts poor outcome after acute intracerebral hemorrhage. Neurology 77(17):1599–1604. https://doi.org/10.1212/WNL.0b013e3182343387
51. Shentu HS et al (2023) A prospective cohort study of inter-alpha-trypsin inhibitor heavy chain 4 as a serologic marker in relation to severity and functional outcome of acute intracerebral hemorrhage. Neuropsychiatr Dis Treat 19:2363–2379. https://doi.org/10.2147/NDT.S433264
52. Wang CL et al (2022) Usability of serum annexin A7 as a biochemical marker of poor outcome and early neurological deterioration after acute primary intracerebral hemorrhage: a prospective cohort study. Front Neurol. https://doi.org/10.3389/fneur.2022.954631
53. Wang CL et al (2022) Elevated serum nuclear factor erythroid 2-related factor 2 levels contribute to a poor prognosis after acute supratentorial intracerebral hemorrhage: a prospective cohort study. Front Aging Neurosci. https://doi.org/10.3389/fnagi.2022.1014472
54. Wang LG et al (2018) Serum tenascin-C predicts severity and outcome of acute intracerebral hemorrhage. Clin Chim Acta 481:69–74. https://doi.org/10.1016/j.cca.2018.02.033
55. Yan XJ et al (2022) Predictive value of serum visinin-like protein-1 for early neurologic deterioration and three-month clinical outcome in acute primary basal ganglia hemorrhage: a prospective and observational study. Clin Chim Acta 531:62–67. https://doi.org/10.1016/j.cca.2022.03.008
56. Zhang CL et al (2023) Prognostic potential of serum mesencephalic astrocyte-derived neurotrophic factor in acute intracerebral hemorrhage: a prospective observational study. BMC Neurol. https://doi.org/10.1186/s12883-023-03254-y
57. Zhang L et al (2023) Increased serum pannexin-1 concentrations reflect illness severity and predict a poor prognosis after acute supratentorial intracerebral hemorrhage: a prospective longitudinal cohort study. Clin Chim Acta. https://doi.org/10.1016/j.cca.2023.117218
58. Zhang X et al (2012) Copeptin is associated with one-year mortality and functional outcome in patients with acute spontaneous basal ganglia hemorrhage. Peptides 33(2):336–341. https://doi.org/10.1016/j.peptides.2012.01.011
59. Zhuge CJ et al (2022) Serum sulfonylurea receptor-1 levels after acute supratentorial intracerebral hemorrhage: implication for prognosis. Neuropsychiatr Dis Treat 18:1117–1126. https://doi.org/10.2147/NDT.S368123