Thieme

# Glycemic Variability and Prognosis of Patients with Intracerebral Hemorrhage: A Meta-Analysis

Authors
Xu Jiao[1, 2 *], Huifang Wang[1, 2 *], Mingfei Li[1, 2], Yun Lu[1, 2]

Affiliations
1 Emergency Department, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China
2 Clinical Medical School, Chengdu University of Traditional Chinese Medicine, Chengdu, China

Key words
intracerebral hemorrhage, glycemic variability, mortality, functional outcome, meta-analysis

received 31.10.2022
accepted after revision 02.01.2023

Bibliography
Horm Metab Res 2023; 55: 176–183
DOI 10.1055/a-2010-2345
ISSN 0018-5043

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Dr. Yun Lu
Hospital of Chengdu University of Traditional Chinese Medicine, Emergency Department, No. 39 Shierqiao Road
610075 Chengdu
China
Tel.: 86-28-87783467
luyun120120@21cn.com

## ABSTRACT

Glycemic disorder may affect the outcomes of patients with intracerebral hemorrhage (ICH). However, the association between glycemic variability (GV) and prognosis in these patients remains to be determined. We performed a meta-analysis to compressive the influence of GV on functional outcome and mortality in patients with ICH. Observational studies comparing the risks of poor functional outcome (defined as modified Rankin Scale > 2) and all-cause mortality between ICH patients with higher versus lower acute GV were retrieved by systematic search of Medline, Web of Science, Embase, CNKI, and Wanfang databases. A random-effect model was used to pool the data after incorporating the between-study heterogeneity. Sensitivity analyses were performed to evaluate the stability of the findings. Eight cohort studies involving 3400 patients with ICH were included in the meta-analysis. The follow-up duration was within 3 months after admission. All of the included studies used standard deviation of blood glucose (SDBG) as the indicator of acute GV. Pooled results showed that ICH patients with higher SDBG were associated with a higher risk of poor functional outcome as compared to those with lower SDBG [risk ratio (RR): 1.84, 95 % confidence interval (CI): 1.41 to 2.42, $p < 0.001$, $I2 = 0$ %]. In addition, patients with higher category of SDBG were also associated with a higher mortality risk (RR: 2.39, 95 % CI: 1.79 to 3.19, $p < 0.001$, $I2 = 0$ %). In conclusion, high acute GV may be a predictor of poor functional outcome and mortality of patients with ICH.

## Introduction

Currently, intracerebral hemorrhage (ICH) remains the most severe cerebrovascular disease, which is associated with an overall mortality of approximately 40 % within the first month of disease onset [1, 2]. Besides, it has been reported that between 61 and 88 % of patients with ICH have poor functional outcomes during the follow-up durations of 12–50 months [3]. Accordingly, identification of novel risk factors, which are associated with the poor prognosis of patients with ICH is still of great clinical significance [4].

It has been recognized that age, severity of initial neurological impairment, hemorrhage volume, and location of the hematoma, etc. may be important predictors for the clinical outcome in patients with ICH [5]. Besides, glycemic disorders have also been suggested as an important risk factor of the poor prognosis of patients with ICH [6]. Indeed, an early meta-analysis confirmed that there is a significant association between early hyperglycemia and early-term death in patients with ICH, regardless of the cut-off point for hyperglycemia [7]. In addition, another meta-analysis also suggested that hyperglycemia may also be a predictor of poof functional outcome in patients with ICH [8]. Interestingly, growing evidence has also suggested an association between hypoglycemia and the early functional outcome and mortality risk in patients with ICH [9, 10], suggesting a more complicated influence of glycemic disorder on the prognosis of patients with ICH.

* These authors contributed equally to this work.

In recent decades, a concept of glucose variability (GV) has been introduced [11]. Unlike the indices for mean blood glucose level, GV focuses on the extent of glucose fluctuation within months to years (chronic GV) or within days (acute GV) [12]. Subsequent studies have linked acute GV to the severity and poor prognosis of various diseases, such as ischemic stroke [13, 14], acute coronary syndrome [15], and sepsis [16]. Although GV is important clinically, its optimum method of characterization remains unclear. Acute GV, also called short-term GV, is characterized by sudden and rapid changes in blood glucose levels within a day or between days. Clinically, acute GV could be calculated from self-monitoring of blood glucose (SMBG) or continuous glucose monitoring (CGM), and various indicators have been derived, such as standard deviation of blood glucose (SDBG), coefficient of variation of blood glucose (CVBG), and the mean amplitude of glycemic excursions (MAGE) etc. [11]. Although some pilot studies have observed the association between acute GV and clinical outcomes in patients with ICH [10, 17–23], the results were not consistent [24]. Therefore, in this study, we performed a meta-analysis to systematically evaluate the association between acute GV and prognosis in patients with ICH.

