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REVIEW

The truths behind the statistics of surgical treatment for hypertensive brainstem hemorrhage in China: a review

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Abstract

Hypertensive brainstem hemorrhage (HBSH) is of high morbidity and mortality rate. But many clinical studies were written in Chinese and had not been reviewed. A systemic review of Chinese clinical studies for HBSH was performed. A systemic literature search in PubMed, Web of Science, China National Knowledge Infrastructure, and Weipu database and Wanfang database up to March 2020 was performed. Clinical control studies including a surgical evacuation (SE) group and a conservative management (CM) group were included. The clinical outcome and mortality rate were compared. Ten cohort studies were included, involving 944 participants (304 in the SE group and 640 in the CM group). All included patients were comatose, with the average age ranged from 45 to 65 years old. Among five studies using mRS or GOS as outcome score, a total of 16.6% (89/535) of patients achieve self-maintenance with minor disabilities, including 26.8% (34/127) in the SE group and 13.5% (55/408) in the CM group. The overall mortality rate in the SE group was 27.6%, ranged from 9.3 to 60% among different studies. The overall mortality rate in the CM group was 60.6%, ranged from 18.5 to 100.0%. Elder and comatose HBSH patients are not contraindicated for surgery. The review showed that this group of patients obtained a better outcome and lower mortality rate after surgical treatment. The quality of included studies was relatively low, but a high-level clinical study on HBSH is of great difficulty, as both clinicians and patients faced various sociological issues rather than pure medical problems.

Keywords Brainstem hemorrhage · Surgery · Outcome · Mortality rate

Introduction

Brainstem hemorrhage (BSH) accounts for 5–10% of intracranial hemorrhage, with overall mortality rate ranged from 25 to 90% [4, 8, 21, 29, 32, 40]. It had been divided into two groups according to different pathophysiologic literature: hypertensive patients and normotensive patients. It was well known that normotensive hemorrhage is commonly caused by a cavernous malformation, which had a significantly better outcome [34, 36]. However, nearly 90% of patients with BSH were hypertensive [6]. Hitherto, there is still no consensus on whether hematoma evacuation improves the outcome of hypertensive brainstem hemorrhage (HBSH) patients after a hundred-year practice. The main reason is the lack of high-quality clinical control studies in the literature. Compared to English publications from other countries, there is a larger amount of clinical studies on HBSH published by Chinese academics. It is very important to share those researches worldwide to help to improve the clinical outcome of patients suffering from HBSH.

Material and methods

Search strategy

A systemic literature search in PubMed, Web of Science, China National Knowledge Infrastructure, and Weipu database and Wanfang database was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA).[31] The search was

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conducted in March 2020. The search term in PubMed was ("brainstem"[Title/Abstract] OR "pontine"[Title/Abstract] OR "medullary"[Title/Abstract]) AND ("hematoma"[Title/Abstract] OR "hemorrhage"[Title/Abstract]) AND ("surgery"[Title/Abstract] OR "approach"[Title/Abstract]). The references of included articles were also reviewed.

Study selection

Two authors (ZHENG and SHI) independently conducted the literature search. A study was included in this systematic review when the following criteria were met: (1) type of research: published randomized controlled trials (RCT) or non-randomized concurrent controlled trials (NRCCT) including a surgical evacuation (SE) group and a conservative management (CM) group. Of note, external ventricular drainage (EVD) was regarded as a life-saving procedure in CM; (2) studies carried out by tertiary hospitals in China. Studies with overlapping populations were excluded; (3) outcome and mortality rate in both the treatment group and control group were available. The outcome should be measured with a quantified scale; (4) full texts were available in English or Chinese. Exclusion criteria: studies included patients with a definite diagnosis of vascular malformation (cavernous malformation, etc.). The difference of opinion on study inclusion was solved by discussion. Disagreements were resolved through discussion with the third author (GONG). The search results were merged using Endnote X9, and the duplicate records were removed.

Methodological quality assessment

Two authors (ZHENG and SHI) independently assessed the full text of all included papers. Publication year, hospital level, patients' baseline information, sample size, and type of surgery, outcome score, mortality rate, and follow-up period were collected. Patients' outcomes and mortality rates were recorded at the end of follow-up.

