Paroxysmal Sympathetic Hyperactivity in Adult Patients with Brain Injury: A Systematic Review and Meta-Analysis

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Key words
- Brain injury
- Meta-analysis
- Paroxysmal sympathetic hyperactivity
- Risk factors

Abbreviations and Acronyms
AHRQ: Agency for Healthcare Research and Quality
BI: Brain injury
CI: Confidence interval
DAI: Diffuse axonal injury
GCS: Glasgow Coma Scale
OR: Odds ratio
PSH: Paroxysmal sympathetic hyperactivity
PSH-AM: PSH Assessment Measure
TBI: Traumatic brain injury

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BACKGROUND: **Paroxysmal sympathetic hyperactivity (PSH) is a syndrome of excessive sympathetic activity, mainly occurring in severe traumatic brain injury. However, few studies have reported the frequency of PSH and its related risk factors in adult patients with brain injury.**

METHODS: **We performed this systematic review and meta-analysis to estimate the combined incidence of PSH and the associated risk factors in adult patients with brain injury. This study was registered with the PROSPERO international prospective register of systematic reviews (https://www.crd.york. ac.uk/PROSPERO/Identifier: CRD 42021260493), and a systematic search was conducted of the scientific databases Embase, PubMed, Web of Science, Cochrane Library, and Google Scholar. All identified observational studies regarding the incidence and risk factors of PSH in adult patients with brain injury were included. Two authors extracted data independently; data were analyzed by STATA version 16.**

RESULTS: **The search yielded 9 studies involving 1643 adult patients. PSH was detected in 438 patients. The combined incidence of PSH in adult patients with brain injury was 27.4% (95% confidence interval [CI], 0.190–0.358). The risk factors include patients' age (SMD = −0.592; I^2 = 77.5%; 95% CI, −1.027 to −0.156; P = 0.008), traffic accident (odds ratio [OR], 1.783; I^2 =18.0%; 95% CI, 1.128–2.820; P = 0.013), admission Glasgow Coma Scale score (SMD = −1.097; I^2 =28.3%; 95% CI, -−1.500 to −0.693; P = 0.000), hydrocephalus (OR, 3.936; I^2 =67.9%; 95% CI, 1.144–13.540; P = 0.030), and diffuse axonal injury (OR, 4.747; I^2 =71.1%; 95% CI, 1.221–18.463; P = 0.025) and were significantly associated with the presence of PSH after brain injury.**

CONCLUSIONS: **PSH occurs in nearly a quarter of adult patients with brain injury. Patient's age, traffic accident, admission Glasgow Coma Scale score, hydrocephalus, and diffuse axonal injury were risk factors for PSH in adult patients with brain injury. These findings may contribute to novel strategies for early diagnosis and interventions that aid in the rehabilitation of patients with brain injury.**

INTRODUCTION

Paroxysmal sympathetic hyperactivity (PSH) is a hyperadrenergic clinical syndrome characterized by episodic tachycardia, hypertension, tachypnea, hyperpyrexia, diaphoresis, and abnormal motor posturing after traumatic brain injury (TBI), according to the recent expert consensus proposed in 2014.[1] The prevalence of PSH is up to 33% after moderate and severe TBI.[2] In addition, the prevalence and incidence of PSH could change over time. Because PSH is often misinterpreted in clinical practice,[3] the appropriate incidence of PSH is probably higher. The coexistence of PSH in patients with severe brain injuries (BI) dramatically enhances the likelihood of worse outcomes: prolonged hospitalization, increased health care costs, and mortality.[4-6] Whereas there have been no unified therapeutic strategies that effectively target PSH, its pathogenesis remains unknown.[7] Therefore, factors associated with PSH could provide early screening tools for prevention or treatments of PSH in patients with BI and are also important for reducing PSH-related adverse events. Previous studies have mentioned that patients with diffuse axonal injury (DAI), younger age, and midbrain and pontine lesions have more significant opportunities to develop PSH.[8,9] However, there are rare reports of meta-analysis of the incidence and risk factors related to the occurrence of PSH in an adult patient with BI. This meta-analysis focused on assessing the occurrence of PSH and investigating the risk factors for the development of PSH in adult patients after BI.