## Materials and Methods

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [25, 26] and Cochrane's Handbook [27] during the design, performing, and presenting of the meta-analysis.

### Search of electronic databases

We identified studies by a systematic search of Medline, Web of Science, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang databases using the following terms: (1) "glycemic" OR "glyceamic" OR "glucose"; (2) "variability" OR "variation" OR "fluctuation"; (3) "brain" OR "cerebral" OR "intracranial" OR "intracerebral" OR "aneurysmal" OR "aneurysm" OR "subarachnoid" OR "stroke"; and (4) "bleeding" OR "hemorrhage" OR "hemorrhagic". Only studies involving human patients and published in English or Chinese were selected. We did not restrict the outcomes of included studies in the literature search strategy, and we used this extensive literature search strategy to avoid missing the potentially relevant studies. An additional manual check-up for the reference lists of relevant original and review articles were performed as supplement. The last literature search was conducted on September 22, 2022.

### Selection of eligible studies

Inclusion criteria were (1) observational studies published as full-length articles, including cohort studies, case-control studies, and cross-sectional studies; (2) included adult patients (18 years or above) who were admitted for ICH as evidenced by cerebral computed tomography and/or magnetic resonance imaging; (3) acute GV was evaluated during hospitalization with one or more parameters; (4) incidence of poor functional outcome and/or early mortality were reported as outcomes of interest and compared between patients with higher versus lower acute GV; and (5) reported relative risk for the incidence of poor functional outcome and/or early mortality comparing between ICH patients with higher versus lower acute GV. The definitions of parameters for acute GV were consistent with the criteria applied of the included studies. Specifically, the SDBG calculated as the square-root of the average of the squared differences between individual blood glucose values and the mean [28]. A poor functional outcome was defined as ICH patients with functional dependency evaluated by modified Rankin Scale (mRS) > 2 during follow-up [29]. Reviews, preclinical studies, studies that did not include patients with ICH, studies without the evaluation of acute GV, or studies that did not report the outcomes of interest were excluded.

### Extraction of data and evaluation of study quality

Two of the authors independently conducted electronic database search, extraction of study data, and assessment of study quality according to the inclusion criteria described above. If there were discrepancies, they were resolved by consensus between the authors. The extracted data included the following: (1) name of the first author, year of the publication, study design, and country; (2) patient characteristics, including the diagnosis, total number, mean age, sex, and proportions of patients with diabetes; (3) parameters used for the evaluating of acute GV, cutoffs for defining of patients with higher versus lower acute GV, and the duration of blood glucose measuring for evaluating GV; (4) follow-up durations, outcomes reported, and numbers of ICH patients with the outcomes during follow-up; and (5) variables adjusted when the association between acute GV and outcome was evaluated. The Newcastle-Ottawa Scale [30] was used for study quality assessment, which included three domains such as defining of study groups, between-group comparability, and validation of the outcome. This scale totally scored from 1 to 9 stars, with 9 stars indicating the highest study quality level.

### Statistical analyses

Risk ratio (RR) and 95 % confidence intervals (CIs) were selected as the general variable for the relationships of acute GV with risks of poor functional outcome and all-cause mortality in patients with ICH during follow-up. In cases where the odds ratio (OR) was described, we converted data to a relative risk for meta-analysis (RR = OR/([1 − pRef] + [pRef × OR]), where pRef is the prevalence of the outcome in the reference group [31]. Data of RRs and standard errors (SEs) were calculated from 95 % CIs or p-values, and an additional logarithmical transformation was performed to stabilize variance and normalize to the distribution [27]. The Cochrane's Q-test was used to evaluate the heterogeneity, and the $I^2$ statistic was also estimated [27]. Heterogeneity was deemed to be significant if $I^2 > 50\,\%$ [32]. We used a random-effect model for data synthesis because this model has incorporated the potential between-study heterogeneity and could provide a more generalized result [27]. Sensitivity analyses were performed by omitting one individual study at a time to examine the robustness of the finding [27, 33]. The funnel plots were constructed and a visual inspection of the symmetry was conducted to reflect the publication bias [34]. The Egger's regression asymmetry test was further performed for the evaluation of potential publication bias [27]. We used the RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata (version 12.0; Stata Corporation) software for the statistical analyses.

