

Effect of hyperglycemia on all-cause mortality from pediatric brain injury

A systematic review and meta-analysis

Shuyun Chen, MS^{a,b,*}, Zhaohu Liu, MS^{a,b}

Abstract

Background: This study aimed to assess the effect of hyperglycemia on all-cause mortality in pediatric patients with brain injury, based on currently available evidence.

Methods: We systematically searched the PubMed, Embase, and Cochrane Library databases with the keywords “hyperglycemia”, “brain injury”, and “pediatrics”. The retrieved records were screened by title, abstract, and full-text to include original articles assessing the effects of hyperglycemia on pediatric brain injury. The extracted data were assessed by a fixed-effects model. The risk of bias in the eligible studies was evaluated with the Newcastle-Ottawa Scale. Publication bias was visually examined with a funnel plot. Begg and Egger tests, respectively, were used to identify small-study effects. Sensitivity analysis was performed to evaluate the robustness of the original effect size.

Results: Nine observational studies were identified from 1439 primary hits. A total of 970 pediatric patients, including 304 with hyperglycemia and brain injury, were included for meta-analysis. Hyperglycemia was strongly associated with a higher risk of all-cause mortality in pediatric patients (odds ratio = 11.60, 95% confidence interval [CI] 7.88–17.08; $I^2=0\%$). The overall quality of eligible studies was low, but the funnel plot indicated no publication bias.

Conclusions: Hyperglycemia is significantly associated with high all-cause mortality in pediatric patients with brain injury. However, the relationship should be confirmed by larger-scale observational studies and randomized controlled trials.

Abbreviations: CI = confidence interval, GCS = Glasgow Coma Scale, NOS = Newcastle-Ottawa Quality Assessment Scale, OR = odds ratio.

Keywords: brain injury, hyperglycemia, meta-analysis, pediatrics, systematic review

1. Introduction

Brain injury is a critical cause of mortality in both adults and children, especially following traffic accidents. [1] It imposes considerable economic burdens on the patients, for whom aggressive treatments are often required. [2] Over the past 2 decades, multiple efforts have been devoted to the prevention and

management of brain injury; however, there are still almost 2 million victims of traumatic brain injury yearly, accounting for nearly one-third of all injury-related deaths. [3] In children, the management of brain and non-cranial injuries is equally important in reducing mortality and improving patient prognosis. [4,5] Non-cranial injuries, such as hypercarbia, anemia, and hyperglycemia, lead to systemic inflammation, homeostatic disturbance, and cell apoptosis, subsequently causing a series of secondary adverse events to the human body. [4]

Hyperglycemia is an independent risk factor for all-cause mortality in critically ill patients, especially those admitted to the intensive care unit. [6] Indeed, the association of hyperglycemia with mortality has been confirmed in adult patients with severe brain injury. [7–10] However, there are comparatively fewer reports evaluating such association in pediatric patients. Therefore, a systematic review and quantitative analysis of currently available evidence may provide useful information to guide clinical practice and the design of future clinical trials. [11]

In this study, we aimed to systematically review eligible studies assessing the effects of hyperglycemia on clinical outcomes of pediatric patients with traumatic brain injury.

2. Materials and methods

This systematic review and meta-analysis complied with the widely recognized Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. [12] This is a meta-analysis. The data in the article are from published articles, so no ethical approval was required.

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The authors declare that they have no conflict of interest.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2.1. Search strategy

On June 12, 2017, the PubMed (since 1946), Embase (since 1947), and Cochrane Library (since inception) databases were searched with various combinations of the keywords “hyperglycemia”, “brain injury”, and “pediatrics” (Supplementary Tables 1, <http://links.lww.com/MD/F237>, 2, <http://links.lww.com/MD/F238> and 3, <http://links.lww.com/MD/F239>. Search strategy). We combined MeSH terms and free words in the search strategy in order to cover as many records as possible. There was no restriction on publication date, but publication language was restricted to English. Furthermore, the reference lists of eligible studies were manually searched to identify any potentially relevant studies.

2.2. Selection criteria

The records retrieved from the above databases were combined to remove duplicate publications. The remaining records were then screened by title, abstract, and full-text, based on the following inclusion criteria:

1. article type as original research;
2. study population as pediatric patients;
3. hyperglycemic patients as a subgroup;
4. normoglycemic patients as a subgroup; and
5. outcome data reported.