METHODS

Study Design

A systematic review and meta-analysis of observational studies were conducted

following the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) 2015 guidelines[10] to estimate the incidence and risk factors of PSH in adult patients with BI. The review protocol was registered in the PROSPERO international prospective register of systematic reviews (https://www.crd.york. ac.uk/PROSPERO/ Identifier: CRD 420212604 93).

Search Strategies

All relevant articles in the following electronic databases were searched without limits of date: Embase, PubMed, Web of Science, Cochrane Library, and Google Scholar. Only articles reported in English were included. The following keywords were used for the search: "brain injury," "risk factors," "predictors," "associated factors," "Paroxysmal Sympathetic Hyperactivity," "paroxysmal autonomic instability with dystonia," "diencephalic epilepsy," "diencephalic seizure," "dysautonomia," "autonomic dysregulation," "autonomic dysfunction," "autonomic instability," "sympathetic storming," and "autonomic storming." We combined these terms with the Boolean logical operators "AND" and "OR." The retrieval time span was limited from the date that the database was established to January 2022.

Inclusion and Exclusion Criteria

The inclusion criteria for this review consisted of the following: 1) only full-text English articles of human beings, published in peer-reviewed journals were included; 2) articles included in this analysis were prospective or retrospective cohorts and case-control studies; 3) studies clearly reported the diagnostic criteria of PSH; 4) all patients were older than 18 years. The exclusion criteria were duplicate reports, pre-experiments, randomized controlled trials, conference reports, review papers, case reports, studies unrelated to the topics, or articles that were not fully accessible.

Data Extraction and Quality Assessment

Data extraction from the included studies was performed by 2 authors independently. The first author's name, publication year, study country, population, sample size, age, diagnostic criteria, study design, gender, incidence or number of PSH cases, and related factors were extracted using Microsoft Excel (Microsoft, Redmond, Washington, USA). Data and materials were extracted directly from the literature. To assess the methodological quality of the studies, we used the Agency for Healthcare Research and Quality (AHRQ) scale.[11] The scale comprises 11 items: the definition of information source,; inclusion and exclusion criteria; time period and continuity for identifying patients; blinding of personnel; assessments for quality assurance; confounding and missing data; and patient response rates and completeness. An item was scored "0" if it was answered "Unclear" or "No" and "1" for the answer of "Yes." The article quality was assessed as follows: low quality, 0–3; moderate quality, 4–7; and high quality, 8–11. If the study was assessed as low quality, it was eliminated. If the data were assessed inconsistently by 2 authors, the data were discussed and corrected through negotiation or adjudication by an experienced third expert.

Statistical Analysis

The incidence and risk factors for PSH were prespecified as the main outcome in this study, and any outcomes involving <2 studies were excluded from the meta-analysis. The extracted data were analyzed by STATA version 16.0 (StataCorp LLC, College Station, Texas, USA). The statistical heterogeneity across studies was evaluated using a Cochrane Q test and I^2 index. If the heterogeneity was high (I^2 >50%), we used a random-effects model. Otherwise, a fixed-effect model was used. The publication bias was assessed using a Begg test and a P value <0.05 was considered as significance of publication bias. Subgroup analysis was conducted if necessary. Because of the small number of studies in this meta-analysis, descriptive measures were also used to evaluate outcomes.

RESULTS

A total of 397 relevant studies were retrieved, 313 articles remained after removing duplications by Endnote bibliographic software, 284 unrelated articles were excluded by screening titles and abstracts, and 23 articles were remained. Among these articles, 2 conference reports, 5 review articles, 3 case reports, 1 randomized controlled trial study, and 1 article published in Chinese were excluded; in addition, 1 article was excluded because of duplication. Afterwards, the AHRQ scale was used for quality assessment of the remaining 10 articles and 1 study was excluded because of a low AHRQ scale score.