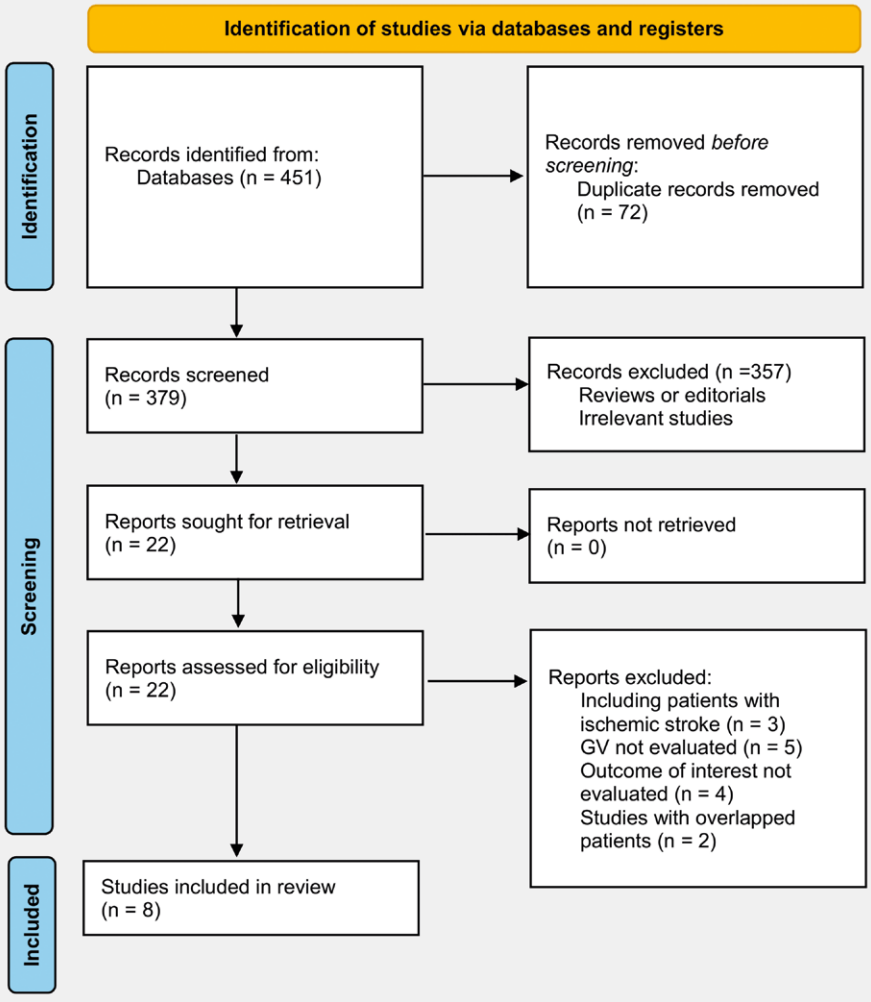
## Results

### Results of database search

The database search process is summarized in ▶ **Fig. 1**. Briefly, 451 articles were found in the initial literature search of the databases; after excluding the duplications, 379 studies remained. An additional 357 studies were excluded through screening of the titles and abstracts mainly because of the irrelevance to the meta-analysis. The remaining 22 studies underwent a full-text review, of which, 14 were further excluded for the reasons listed in ▶ **Fig. 1**. Finally, ten observational studies [10, 17–23] were included.

### Characteristics of the included studies

Overall, eight cohort studies involving 3400 patients with ICH were included in the meta-analysis. The characteristics of the studies are summarized in ▶ **Table 1**. Briefly, these studies were published between 2014 and 2020, and performed in China [18, 21–23], Japan [19, 20], and the United States [10, 17]. All of the included studies were retrospective cohort studies, expect one study, which was a prospective cohort study [20]. As for the diagnosis, five studies included patients with overall or severe ICH, while the other three studies included patients with subararachnoid hemorrhage (SAH). The mean ages of the patients varied between 53 and 67 years, and the proportions of men ranged from 29 to 66 %. All of the included used SDBG as the indicator of acute GV, and the cutoffs for the determination of patients with higher versus lower acute GV were medians [10, 17–21, 23] or tertiles (third versus first tertile) [22] of SDBG. Duration of blood glucose measuring for the calculation of SDBG varied from 72 hours of CGM to 14 days after admission, and the follow-up durations were during hospitalization for two studies [17, 19], 1 month for four studies [18, 21–23], and 3 months for the other two studies [10, 20]. The incidence of poor functional outcome in ICH patients was reported in five studies [19–23], and the incidence of all-cause mortality was reported in four studies [10, 17, 18, 22]. Multivariate analyses were performed in all of the included studies when the association between acute GV and the outcome of patients with ICH was estimated, and variables such as age, sex, Glasgow Coma Scale, Acute Physiology and Chronic Health Evaluation II Score, the National Institutes of Health Stroke Scale, comorbidities, and the location and volume of the hematoma.