In this study, the primary outcome was all-cause mortality because it is clinically important and was identified as the most frequently reported outcome in the eligible studies. Other outcomes, such as changes of the Glasgow Coma Scale (GCS) score after hospital admission, which are also important in clinical practice, were not reported in enough eligible subgroups to warrant a quantitative synthesis in meta-analysis. The retrieved records were independently screened by 2 investigators, and disagreements were resolved by consensus.

2.3. Data extraction

Data were extracted using a uniform data extraction form. The following items were extracted: first author, publication year, study design, sample size, number of hyperglycemic patients, age, sex, GCS score, Injury Severity Score, glucose cut-off value, length of hospital stay, follow-up period, and percentages of patients with polytrauma, insulin therapy, traffic accident, and neurosurgery. All data were independently extracted by 2 investigators; disagreements were resolved by discussion involving a third investigator.

2.4. Quality and risk of bias assessments

The quality of eligible studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS),^[13] the most widely used tool for the semi-quantitative assessment of non-randomized studies in meta-analysis. This scale attributes 9 points to each individual study: 4 for participant selection, 2 for group comparability, and 3 for outcome assessment.

2.5. Statistical analysis

Odds ratio (OR) and confidence interval (CI) were determined for each individual study. A fixed-effects model was used to pool study results since we assume that the different effect estimates

are attributed to random sampling errors.^[14–16] In addition, the random-effect model was used for the sensitivity analysis. Q statistic and the I^2 were used to quantitatively assess between-group heterogeneity.^[17] The I^2 reflects the percentage of overall variability caused by between-group heterogeneity, and an arbitrary I^2 threshold of 25% represents heterogeneity.^[18] Meta-regression analysis was performed to identify factors contributing to inter-study inconsistencies. The Thompson and Sharp publication bias test was used to evaluate the effects of small studies.^[19,20] Publication bias was visually examined using a funnel plot.^[21] Sensitivity analysis was performed to assess whether the effect size was likely to change with the removal of any single study or when using the random-effect model. All statistical analyses were performed with the Stata 14.0 software (Stata, College Station, Texas, USA) and R project (<https://cran.r-project.org/index.html>).

3. Results

As shown in Fig. 1, the search yielded 1206 records in Embase, 356 in PubMed, and 20 in the Cochrane Library. After duplicate removal, a total of 1439 records were primarily screened based on article type. Thus 34 non-English articles, 226 reviews, and 374 letters by the same authors were excluded, leaving 805 records for the second round of literature screening. Based on the PICO (Patient, Intervention, Comparison, and Outcome) principle, 427 records not enrolling pediatric patients, 216 not assessing brain injury, 122 not studying hyperglycemia, and 31 having no control patients were further excluded. Therefore, a total of 9 studies were finally included in the current systematic review and meta-analysis.^[22–30]

3.1. Baseline characteristics

All 9 eligible studies had an observational retrospective design. Overall, these studies included 970 pediatric patients with brain injury, of whom 304 had hyperglycemia. Median or mean patient ages in the eligible studies ranged from 7 months to 13 years. The study population had a male predominance, with a GCS score ranging between 6 and 9. Most studies adopted 200 mg/dl as the cut-off value for hyperglycemia. Percentages of polytrauma (10%–79%), insulin therapy (6%–42%), and neurosurgery (13%–100%) varied in different studies. However, a relatively higher percentage of patients were traffic accident victims (31%–81%), with 4 out of 5 studies reporting a rate above 50%. The length of hospital stay ranged from 1 to 23 days. The median follow-up period was 1 month. More details are provided in Table 1.

3.2. All-cause mortality

Table 2 summarizes the numbers of death and survival patients in the hyperglycemia and control groups, respectively. Most studies reported higher absolute death rates in the hyperglycemia group than in patients with normoglycemia. Mortality rates ranged from 16.1% to 73.7% in the hyperglycemia group, and from 0 to 21.8% in normoglycemic patients. As shown in Figure 2, the effect size for all-cause mortality in the hyperglycemia group vs normoglycemia group was 11.60 (95% CI 7.88–17.08; $I^2=0\%$, $P_{\text{heterogeneity}}$ (Q-statistic)=.629). This odds ratio indicated that hyperglycemia was associated with a higher risk of all-cause mortality in pediatric patients with brain injury.