The quality of NRCCT was assessed with the Methodological Index for Non-Randomized Studies (MINORS) guidelines [41]. The studies with a total score of ≥ 16 points were regarded as high quality, and vice versa. The quality of randomized controlled trial (RCT) was assessed using the Cochrane collaboration's tool for assessing the risk of bias.

Various outcome scores were applied in different studies. A good outcome was defined if (1) GOS > 3[12, 17, 19], (2) mRS < 3[24, 39], (3) National Institute of Health stroke scale (NIHSS) decrease 45% after treatment[5, 22, 37], (4) Barthel index > 40[50] or > 60[26].

No meta-analysis was performed to obtain pooled estimates because the studies were heterogenous according to the MINORS and Cochrane evaluations. Statistical analyses of categorical variables were carried out with chi-square tests or Fisher's exact tests using SPSS 23.0 (Chicago, IL, USA).

Results

Search results. The initial search obtained 428 articles, including 207 articles in Chinese and 221 articles in other languages. There were 64 studies excluded because of duplication. After reading the title and abstracts, a total of 340 studies were excluded due to inappropriate article types. Fourteen studies were excluded after the full-text review. Reasons for exclusion were as follows: lack of data on outcome score and mortality[7, 15, 16, 18, 40, 48], no CM group[9, 38], not tertiary hospital[25], no enough follow-up duration[46], lack of patient inclusion criteria[3], only external ventricular drainage for treatment group[49, 51], overlapped patients population[10]. The PRISMA flow diagram was described (Fig. 1).

Ten studies were selected for systemic analysis, including 2 RCTs[12, 17] and 8 NRCCTs [5, 19, 22, 24, 26, 33, 39, 50] (Table 1). The sample size ranged from 21 to 326, including 304 surgically treated patients and 640 conservatively treat with/without EVD patients, comprising 944 participants. Most included patients were comatose (GCS ≤ 8 in seven studies), with the average age ranging from 45 to 65 years old (average age was not reported in one study). Excluding three studies that did not report hemorrhage location precisely, the remaining seven studies report 164 (20.5%), 584 (73.1%), and 51 (6.4%) cases of mesencephalic, pontine, and medullary HBSH, respectively.

Characteristics and quality of included studies

Study quality of NRCCTs ranged from 13 to 20 out of 24 on the MINORS Scale. Three studies had a MINORS score less than 16 and were regarded as "low-quality." Both two RCTs included were regarded as "high risk of bias" according to the Cochrane tool. All included studies stated that the baseline of SE and CM groups were comparable, but only 6 studies provided the statistical valve ($P > 0.05$). All studies reported adequate follow-up time without patient loss.

As the quality of included articles was low, a meta-analysis was waived.

Overall outcome

The outcome scores were obtained from all ten studies. The result of five studies supported that patients who underwent SE having a better outcome (Table 2). Among five studies using mRS or GOS as outcome score, a total of 16.6% (89/535) of patients achieve self-maintenance with minor disabilities, including 26.8% (34/127) in the SE group and 13.5% (55/408)