▶ **Fig. 1** Flowchart of the database search.

▶ **Table 1** Characteristics of the included observational studies.

| Study [Ref] | Design | Location | Diagnosis | No. of patients | Mean age (years) | Men (%) | DM (%) | GV measurements and cutoff | Duration of BG measuring for evaluating GV | Follow-up duration | Outcomes reported and number of patients with outcomes | Variables adjusted |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kurtz 2014 [17] | RC | USA | SAH | 28 | 54 | 32 | 11 | SDBG (median) | During ICU stay | During hospitalization | All-cause mortality (7) | Age, GCS, Hunt and Hess grade, and DCI |
| Guo 2015 [18] | RC | China | Severe ICH | 90 | 63 | 56 | 0 | SDBG (median) | 72 h CGM | 28 days | All-cause mortality (38) | Age, APACHE II Score, and hypoglycemic events |
| Wada 2018 [20] | PC | Japan | ICH | 42 | 67 | 59 | 21 | SDBG (median) | 72 h CGM | 3 months | Poor functional outcome (23) | Age, sex, history of CAD, history of CHF, and NIHSS score on admission |
| Okazaki 2018 [19] | RC | Japan | SAH | 122 | 62 | 29 | NR | SDBG (median) | During ICU stay | During hospitalization | Poor functional outcome (54) | Age, Hunt and Kosnik grade, and minimal BG during ICU |
| Wu 2018 [21] | RC | China | ICH | 366 | 64 | 59 | 30 | SDBG (median) | 7 days | 30 days | Poor functional outcome (171) | Age, GCS, hematoma location and volume, IVH, and diabetic status |
| Chen 2020 [22] | RC | China | Severe ICH | 137 | 61 | 66 | NR | SDBG (T1: T3) | 14 days | 28 days | Poor functional outcome (66) and all-cause mortality (42) | Age, GCS, hematoma location and volume |
| Gao 2020 [23] | RC | China | Severe ICH | 164 | 57 | 54 | 33 | SDBG (median) | 7 days | 30 days | Poor functional outcome (126) | Age, GCS, minimal BG during hospitalization |
| Sadan 2020 [10] | RC | USA | SAH | 2451 | 53 | 30 | 9 | SDBG (median) | 5 days | 3 months | All-cause mortality (693) | Age, gender, Hunt and Hess grade, smoking, history of CAD, HTN, DM, and surgical treatment |

DM: Diabetes mellitus; GV: Glucose variability; BG: Blood glucose; RC: Retrospective cohort; PC: Prospective cohort; SAH: Subararachnoid hemorrhage; ICH: Intracerebral hemorrhage; NR: Not reported; SDBG: Standard deviation of blood glucose; ICU: Intensive care unit; CGM: Continuous glucose monitoring; GCS: Glasgow Coma Scale; DCI: Delayed cerebral ischemia; APACHE II: Acute Physiology and Chronic Health Evaluation II; CAD: Coronary artery disease; CHF: Congestive heart failure; NIHSS: The National Institutes of Health Stroke Scale; IVH: Intraventricular hemorrhage; HTN: Hypertension; T3:T1: Tertile 3 vs. tertile 1.

The quality of the included studies was generally good, with NOS varying from seven to nine stars (▶ **Table 2**).

### Results of the pooled analyses

The association between acute GV and the incidence of poor functional outcome in patients with ICH were reported in five studies [19–23]. Because one study [21] reported the association according the diabetic status of the patients (diabetic or non-diabetic), these two datasets were included into the meta-analysis separately. Overall, five studies with a total of 831 patients reported the incidence of poor functional outcome, and 440 (52.9 %) of them developed poor functional outcome. Pooled results showed that ICH patients with higher SDBG were associated with a higher risk of poor functional outcome as compared to those with lower SDBG (RR: 1.84, 95 % CI: 1.41 to 2.42, $p < 0.001$; ▶ **Fig. 2a**) with no significant heterogeneity ($I^2 = 0$ %, p for Cochrane's Q-test = 0.94). Sensitivity analyses by excluding one dataset at a time showed consistent results (RR: 1.77 to 2.00, p all < 0.05). In addition, four studies [10, 17, 18, 22] with 2706 ICH patients reported the association between acute GV and risk of all-cause mortality. Of them, 780 (28.8 %) died during a follow-up duration with 3 months. Pooled results of these four studies showed that ICH patients with higher category of SDBG were also associated with a higher mortality risk (RR: 2.39, 95 % CI: 1.79 to 3.19, $p < 0.001$; ▶ **Fig. 2b**) with no significant heterogeneity ($I^2 = 0$ %, p for Cochrane's Q-test = 0.70). Sensitivity analyses by omitting one study at a time showed consistent results (RR: 2.21 to 2.71, p all < 0.05).