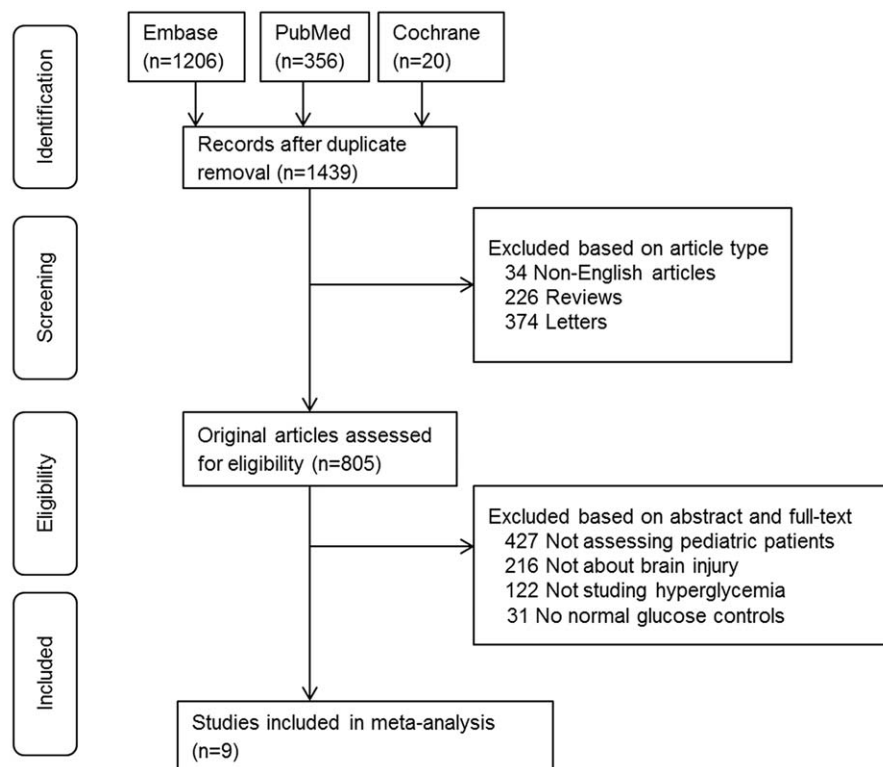


Figure 1. PRISMA flowchart of study selection.

A sensitivity analysis was performed. Excluding each study sequentially from the pooled analysis or using random-effect models did not change the overall conclusion (Supplementary Fig. 1, <http://links.lww.com/MD/F232>, sensitivity analysis of removal of any single study and Supplementary Fig. 2, <http://links.lww.com/MD/F233>, sensitivity analysis of the random-effect model).

Meta-regression analysis was performed to identify potential factors affecting the effect size. Since age, sex, and follow-up duration were reported in all eligible studies; they were used as variables in meta-regression analysis. The results showed that none of them was likely to significantly change the effects of hyperglycemia on all-cause mortality (age, $P = .93$; sex, $P = .99$; follow-up duration, $P = .78$) (Supplementary Fig. 3, <http://links.lww.com/MD/F234>,

meta-regression between age and the effect size for all-cause mortality, Supplementary Fig. 4, <http://links.lww.com/MD/F235>, meta-regression between follow-up duration and the effect size for all-cause mortality and Supplementary Fig. 5, <http://links.lww.com/MD/F236>, meta-regression between age and the effect size for all-cause mortality).

3.3. Publication bias and risk of bias

Publication bias was visually assessed using a funnel plot. As shown in Figure 3, there were several studies on the left, indicating a low risk of publication bias. The Thompson and Sharp publication bias test showed that there was a potential small-study effect ($P = .104$).

Table 1
Basic Characteristics of eligible studies.