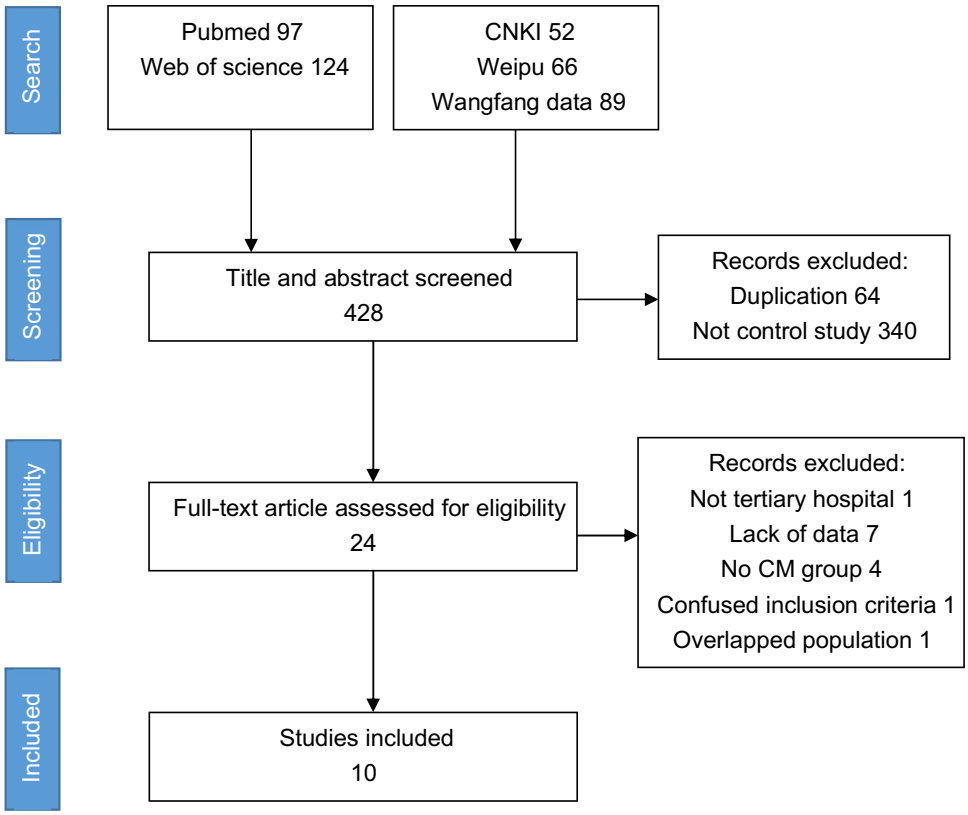

Fig. 1 The PRISMA flow diagram

in the CM group. The follow-up period was 3 to 6 months in those studies.

Overall mortality rate

The mortality rates were obtained from all ten studies. The result of seven studies showed a significantly lower mortality rate in the SE group (Table 2). The overall mortality rate for all patients was 50.0% (472/944). The overall mortality rate in the SE group was 27.6%, ranged from 9.3 to 60% among different studies. The overall mortality rate in the CM group was 60.6%, ranged from 18.5 to 100.0%. The follow-up period was 1 to 12 months.

Overall complications

Only four studies reported complications in HBSH patients (Table 3). LV et al. observed a higher occurrence rate of pneumonia in the CM group ($P=0.007$). Huang et al. showed that hydrocephalus significantly increased in the CM group ($P<0.001$).

Discussion

Recently, there has been a strong tendency for surgically treating HBSH in China. A total of 20 clinical studies were published in Chinese during the last 3 years. Comparing to worldwide studies in the same period, merely several cases were reported by Japan[14]. Western countries started operating HBSH in the early 1900s[29]. However, due to the low incidence rate, only small single-institution series were available, which were generally with regional and investigator biases[8, 23]. The east and southeast Asian population had a two times higher incidence rate for intracranial hemorrhage compared to other populations. [43] Together with the improvement in medical service in China over the past 20 years, more HBSH patients are willing to pursue better management nowadays.

Chinese reports consist of a larger sample size compared to other countries, but are mostly written in Chinese. This is the reason why we decided to run a systemic review in English for Chinese papers. Another reason

Table 1 Overviews of the ten studies included in the review

Author	Year	Design	Mean age (years)	History of hypertension	Preoperative angiography	Patient inclusion	Hemorrhage location (*n*)			Mean HV (ml)	Follow-up (months)	MINORS/Cochrane
							MES	PON	MED			
ZHANG SW	2019	NRCCT	50.5	47 (85.5%)	No	GCS 3–8 HV > 5 ml	9	45	1	8.4 ± 1.5	3	16
LAN ZG	2019	NRCCT	51.5	All	Yes	GCS 3–8	54	208	24	8.7 ± 0.5	6	20
LV CL	2019	NRCCT	NM	All	No	GCS 3–7	37	71	0	11.3	3	16
ZHANG YQ	2017	NRCCT	47.1 ± 8.4	All	Yes	GCS 3–8 HV ≥ 5 ml	43	14	8	8.1 ± 1.4	3	17
HUANG KY	2016	NRCCT	48.5 ± 5.1	All	No	Comatose HV 5–10 ml	NM			NM	12	15
ZONG L	2016	NRCCT	58.9 ± 6.3	All 8 surgery patients	No	GCS 3–5 HV 5–20 ml	40		0	NM	3	13
CHEN QM	2015	NRCCT	52.5	All	No	GCS 3–8	NM			NM	3	15
KU HB	2014	RCT	65.2	115 (84.6%)	No	GCS 3–10 HV 5–20 ml	0	136	0	11.8	1	High risk
WANG J	2014	NRCCT	54.5	All	No	GCS 3–8	21	89	18	8.0	3	16
HUANG JL	2010	RCT	57	All	No	GCS 3–8 HV ≥ 7 ml	0	21	0	11.5	6	High risk