### Publication bias

▶ **Fig. 3a,b** display the funnel plots regarding the relationship between SDBG with the risks of poor functional outcome and all-cause mortality in patients with ICH visual inspection found symmetry of the plots, which suggested low risks of publication biases. The Egger's regression tests were unable to perform since the limited datasets available for each outcome.

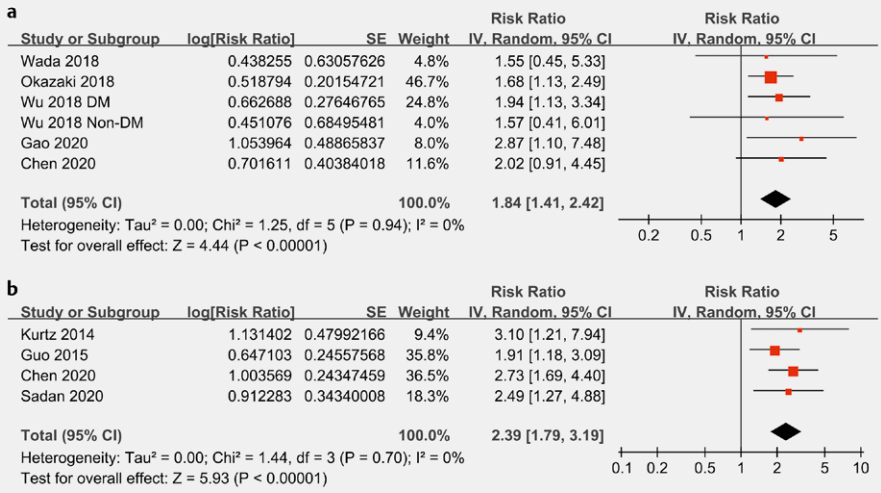
## Discussion

In this meta-analysis, we combined the results of eight available cohort studies, and the results showed that compared to ICH patients with a lower SDBG at admission, those with a higher SDBG were associated with higher risks for the development of poor functional outcome and all-cause mortality during the follow-up duration within 3 months. Additionally, sensitivity analyses by excluding one dataset at a time showed consistent results. Taken together, these results suggested that a higher acute GV evidenced by increased SDBG at admission may be a predictor of poor functional outcome and early mortality in patients with ICH.

To the best of our knowledge, this study may be the first meta-analysis, which summarized the relationship between acute GV and prognosis of patients with ICH. Although two recent meta-analyses have showed that increased acute GV in patients with acute stroke is associated with poor functional outcome [13] and increased mortality risk [14], patients included in these studies were predominantly with acute ischemic stroke (AIS), and it remains unknown whether the association remains in patients with ICH. Understanding the role of acute GV in patients with ICH is essential because the pathogenesis and clinical course are different between ICH and AIS. Methodologically speaking, this study also has several strengths. First, an extensive literature search was performed in five electronic databases, aiming to retrieve all available studies for a comprehensive meta-analysis on this topic. Second, all of the included studies were cohort studies, which could provide a longitudinal association between acute GV and poor prognosis of patients with ICH. Besides, multivariate analyses were applied in all of the included studies when the association between acute GV and poor prognosis was estimated, which suggested that the association was less likely to be affected by potential confounding factors, such as age, comorbidities, and severity of ICH. Finally, sensitivity analyses were performed to evaluate the influence of individual study on the pooled results, and the consistent results further confirmed the stability of the meta-analysis result, which was not predominantly driven by either of the included dataset. Taken together, results of the meta-analysis showed that increased acute

▶ **Table 2** Details for the assessment of the study quality via the Newcastle-Ottawa Scale.

| Study [Ref] | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Outcome not present at baseline | Control for age | Control for other confounding factors | Assessment of outcome | Enough long follow-up duration | Adequacy of follow-up of cohort | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| Kurtz 2014 [17] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 8 |
| Guo 2015 [18] | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 7 |
| Wada 2018 [20] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 |
| Okazaki 2018 [19] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 8 |
| Wu 2018 [21] | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 7 |
| Chen 2020 [22] | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 7 |
| Gao 2020 [23] | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 8 |
| Sadan 2020 [10] | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |




▶ **Fig. 2** Forest plots for the meta-analyses of the association between acute GV and clinical outcomes in patients with ICH. **A**: The association between SDBG and poor functional outcome of patients with ICH and **B**: The association between SDBG and all-cause mortality of patients with ICH.