Overall, we selected 9 studies that were relevant in the systematic review (Figure 1). Characteristics of the 9 studies are described in this systematic review. All the selected studies were published between 2007 and 2021. Six studies were prospective or retrospective cohorts, and the other 3 articles were case-control studies; 4 studies were conducted in the United States, 3 in Europe, and 2 in China. All patients in this review had BI with various causes. The outcomes of methodological quality assessment of the enrolled studies were generally moderate and high with low risk of bias as shown in Table 1. The results of the sensitivity and heterogeneity test for the related factors and outcome for included studies are shown in Table 2.

Main Clinical Outcomes

The pooled incidence of PSH in adult patients with BI was 27.4% (95% confidence interval [CI], 0.190–0.358), a random-effect model was used in the meta-analysis for significant heterogeneity among studies (I^2 = 93.9%) (Figure 2). To explore the source of heterogeneity, we performed subgroup analysis on the incidence of PSH: 1) country: the incidence of PSH in the United States was 37.3% (I^2 = 97.3%; 95% CI, 0.152–0.594); in China, it was 16.4% (I^2 = 17.5%; 95% CI, 0.106–0.221); and in Europe, it was 23.1% (I^2 = 66.2%; 95% CI, 0.180–0.282); 2) diagnostic criteria: the incidence of PSH assessed by PSH-AM was 29.8% (I^2 = 94.9%; 95% CI, 0.182–0.414) and 22.3% (I^2 = 90.8%; 95% CI, 0.100–0.347) by other assessment tools for PSH; and 3) population: the incidence of PSH was 28.2% (I^2 = 95.4%; 95% CI, 0.158–0.406) in TBI.

Publication Bias

The included studies were assessed for publication bias based on their pooled analysis. According to the Begg funnel plot (P = 0.348) (Figure 3) and Egger test