First author, year	Design	Population (n)	Hyperglycemia (n)	Age (yrs)	Male (%)	GCS	ISS	Glucose cut-off (mg/dl)	Polytrauma (%)	Insulin (%)	Traffic accident (%)	LOS (d)	Neurosurgery (%)	Follow-up (d)
Sharma D, 2009 ^[22]	Obs.	105	47	5	62	9	NA	200	10	6	NA	NA	100	0
Parish R, 1988 ^[19]	Obs.	36	15	7	77	6	18	270	NA	9	NA	8	NA	7
Melo J, 2010 ^[23]	Obs.	286	98	7	68	7	NA	200	79	NA	58	NA	13	180
Marton E, 2007 ^[21]	Obs.	16	5	0.6		7	NA	200	13	NA	31	6	88	360
Chiaretti A, 1998 ^[20]	Obs.	50	31	6	68	9	NA	150	42	NA	NA	NA	NA	30
Seyed S, 2012 ^[24]	Obs.	106	19	13	75	6	NA	150	78	NA	82	16	25	16
Elkon B, 2014 ^[26]	Obs.	270	53	6	66		29	200	40	31	55	1	21	1
Smith R, 2012 ^[25]	Obs.	57	17	7	62	6	26	200	NA	42	NA	23	NA	180
Chong S, 2015 ^[27]	Obs.	44	19	9	64	7	NA	200	48	11	50	NA	71	30

GCS = Glasgow Outcome Score, ISS = Injury Severity Score, LOS = length of stay, NA = not available, Obs = observational.

Table 2
Summary of all-cause mortality.

First author, year	Hyperglycemia		Control	
	Death	Survival	Death	Survival
Sharma D, 2009 ^[22]	12	35	3	55
Parish R, 1988 ^[19]	5	10	2	19
Melo J, 2010 ^[23]	69	29	26	162
Marton E, 2007 ^[21]	1	4	0	11
Chiaretti A, 1998 ^[20]	5	26	0	19
Seyed S, 2012 ^[24]	14	5	19	68
Elkon B, 2014 ^[26]	30	23	13	204
Smith R, 2012 ^[25]	3	14	2	38
Chong S, 2015 ^[27]	7	12	2	23

The NOS system showed that the median quality score of the eligible studies was 5 (Table 3). Patient selection and outcome exposure acquired a fair score; however, the comparability of intervention and control groups was poor or unclear in most studies.

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis assessing the relationship between hyperglycemia and all-cause mortality in pediatric patients with brain injury. Our results showed that hyperglycemia was strongly associated with poor prognosis in pediatric patients, an observation quite consistent across various studies. Hyperglycemic pediatric patients also have lower GCS scores and longer hospital stay.^[26,30] Managing critically ill children with a brain injury requires not only a precise assessment of brain lesions using transcranial Doppler ultrasonography and body CT scan, but also a careful evaluation of extra-cranial factors such as systemic hypotension, hypoxia, and hyperglycemia.^[31] A

combination of treatments such as nutritional support, glucose control, and moderate hypothermia may help greatly reduce the mortality of pediatric patients with brain injury. Nevertheless, no consensus has been reached regarding the optimal blood glucose levels of these patients.

The etiology of hyperglycemia following brain injury is complex and related to the activation and dysfunction of multiple organs.^[22] Stresses imposed by brain injury stimulate liver gluconeogenesis, increase adrenal corticoid secretion, elevate serum growth hormone levels, and suppress insulin release, resulting in hyperglycemia. In the eligible studies, hyperglycemia prevalence rates were high (17.9% to 62.0%) among pediatric patients with brain injury, depending on population features.^[23,27] Although this meta-analysis showed that all-cause mortality was significantly and consistently higher in hyperglycemic than normoglycemic children, it is noteworthy that mortality is likely to vary among hyperglycemic patients of different characteristics. Elkon B et al showed that head-injured children with severe hyperglycemia (>200mg/dl) have much poorer outcomes than those with mild and moderate hyperglycemia.^[29] Smith R et al showed that