GV as indicated by SDBG may be a predictor of poor functional outcome and early mortality in ICH patients. These results highlight the importance of blood glucose monitoring in the acute phase of ICH and evaluating acute GV may provide additional prognostic information for these patients. In addition, studies may be considered to determine possible clinical benefits of lowering acute GV for patients with ICH.

The potential mechanisms underlying the association between a higher acute GV and poor prognosis in patients with ICH are still need to be determined. Pathophysiologically, a higher level of glucose fluctuation has been associated with the severity of systemic oxidative stress [35, 36], which is considered as the key mechanism underlying the association between acute GV and cardiovascular complications in patients with diabetes. Interestingly, oxidative stress has been increasingly recognized as a key mechanism, which is responsible for the secondary brain injury in patients with ICH [37], probably via the induction the subsequent mechanisms involving inflammatory response, apoptosis, autophagy, and blood-brain barrier disruption [38, 39]. Therefore, it could be hypothesized that increased glucose fluctuation in patients with ICH may deteriorate the cerebral dysfunction by enhancing systemic oxidative stress inducing subsequent adverse molecular pathways, which may cause neural injury. Experimental studies are warranted in the future for validating these hypotheses.

This meta-analysis also has limitations. First, all of the included studies used SDBG as the indicator of acute GV. The association between other parameters for acute GV and the prognosis of patients ICH should be further investigated, such as the coefficient of variation of blood glucose and the mean amplitude of glycemic excursion etc. [28]. More importantly, it is necessary to determine the optimal parameter and cutoff of GV, which are also with the poor prognosis in patients with ICH. Besides, the optimal cutoff of SDBG for predicting the poor functional outcome and early mortality in ICH patients remains to be determined in the future. In addition, the number of the included studies and sample size of the studies are small, and the results of the meta-analysis should be validated in large-prospective cohort studies. Moreover, although no significant statistical heterogeneity was observed for the meta-analyses, clinical heterogeneity may be significant among the included studies, which is probably caused by different diagnosis of the patients, measuring methods (frequency and times of BG measuring) for SDBG, cutoffs of SDBG for defining patients with high GV, and follow-up durations, etc. Besides, we could not determine if differences in study characteristics may affect the association between acute GV and prognosis of ICH patients, such as the diabetic status of the patients. Finally, as a meta-analysis of observational study, we could not determine if the association between acute GV and poor prognosis of ICH is causative. As mentioned before, clinical studies may be considered to evaluate the potential clinical benefit of reducing acute GV in patients with ICH.

In conclusion, results of the meta-analysis suggest that a high acute GV as evidenced by increased SDBG may be a predictor of poor functional outcome and early mortality of patients with ICH. Although the results should be validated in large-scale prospective cohort studies, these findings suggest that evaluating acute GV may improve the prognostic stratification of patients with ICH.