GOS Glasgow Outcome Scale, *GCS* Glasgow Coma Scale, *HV* hematoma volume, *MED* medullary, *MES* mesencephalic, *NRCCT* non-randomized concurrent controlled trials, *NM* not mention, *mRS* modified Rankin scale, *PON* pontine, *RCT* randomized controlled trials

Table 2 Patient outcome and complications compared in ten studies

Author	Year	Treatment	EVD in CM group	Outcome assessment	Good outcome		*P* value	Mortality rate		*P* value	Follow-up (months)
					Surgery	Control		Surgery	Control		
ZHANG SW	2019	Stereotactic aspiration	Yes	mRS < 3	7/19 36.8%	6/36 16.7%	0.094	4/19 21.1%	16/36 44.4%	0.086	3
LAN ZG	2019	Microscope	No	mRS < 3	11/46 23.9%	45/240 18.8%	0.419	14/46 30.4%	169/240 70.4%	**< 0.001**	6
LV CL	2019	Stereotactic aspiration	No	NIHSS ↓45%	25/43 58.1%	20/65 30.8%	**0.005**	4/43 9.3%	12/65 18.5%	0.190	3
ZHANG YQ	2017	Aspiration	No	Barthel index > 40	8/32 25.0%	1/33 3.0%	**0.010**	18/32 56.3%	27/33 81.8%	**0.026**	3
HUANG KY	2016	Microscope	YES	NIHSS ↓45%	17/30 56.7%	12/30 40.0%	0.196	4/30 13.3%	11/30 36.7%	**0.037**	12
ZONG L	2016	Microscope	No	Barthel index > 60	4/8 50.0%	11/32 34.4%	0.414	2/8 25.0%	13/32 40.6%	0.414	3
CHEN QM	2015	Microscope	No	GOS > 3	1/15 6.7%	0/30 0%	0.333*	9/15 60.0%	29/30 96.7%	**0.001**	3
KU HB	2014	Stereotactic aspiration	Yes	NIHSS ↓45%	25/64 39.0%	9/72 12.5%	**< 0.001**	13/64 30.3%	42/72 58.3%	**< 0.001**	1
WANG J	2014	Microscope	No	GOS > 3	10/37 27.2%	4/91 4.4%	**< 0.001**	14/37 37.8%	58/91 63.7%	**0.007**	3
HUANG JL	2010	Stereotactic aspiration	No	GOS > 3	5/10 50.0%	0/11 0%	**0.012***	2/10 20.0%	11/11 100.0%	**< 0.001***	6

CM conservative treatment, *EVD* external ventricular drainage, *GOS* Glasgow Outcome Scale, *mRS* modified Rankin scale, *NIHSS* National Institute of Health stroke scale, *Fisher's exact test, **bold type** indicates significant difference ($P < 0.05$)

Table 3 Major complications reported by four studies

Author	Year	Pneumonia		*P* value	Stress ulcer		*P* value	Renal failure		*P* value	Others	
		Surgery	Control		Surgery	Control		Surgery	Control		Surgery	Control
LAN ZG	2019	14/46	89/240	0.390	12/46	57/240	0.734	NM	NM		NM	NM
LV CL	2019	1/43	13/65	**0.007**	5/43	5/65	0.754	2/43	6/65	0.607	NM	NM
WANG J	2014	6/128			3/128			12/128			Respiratory failure 47/128	
HUANG JL	2010	1/10	2/11	1.000	1/10	2/11	1.000	1/10	3/11	0.652	Hydrocephalus 1/10 Hepatic failure 1/10 MODS 1/10	Hydrocephalus 10/11 Hepatic failure 1/11 MODS 1/11

MODS multiple organ dysfunction syndrome, *NM* not mention, **bold type** indicates significant difference ($P < 0.05$)

is that different health care systems and cultures dictate health care decision-making for both patients' families and clinicians [35]. A study exclusively for one country can avoid certain non-medical biases.

Surgery or conservative treatment?