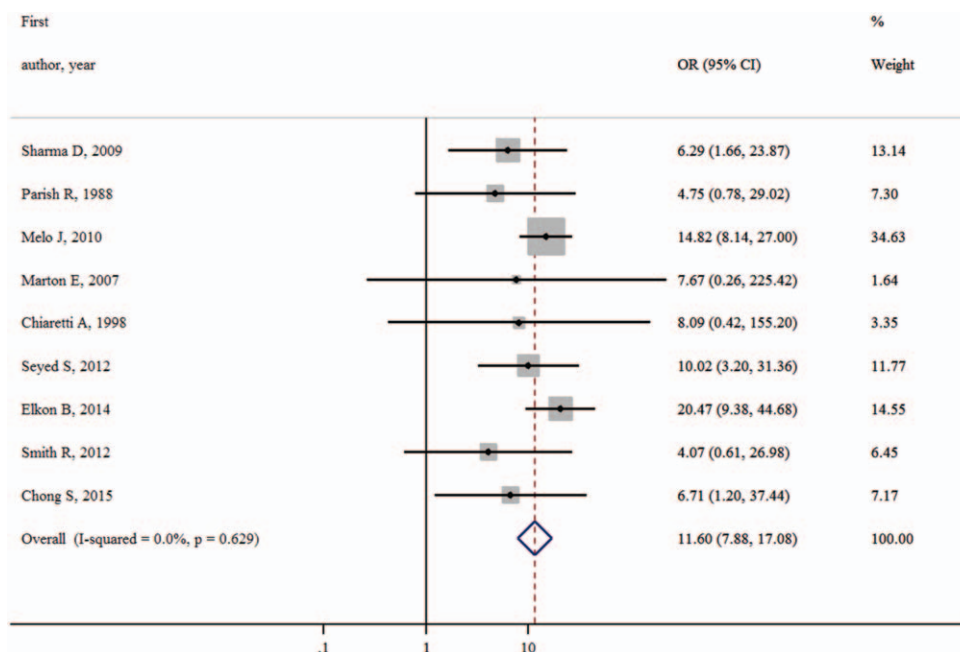


Figure 2. Effect size of all-cause mortality from hyperglycemia in pediatric patients.

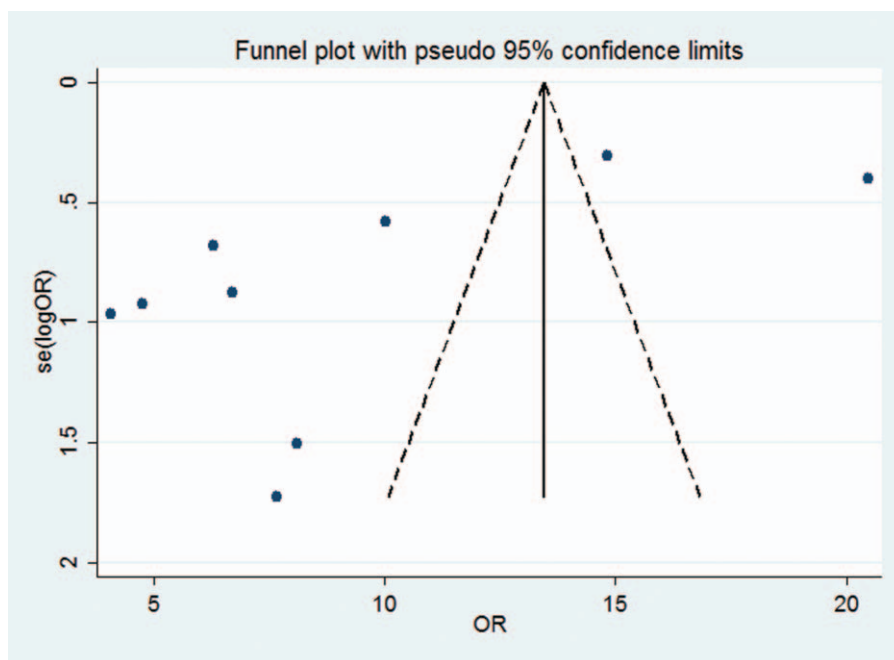


Figure 3. Funnel plot of all-cause mortality in eligible studies, using the odds ratio as the horizontal axis.

children with severe traumatic brain injury and persistent hyperglycemia have significantly poorer outcomes than those with only early hyperglycemia (<48 hours) following brain injury.^[28] Since heterogeneity was low in the eligible studies, it appears that age, sex, and follow-up duration in eligible studies are unlikely to make a difference in all-cause mortality of pediatric patients with brain injury. This possibility was supported by our meta-regression analysis, which showed that none of the above factors significantly contributed to inter-group heterogeneity.

Following primary brain injury, hyperglycemia induces secondary attacks in a variety of ways. First, hyperglycemia contributes to lactic acid accumulation by inhibiting the tricarboxylic acid cycle and promoting anaerobic glycolysis.^[32,33] Meanwhile, hyperglycemia is associated with low pH and blood-brain barrier alterations in patients with severe brain injury.^[33] Moreover, increased lactic acid also reduces adenosine triphosphate production, impairs the normal function of the

potassium-sodium-adenosine triphosphate pump, and increases the extracellular levels of sodium. In the brain, such pathophysiological changes result in brain cell edema and potentially cerebral hernia.^[34] Secondly, hyperglycemia causes electrolyte disturbances. It increases intracellular calcium influx and promotes excessive accumulation of glutamate. Elevated glutamate promotes calcium ion influx into the cytoplasm, leading to intracellular calcium overload and subsequent cell apoptosis through the caspase signaling pathway.^[35] Thirdly, hyperglycemia induces the release of pro-inflammatory cytokines such as interleukin 1 and tumor necrosis factor-alpha, both of which are detrimental to the normal body functions.^[36] Increased levels of pro-inflammatory cytokines are associated with poor prognosis in patients with a traumatic injury.^[37]

In the future, effective measures may be utilized to lower blood glucose levels in such pediatric patients in order to reduce mortality. Although the current results have emphasized the

Table 3
Methodological quality of cohort studies included in the meta-analysis¹.

First author	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important or additional factors	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality scores
Sharma D, 2009 ^[22]	☆	☆	☆	—	—	☆	—	☆	5
Parish R, 1988 ^[19]	☆	—	☆	—	☆	☆	—	☆	5
Melo J, 2010 ^[23]	☆	☆	☆	—	—	☆	☆	☆	6
Marton E, 2007 ^[21]	—	☆	☆	—	—	☆	☆	☆	5
Chiaretti A, 1998 ^[20]	☆	☆	☆	—	—	☆	—	☆	5
Seyed S, 2012 ^[24]	☆	☆	☆	—	—	☆	—	☆	5
Elkon B, 2014 ^[26]	☆	☆	☆	—	—	☆	—	☆	5
Smith R, 2012 ^[25]	—	—	☆	—	☆	☆	☆	☆	5
Chong S, 2015 ^[27]	☆	☆	☆	—	—	☆	—	☆	5

¹ A study could be awarded a maximum of one star for each item except for "Control for important or additional factor".

deleterious effects of hyperglycemia on pediatric outcomes, normal glucose levels are equally important for normal brain activity. Indeed, hypoglycemia does not confer a better prognosis compared with hyperglycemia in children.^[38] Therefore, the cut-off value for glucose control should be further assessed to achieve the optimal glucose level, considering the relatively immature glucose regulation system of children.^[39]

Some limitations should be noted for this study. First, all the nine reports included were observational studies and published in English; as a systematic review and meta-analysis, our study results were inevitably affected by the study design of the original studies. Secondly, the overall population assessed was small, with only 970 individuals included. Although all eligible studies consistently showed that hyperglycemia is associated with a higher risk of death. Thirdly, the overall risk of bias was relatively high in the eligible studies. Many confounding factors, e.g., human factors, might have affected the reliability of the eligible studies, and therefore that of the present systematic review and meta-analysis. Such a risk of bias should not be neglected while interpreting these results. Although all studies were in the same direction, some of them report no statistically significant differences, such as Marton et al.^[24] and Smith et al.^[28] In addition, the number of patients, their age, and their glucose cut-offs are different in these studies. Therefore, a combined analysis is clinically needed and relevant to enlarge the sample size and obtain a clear conclusion.

5. Conclusions

In conclusion, this study showed that hyperglycemia is associated with a high risk of all-cause mortality in pediatric patients with brain injury. There is still a need for less biased studies and research in related topics, and hyperglycemia in such patients require more attention.

Author contributions

Conceptualization: Shuyun Chen.

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Investigation: Shuyun Chen, Zhaohu Liu.

Methodology: Shuyun Chen, Zhaohu Liu.

Project administration: Shuyun Chen.

Resources: Zhaohu Liu.

Software: Zhaohu Liu.

Supervision: Zhaohu Liu.

Writing – original draft: Shuyun Chen.

Writing – review & editing: Shuyun Chen, Zhaohu Liu.

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