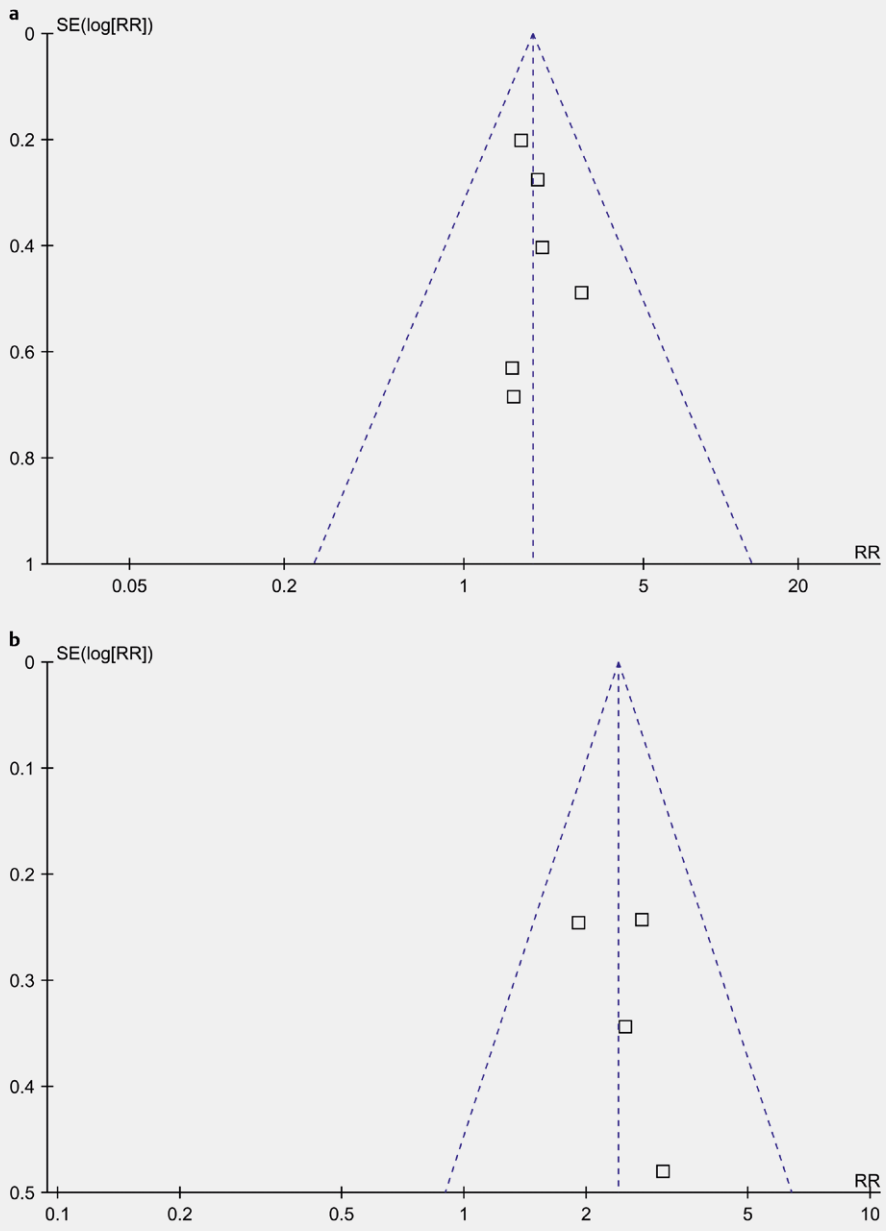
## Funding Information

Science & Technology Department of Guangdong Province — 2020B1111100009

Science & Technology Department of Sichuan Province — 2019YFS0040

## Conflict of Interest

The authors declare that they have no conflict of interest.




▶ **Fig. 3** Funnel plots for the publication biases underlying the meta-analyses of the association between acute GV and clinical outcomes in patients with ICH. **a**: Funnel plots for the meta-analysis of the association between SDBG and poor functional outcome and **b**: Funnel plots for the meta-analysis of the association between SDBG and all-cause mortality.

## References


[1] Cordonnier C, Demchuk A, Ziai W et al. Intracerebral haemorrhage: current approaches to acute management. Lancet 2018; 392: 1257–1268

[2] Greenberg SM, Ziai WC, Cordonnier C et al. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American heart association/American stroke association. Stroke 2022; 53: e282–e361

[3] van Asch CJ, Luitse MJ, Rinkel GJ et al. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol 2010; 9: 167–176

[4] Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2014; 85: 660–667

[5] Pinho J, Costa AS, Araujo JM et al. Intracerebral hemorrhage outcome: A comprehensive update. J Neurol Sci 2019; 398: 54–66

[6] Dorn AY, Sun PY, Sanossian N et al. Admission glycemic gap in the assessment of patients with intracerebral hemorrhage. Clin Neurol Neurosurg 2021; 208: 106871

[7] Tan X, He J, Li L et al. Early hyperglycaemia and the early-term death in patients with spontaneous intracerebral haemorrhage: a meta-analysis. Intern Med J 2014; 44: 254–260

[8] Zheng J, Yu Z, Ma L et al. Association between blood glucose and functional outcome in intracerebral hemorrhage: a systematic review and meta-analysis. World Neurosurg 2018; 114: e756–e765

[9] Naidech AM, Levasseur K, Liebling S et al. Moderate hypoglycemia is associated with vasospasm, cerebral infarction, and 3-month disability after subarachnoid hemorrhage. Neurocrit Care 2010; 12: 181–187

[10] Sadan O, Feng C, Vidakovic B et al. Glucose variability as measured by inter-measurement percentage change is predictive of in-patient mortality in aneurysmal subarachnoid hemorrhage. Neurocrit Care 2020; 33: 458–467

[11] Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol 2019; 7: 221–230

[12] Rodbard D. Glucose variability: a review of clinical applications and research developments. Diabetes Technol Ther 2018; 20: S25–S215