This question has been studied for a hundred years, yet a uniform consensus has not been met. Arseni et al. distinct two groups of BSH and its terminology: hematoma and hemorrhage [1]. He defined that a "hemorrhage" was "diffuse and dilaceration," and a "hematoma" was "localized." Only patients with "brain stem hematoma" require surgery as the hematoma will evolve into an intracranial space-occupying lesion. Some surgeons believed that there is no role of surgery in primarily comatose patients having HBSH because of uniformly disastrous outcome.[36]

In this review, we focus on clinical studies comparing SE and CM in HBSH patients. The included patients were generally elder, most of them had a history of hypertension. More importantly, all studies only operated on patients who appear comatose (GCS < 10), representing the typical patients whom other countries' clinicians recommend not to operate on.

Five studies showed that the SE group had a superior outcome to the CM group. Among them, four studies underwent hematoma aspiration and one was microscopic surgery. Another five studies also trended toward surgical treatment but did not achieve statistical significance.

As alluded to earlier, the mortality rate of BSH varies greatly in literature. Our review showed that the mortality in the SE group was approaching the minimum level of literature reported. Most included studies suggested that the survival rate was much higher in the SE group. We also found a slightly lower overall mortality rate in the hematoma aspiration group than the microscopic surgery group (24.4% versus 31.6%, $P = 0.162$). This indicated that hematoma aspiration may be suitable for older patients in this review because it was of less surgical trauma and shorter operation time. However, the major complications such as rehemorrhage rate were only mentioned in one study.[12]

The mortality rate of the CM group was on the average level reported in the literature. Of note, only three studies claimed that they would perform EVD as a life-saving procedure in the CM group. The mortality rate in these three studies was 36.7%, 44.4%, and 58.3%, which were slightly lower than average mortality in the pool. Absent of EVD when necessary was thought to increase the mortality rate in the CM group.

Patient selection: alert or comatose?

It had been replicated by many researchers that patients with a lower conscious level would have a worse outcome, no matter surgery or not [2, 13, 20, 21, 30, 36]. The question of why Chinese surgeons are willing to operate on comatose patients is in fact not a medical but a sociological problem.

As the mean age of patients was 50 to 60 years old in the included studies, the treatment plan was mostly decided by patients' spouses and children. In traditional Chinese families, the concept of "filial piety" played a unique and positive role in family associations.[42] However, when it comes to the decision on the treatment plan for life-threatening diseases such as HBSH, even though a dismal prognosis was carefully informed, Chinese families were more likely to choose surgery. Because receiving conservative treatment may represent "palliative care" or "giving up."[27]

Another very important aspect is the tense doctor-patient relationship in China. Chinese doctors are very likely to expose to violent confrontations if the patients and their families were unsatisfied.[44] Under this circumstance, the risk of operating an alert patient obviously overpass to that of a comatose one, especially when there was not an official guideline or a book-written indication for the disease. The surgeon would readily lose in a lawsuit, even he/she did only what the patient's family asked.

The most "safety" manner is that the surgeons manage all the HBSH patients conservatively. But here they face the policy of the Chinese health care system. Most provinces in China now implement the "Per case for simple illness" or "Per case for complex conditions" payment system[47]. A fixed fee for each disease was set based on the average medical expense in the local city. For example, the "conservative treatment fee" for brainstem hemorrhage is 36612.0 CNY in our distinct, and it doubles to 77,436.0 CNY if the patient underwent surgical treatment. The age of the patient, the location and amount of the hematoma, and the complications followed by the primary disease were not on the consideration of this system. The department must be responsible for its own profits and losses while considering the treatment plan for patients. A patient with HBSH may easily develop pneumonia during conservative treatment, and he/she has to be on a ventilator in an intensive care unit (ICU) for a long period. If so, he/she will definitely cost more than the health care system covered. In this circumstance, the doctor may prefer the surgical treatment, which provides an extra medical fee and a potential possibility for the patient leaving ICU earlier.

As a result, the decision of Chinese surgeon to operate comatose patients was largely economic and sociological considerations, rather than medical necessity. But it gave us the chance to observe the clinical outcome in these patients, and the result was encouraging. Depressed mental status in HBSH patients is attributed to the destruction of the reticular formation and acute obstructing hydrocephalus. The former one acts immediately after the onset, and its delayed perifocal edema may lead to aggravation of neurological deficits. While the neurological damage is irreversible, hematoma evacuation can prevent secondary damage from the hematoma [1, 2]. It showed that 36% of HBSH patients would develop hydrocephalus initially.[24] Acute hydrocephalus is caused by the direct oppression of the hematoma or blockage of intraventricular hemorrhage. It is manageable and reversible but makes patients look worse than they really are. One RCT study[17] showed that 91% of patients in the CM group without EVD eventually developed hydrocephalus, contributing to a 100% mortality in the group. Aggressively managing hydrocephalus will remarkably improve the patient's outcome.

Barriers in HBSH clinical study

Above we have seen the charming outcome from surgically treated HBSH. In fact, we are still far away from achieving high-quality evidence. It is noteworthy that all included studies strongly supported the same conclusion: the SE group was superior to the CM group over patients' outcome or mortality rate. This implies a typical publication bias, which is likely attributed to the well-known Cash-per-publication Reward Policy[45] in China. As studies with positive results are much easier to be accepted, they are more profitable. Besides monetary rewards, clinical doctors require a certain amount of papers or impact factors for promotion. Both "fame and gain" lead to inevitable publication bias in Chinese articles. This explains why studies reporting negative results are extremely sparse in China.

Only four studies reported systemic complications between SE and CM groups (Table 3). However, complications vary greatly in HBSH patients. For example, patients having no spontaneous respiration will bear a higher risk of pneumonia on long-term ventilator usage. It is idle to compare complications irrespective of patients' general condition on admission and hematoma's location and volume. While the inclusion criteria of the included studies were not uniform, a statistical analysis was not performed.

When referred to the mortality rate, families' decision on the treatment plan is critical. Only two studies clearly stated that "patients whose families decided giving up treatment were excluded"[17, 50], and one study[24] stated that "patients whose families refused to have surgery were served as the control group." This resulted in significant selection bias for further analysis because (1) family refused to have surgery may imply that they were unable or unwilling to financially support the advanced treatment; (2) these patients may receive a relatively negative treatment, or "futile

treatment"[11], from the aspect of medical staff. These will increase the mortality rate in the CM group.

The ideal approach is to conduct a multi-center RCT, but one will face an ethical issue as the 2016 International ethical guidelines for health-related research involving humans states had pointed out: "clinical trials in contexts of high-mortality diseases are morally suspect because equipoise does not exist between a standard of care that offers little prospect of clinical benefit and an unvalidated medical intervention that might offer some clinical advantage"[28]. This perfectly describes the situation in HBSH. As the patients in severe hemorrhage would ultimately die in conservative treatment, surgery which has successful reports is worth attempting.

Limitations

The limitations of this study are massive. The quality of the included studies was low-moderate, and the follow-up period of seven studies was less than 6 months, which hinder the production of reliable results.

Although most of the patients are proven to have hypertension in admission, only two included studies performed angiography prior to the treatment. A total of 60 patients (6.4%) in the pooled data neither have a history of hypertension nor underwent angiography. There is no guarantee that some cases of brainstem cavernous malformation would mix in the review.

BSH had been divided into four groups based on different morphology and outcome, namely "massive type," "bilateral tegmental type," "basal tegmental type," and "small unilateral tegmental type." Among them, only small unilateral tegmental type has a superior survival rate than other types (94.1% versus 18.2%) [4]. It was a pity that none of the studies carried out such a classification system. All ten studies classified hemorrhage by anatomical location (medullary, pontine and mesencephalic, etc.), and not all of them reported the outcome and mortality accordingly. This makes it impossible to furtherly discuss with different subgroups.

Conclusion

Our findings ran contrary to the theory that "old, hypertensive, and comatose" patients were not the candidates for surgery. A high-level clinical study on HBSH is of great difficulty, as patients' outcome greatly depends on the location and volume of the hematoma, while excessive grouping makes it hard to achieve enough sample size for analysis. The sociological problems both the clinicians and patients' families faced also impede us to conduct an objective and strict clinical research. Also, based on the policies for doctor promotion and publication reward, this kind of long-period and delicate study is unlikely to appear in China nowadays.

Author contribution Zheng and Shi independently assessed the full text of all included papers. Gong made the final decision for which study would be included. Zheng composed the paper.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval This study is approved by the Beijing Tiantan Hospital Institutional Review Board.

Consent to participate All clinical data are collected in the cited literatures.

Consent to publication All authors are consent to publish in Neurosurgical Review.

Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals Not applicable.

Conflict of interest The authors declare no competing interests.

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