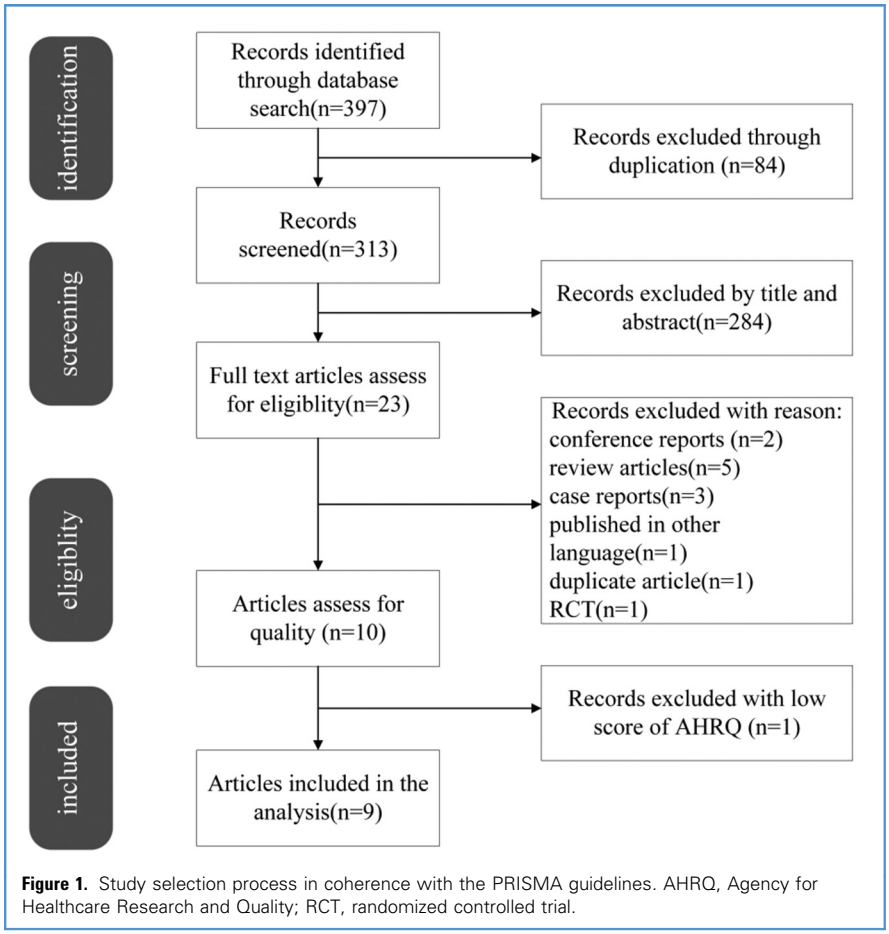

Figure 1. Study selection process in coherence with the PRISMA guidelines. AHRQ, Agency for Healthcare Research and Quality; RCT, randomized controlled trial.

($P = 0.366$), there was no publication bias in the articles included in this meta-analysis.

General Data

Five studies[3,12,14,17,18] examined the effect of age on PSH; the results showed that young age was an independent strong predictor for the incidence of PSH (SMD = −0.592; I^2 =77.5%; 95% CI, −1.027 to −0.156; $P = 0.008$). Seven studies[12-16,18,20] were used to assess the influence of gender for PSH; however, there was no significant evidence of the association between gender and PSH (odds ratio [OR], 1.138; I^2 =0.0%; 95% CI, 0.769−1.686; $P = 0.518$).

Four studies[3,12-14] assessed the association between the mode of injury and PSH, and we combined the data of fall and traffic accident, respectively. Results of meta-analysis showed an OR of 0.993 with fall, and no significant association with the incidence of PSH was observed (I^2 = 0%; 95% CI, 0.583−1.692; $P = 0.980$), whereas the pooled OR of traffic accident is 1.783 (I^2 =18.0%; 95% CI, 1.128−2.820; $P = 0.013$), which showed a statistically significant association with PSH ($P < 0.05$).

Only 2 studies[3,14] explored the association between admission Glasgow Coma Scale (GCS) score and PSH, and the results suggested that the admission GCS score was significantly associated with the present of PSH during hospitalization (SMD = −1.097; I^2 = 28.3%; 95% CI, −1.500 to −0.693; $P = 0.000$).

Disease History or Comorbidities

In the current study, the relationship between hydrocephalus and PSH was assessed by using 3 studies.[3,12,13] We found that patients' having hydrocephalus was significantly associated with the presence of PSH (OR, 3.936; I^2 =67.9%; 95% CI, 1.144−13.540; $P = 0.030$).

Three studies[3,13,14] were used to evaluate the effect of hypertension on PSH, but there was no significant evidence of association between hypertension and PSH (OR, 0.573; I^2 =0%, 95% CI, 0.256−1.284; $P = 0.176$).

Three studies[3,12,14] reported the relationship between DAI and PSH. The results showed that patients' having DAI was significantly associated with the presence of PSH (OR, 4.747; I^2 =71.1%; 95% CI, 1.221−18.463; $P = 0.025$).

Others

Neurosurgery history was also examined by 3 studies[3,12,13] in the current study. We found that the combined effect of neurosurgery history for PSH was not statistically significant (OR, 0.788; I^2 =3.3%; 95% CI, 0.498−1.457; $P = 0.558$). In addition, 3 studies[12,13,16] examined the relationship between tracheotomy and PSH. The results showed that tracheotomy was significantly associated with PSH (OR, 3.277; I^2 =40.9%; 95% CI, 1.916−5.607; $P = 0.000$). Likewise, 3 studies[12,13,16] were included to assess the influence of mechanical ventilation on PSH. However, there was no statistically significant evidence of an association between mechanical ventilation and PSH (OR, 1.129; I^2 =0.0%, 95% CI, 0.673−1.894; $P = 0.645$).

Outcomes

In the qualitative analysis, PSH was associated with many poor outcomes, mainly including the increased length of intensive care unit or hospital stay, lower GCS score after discharge, and higher rate of mortality.[12,14-16,18,21-23] In this quantitative analysis, only mortality had usable data from 2 studies.[12,14] and the result showed that PSH was not significantly associated with higher possibility of death compared with non-PSH patients (OR, 0.777; I^2 =0.0%; 95% CI, 0.213−2.837; $P = 0.702$).

DISCUSSION

PSH is defined as a syndrome of excessive sympathetic activity, mainly observed in severe TBI.[24] Many studies have shown that the condition can have striking manifestations, with paroxysmal tachycardia, arterial hypertension,

Table 1. Publication Search and Characteristics of the Studies

Reference	Country	Population	Diagnostic Criteria	Study Design	Sample Size	Paroxysmal Sympathetic Hyperactivity Cases	Agency for Healthcare Research and Quality Score
Podell et al., 2021[12]	United States	TBI	PSH-AM	Case-control	333	124	7
Li et al., 2019[13]	China	TBI	PSH-AM	Cohort	120	17	7
Samuel et al., 2018[14]	United States	TBI	PSH-AM	Cohort	65	45	8
Eijck et al., 2018[15]	Netherlands	TBI	PSH-AM	Cohort	116	19	7
Lv et al., 2011[3]	China	TBI	PSH-AM	Cohort	79	16	8
Totikov et al., 2019[16]	German	BI	PSH-AM	Case-control	387	97	7
Rabinstein, 2007[17]	United States	TBI	Other	Cohort	43	14	7
Hinson et al., 2017[18]	United States	TBI	Other	Cohort	167	19	7
Dolce et al., 2008[19]	Italy	BI	Other	Case-control	333	87	8

TBI, traumatic brain injury; PSH-AM, PSH Assessment Measure; BI, brain injuries.

tachypnea, hyperthermia, and decerebrate posturing occurring as a response to afferent stimulation.[2] Clinical features resembling PSH were first described in 1954 by Wilder Penfield,[25] and in 2014, 60 years after the first reported case, a panel of experts formalized the definition and diagnostic criteria for PSH.[1] PSH has a prognostic role in patients with BI, which has been widely shown to have negative effects, such as prolonged hospitalization and increased morbidity and mortality.[5] However, there is a dilemma: on the one hand, supportive interventions aimed to avoid the triggers that raise the paroxysms and alleviate the excessive sympathetic outflow are still lacking[2] and few randomized controlled trials of these interventions have been conducted; on the other hand, pharmacologic therapies including opioids, especially morphine, are commonly used as first-line drugs,[26] and some other medications, such as gabapentin, clonidine patches, dexmedetomidine, and propranolol are also considered to be effective in the control of excessive sympathetic outflow.[27-30] Because of the paucity of data on incidence and pathogenesis of PSH, we conducted a systematic review and meta-analysis to determine the synthesized data of the incidence and associated risk factors of PSH in patients with BI.

The synthesized incidence of PSH was 27.4%, and the heterogeneity between the included studies was high ($I^2 = 93.9\%$). The findings of our study are largely concentrated in North America, Europe, and China. Among these studies, the incidence of PSH was highest in that of Samuel et al. (69.2%)[14] and lowest in that of Hinson et al. (11.4%).[18] The incidence of the remaining 7 studies is more balanced, distributed between 14.2% and 37.2%. A possible explanation for the variation might be patients' average age, sample size, study design, diagnostic criteria, population, and sociodemography. In this meta-analysis, we identified only a few factors that accounted for a small proportion of heterogeneity in these studies.

Subgroup analysis showed that the presence of PSH was higher in North America than in China and Europe. It is perhaps relevant for health care workers from the United States and Canada to pay more attention to screening for PSH. Frequent screening might increase the detection rate of PSH. We also found that the incidence of PSH assessed by PSH-AM was higher than other assessment tools. The diagnosis of PSH is based on a high degree of suspicion and exclusion of other clinical diagnoses.[31] The definition for PSH could be full of challenges for various reasons.[32] The PSH Assessment Measure (PSH-AM) was set in a consensus committee in September 2014 by Baguley et al.[1] PSH-AM has 2 assessment tools (Clinical Feature Scale tool and Diagnostic Likelihood Tool), is easy to apply in daily practice, and gives health care providers more opportunity to assess the probability and severity of PSH in clinical practice than previously.[15] In addition, the subgroup analysis confirmed that PSH occurs more frequently in patients with TBI, which is similar to findings in previous research.[33]

According to the current systematic review and meta-analysis, PSH seems to be more frequent in younger populations ($P < 0.0$) when all age groups are included for comparison. Some previous studies[17,19] have reported that lower age was correlated with the occurrence of PSH, and younger patients were more likely to develop PSH after brain damage in adults. To explain this phenomenon, recent research[34] has provided a theory that the causative brainstem or diencephalic centers involve inhibitory control centers, the damage of which would release excitatory signals in spinal cord processes, resulting in autonomic overreactions. In particular, the response of the autonomic nerve system to external stimulation in younger patients is perceived to be stronger than in the elderly.[3]

Although Farias-Moeller et al.[23] showed that females were more likely to develop PSH compared with male patients in the aseptic encephalitis, there is no evidence that the incidence of PSH was different

Table 2. Sensitivity and Heterogeneity Test for the Related Factors and Outcome for Included Studies

Study Number	Related Factors	Standard Mean Difference/Odds Ratio	95% Confidence Interval	Heterogeneity of the Included Studies, I^2 (%)	*P*
1	Age	−0.592*	−1.027 to −0.156	77.5	0.008
2	Gender	1.138†	0.769–1.686	0.0	0.518
3	Fall	0.993†	0.583–1.692	0.0	0.980
4	Traffic accident	1.783†	1.128–2.820	18.0	0.013
5	Admission Glasgow Coma Scale score	−1.097*	1.500 to −0.693	28.3	0.000
6	Hydrocephalus	3.936†	1.144–13.540	67.9	0.030
7	Hypertension	0.573†	0.256–1.284	0.0	0.176
8	Diffuse axonal injury	4.747†	1.221–18.463	71.1	0.025
9	Neurosurgery	0.788†	0.498–1.457	3.3	0.558
10	Tracheotomy	3.277†	1.916–5.607	40.9	0.000
11	Mechanical ventilation	1.129†	0.673–1.894	0.0	0.645
12	Mortality	0.777†	0.213–2.837	0.0	0.702

*Standard mean difference.
†Odds ratio.

in males and females after BI in this meta-analysis. In the current study, a low GCS score was significantly associated with PSH symptoms. Generally, a low GCS score indicates severe neurologic impairment and severe craniocerebral injury, especially TBI, usually originating in injuries in the deep gray matter nuclei or brainstem, which are the critical regions of interest in PSH according to the latest disconnection theory.[34,35] Therefore, a low GCS score can be regarded as a significant predictor of PSH.

Traffic accidents, mainly motorcycle collisions and motor vehicle collisions, were an important factor affecting the incidence of PSH, probably because motor vehicle accidents often cause high-velocity injuries resulting in DAI, which is postulated to be an underlying mechanism for PSH.[36] Nevertheless, our results suggested that falls are not related to PSH, which we do not have enough evidence to explain precisely. However, we hope that our results can be used to assess the likelihood of PSH in patients with BI.

Hydrocephalus is the accumulation of cerebrospinal fluid within the cerebral ventricles, which is typically associated with increased intracranial pressure.[37] This study showed that the presence of hydrocephalus was significantly connected to the occurrence of PSH. Although the mechanism of the impact of hydrocephalus on PSH has not been defined, a recent study[9] confirmed that injuries to deep brain structures, such as hydrocephalus and intracerebral hemorrhages, are more likely to cause PSH. Given this perspective, we suppose that the increased risk of developing PSH in patients with hydrocephalus might be related to the increased intracranial pressure caused by hydrocephalus. The related mechanisms should be investigated further.

In the current study, DAI was shown to be a powerful risk factor for the development of PSH. Only limited clinical research on the relationship between DAI and PSH has been published. Gonzalez et al.[38] reported that the incidence of PSH in patients with DAI was 19%, and patients with PSH after DAI experienced a greater frequency of unfavorable outcomes.[39] Furthermore, Lv et al.[3] found that the MRI scale of all patients with PSH after severe TBI was II or III, which indicated injury in the corpus callosum or lower sites. Consequently, these investigators considered that injury of the deep brain was mostly caused by DAI, especially in deep gray matter nuclei or brainstem, and was the crucial structural cause for the progression of PSH. For this reason, patients with DAI should be monitored routinely for PSH.

To our knowledge, the influence of tracheostomy on the presence of PSH has been given little attention.[40] In this meta-analysis, patients who underwent tracheostomy had a higher rate of PSH. Previous literature[41] has mentioned that hypoxia was common in patients with TBI. Tracheostomy is an effective and safe technique to provide stable respiratory passages for improving cerebral aerobic metabolism for injured brain tissue and has been recommended for patients with severe TBI.[42] The mechanism of tracheostomy on PSH was not well defined, but it was reported that anoxia was more frequent in patients with PSH,[43] so we speculate that tracheostomy is more of a consequence of a debilitating BI. No animal experiment that focused on the relationship between the anoxia and presence of PSH has been found. Accordingly, further efforts are needed to clearly define the mechanism of tracheostomy in the association of anoxia and the development of PSH.

In addition, the results showed that a history of hypertension and stroke was not a significant factor in PSH. Hypertension was the most frequent comorbid condition.[44] A previous study[45] confirmed that hypertensive conditions on the endothelial compartment led to increased permeability of the blood-brain barrier, which in turn leads to BI, but this was not the main cause of BI in this study. Neurosurgery and mechanical ventilation did not have any associations with PSH. Further investigations into the mechanisms of these results are recommended.

Although PSH is generally associated with adverse outcomes, such as prolonged intensive care unit or hospital stay, the results of this study confirmed that PSH did not increase the risk of death in adult patients with BI. To our knowledge, patients with PSH had a more difficult clinical course in rehabilitation and might

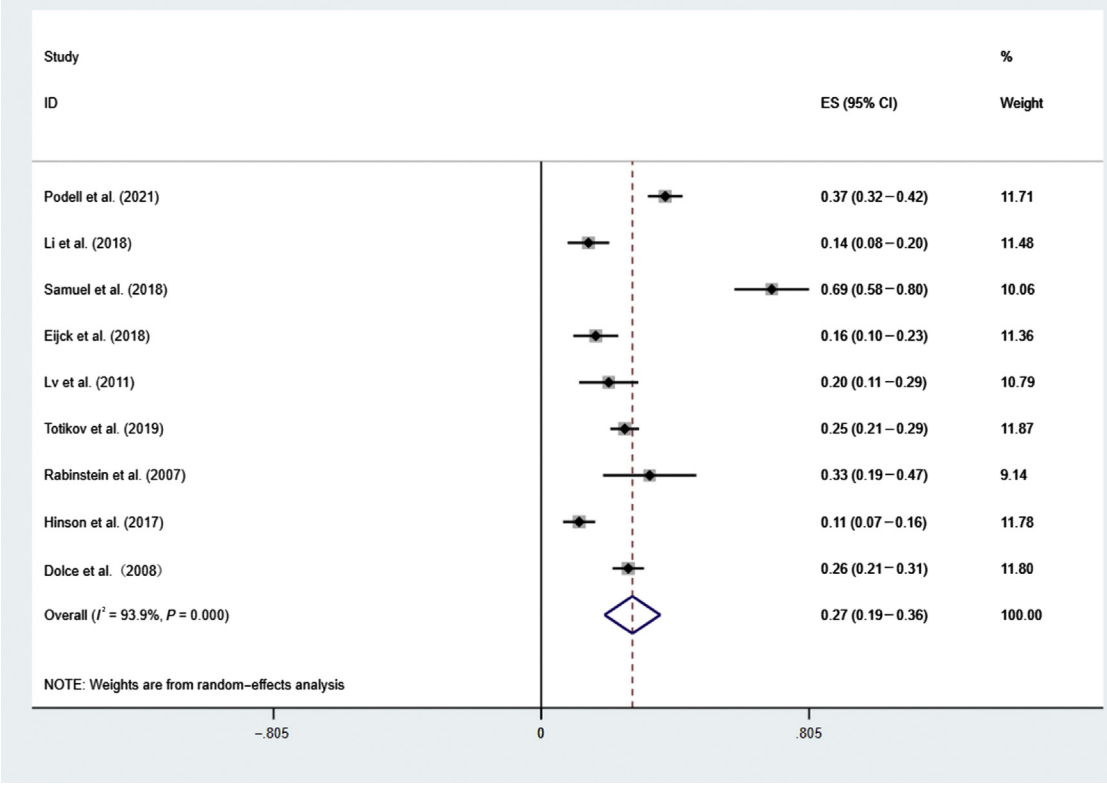

Figure 2. Forest plot of the incidence of paroxysmal sympathetic hyperactivity. CI, confidence interval; ES, effect size.

have more need for feeding and breathing devices, which could result in complications such as infections, which lead to death directly or indirectly.[46,47] In this study, we combined the data of only 2 studies for mortality, and more research is needed to explore this result.

The present study has several limitations. First, some of the included studies had a small sample size, which could affect the estimated results; besides, there were obvious variances in the design of each study, including cohort and case-control studies, which can also be a source of uncertainty for this meta-analysis. Second, there was significant unexplained heterogeneity of some of the pooled results, and the additional subgroup analysis cannot completely account for the obvious heterogeneity. We did not conduct a gray literature search, which may have contained important perspectives. These limitations mean that the results of this review must be interpreted cautiously.

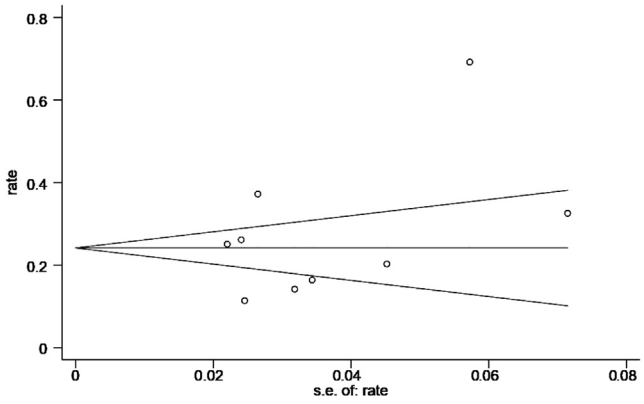

Figure 3. Begg funnel plot with pseudo 95% confidence limits. s.e., standard error.

CONCLUSIONS

PSH has been identified as a syndrome of excessive sympathetic activity, mostly prevalent in patients with TBI, and has been proved to be detrimental to patients by current findings. However, the development and underlying mechanism of

PSH in different types of brain damage was little known. Therefore, this study has practical implications. The present meta-analysis shows that the combined incidence of PSH in adult patients with BI was 27.4%, and risk factors including younger age, traffic accidents, low admission GCS score, hydrocephalus, DAI, and tracheostomy were significantly associated with PSH for adult patients after BI. These findings not only contribute to a better understanding of PSH but also provide timely and necessary evidence for further research. Still, because of a lack of reports mentioning the difference in the incidence, development, and outcomes of PSH between adults and children, further related study is also needed. In addition, considering that some PSH cases may have been missed and there is a lack of nonpharmacologic treatment, we suggest that PSH should be routinely monitored in high-risk populations, and future studies should focus on the therapeutic interventions for PSH.

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