[13] Lin J, Cai C, Xie Y. Acute glycemic variability and functional outcome in patients with acute ischemic stroke: a meta-analysis. Horm Metab Res 2022; 54: 371–379

[14] Lin J, Cai C, Xie Y et al. Acute glycemic variability and mortality of patients with acute stroke: a meta-analysis. Diabetol Metab Syndr 2022; 14: 69

[15] Pu Z, Lai L, Yang X et al. Acute glycemic variability on admission predicts the prognosis in hospitalized patients with coronary artery disease: a meta-analysis. Endocrine 2020; 67: 526–534

[16] Li X, Zhang D, Chen Y et al. Acute glycemic variability and risk of mortality in patients with sepsis: a meta-analysis. Diabetol Metab Syndr 2022; 14: 59

[17] Kurtz P, Claassen J, Helbok R et al. Systemic glucose variability predicts cerebral metabolic distress and mortality after subarachnoid hemorrhage: a retrospective observational study. Crit Care 2014; 18: R89

[18] Guo MF, Sun BL. Relationship between blood glucose and its variability with prognosis in patients with severe intracerebral hemorrhage. Zhejiang Clin Med 2015; 17: 1953–1954

[19] Okazaki T, Hifumi T, Kawakita K et al. Blood glucose variability: a strong independent predictor of neurological outcomes in aneurysmal subarachnoid hemorrhage. J Intensive Care Med 2018; 33: 189–195

[20] Wada S, Yoshimura S, Inoue M et al. Outcome prediction in acute stroke patients by continuous glucose monitoring. J Am Heart Assoc 2018; 7:

[21] Wu YC, Ding Z, Wu J et al. Increased glycemic variability associated with a poor 30-day functional outcome in acute intracerebral hemorrhage. J Neurosurg 2018; 129: 861–869

[22] Chen SP, Lei KL, Sun HL. The correlation analysis between blood glucose variability and prognosis in patients withs evere acute cerebral hemorrhage. Chin J Pract Nerv Dis 2020; 23: 1973–1978

[23] Gao PT, Fu ZQ. The correlation between blood glucose variability and neurological function recovery in patients with severe cerebral hemorrhage. Stroke Nerv Dis 2020; 27: 604–613

[24] Santana D, Mosteiro A, Pedrosa L et al. Clinical relevance of glucose metrics during the early brain injury period after aneurysmal subarachnoid hemorrhage: an opportunity for continuous glucose monitoring. Front Neurol 2022; 13: 977307

[25] Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71

[26] Page MJ, Moher D, Bossuyt PM et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021; 372: n160

[27] Higgins J, Thomas J, Chandler J et al. Cochrane handbook for systematic reviews of interventions version 6.2. The Cochrane Collaboration 2021 www.training.cochrane.org/handbook

[28] Breyton AE, Lambert-Porcheron S, Laville M et al. CGMS and glycemic variability, relevance in clinical research to evaluate interventions in T2D, a literature review. Front Endocrinol (Lausanne) 2021; 12: 666008

[29] Acosta JN, Leasure AC, Kuohn LR et al. Admission hemoglobin levels are associated with functional outcome in spontaneous intracerebral hemorrhage. Crit Care Med 2021; 49: 828–837

[30] Wells GA, Shea B, O'Connell D et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2010 http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

[31] Ziff OJ, Lane DA, Samra M et al. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. BMJ 2015; 351: h4451

[32] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539–1558

[33] Patsopoulos NA, Evangelou E, Ioannidis JP. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. Int J Epidemiol 2008; 37: 1148–1157

[34] Egger M, Davey Smith G, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629–634

[35] Valente T, Arbex AK. Glycemic variability, oxidative stress, and impact on complications related to type 2 diabetes mellitus. Curr Diabetes Rev 2021; 17: e071620183816

[36] Papachristoforou E, Lambadiari V, Maratou E et al. Association of glycemic indices (hyperglycemia, glucose variability, and hypoglycemia) with oxidative stress and diabetic complications. J Diabetes Res 2020; 7489795

[37] Zheng Y, Li R, Fan X. Targeting oxidative stress in intracerebral hemorrhage: prospects of the natural products approach. Antioxidants (Basel) 2022; 11

[38] Zhang Y, Khan S, Liu Y et al. Oxidative stress following intracerebral hemorrhage: from molecular mechanisms to therapeutic targets. Front Immunol 2022; 13: 847246

[39] Yao Z, Bai Q, Wang G. Mechanisms of oxidative stress and therapeutic targets following intracerebral hemorrhage. Oxid Med Cell Longev 2021; 8815441: